Can Nutrition Affect Chemical Toxicity?

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Universally, the general population is exposed to a variety of "toxic" substances. Some of these are from manufactured goods and some from air and water pollution. Toxins are also normally found in many foods; however, unless the exposure is overwhelming, we are many times (even unknowingly) protected by the foods we eat. A judicious choice of food will counteract noxious agents. Therefore, the diet can be a major factor in determining who does and who does not show toxic symptoms following exposure. This review will cover three aspects. The first will be on protectors against metal toxicity. For example, whereas humans can consume fish that have absorbed mercury from contaminated bay water, selenium can act as a natural antagonist for mercury poisoning. (Naturally, too much selenium itself can be detrimental!) Some vegetables can accumulate cadmium from contaminated soil, and zinc from a variety of nuts is an antagonist of cadmium toxicity. Nitrites in preserved meats can be converted into nitroamines by saliva or mild stomach acid. Vitamin C found in oranges and bell peppers can inhibit that conversion. In addition, calcium antagonizes both lead and aluminum toxicity. The second aspect is on oxidants and antioxidants. Oxidative stress can lead to some cancers, atherosclerosis, and adverse effects of aging. Antioxidants are the best protectors of the damage caused by reactive oxygen species (ROS). The most effective antioxidants are found in highly colored fruits and vegetables such as carrots, tomatoes, and berries, called carotenoids. Flavonoids (polyphenols), another class of effective antioxidants that negate ROS, may or may not be colored. The third aspect is on gaps in current knowledge. Many foods naturally contain chemicals that are, in larger concentrations, quite toxic or carcinogenic. Biotransformations (detoxification mechanisms) involving type I and type II enzymes are known. Some foods do modify these enzymes either positively or negatively. Grapefruit contains a substance that inhibits an isoform of P450, making some cardiac drugs, as substrates, more toxic. There is inadequate information on what specific components are in a variety of foods that are associated with cancer prevention. The experimental carcinogenic compound (and suspected as a human carcinogen) found in overcooked, burnt, and fried meats and fish, namely IQ (2-amino-3-methyl-3H-imidazo[4,5f]quinoline, will be used as a prototype for what needs to be known about foods that *will* affect toxins.

Keywords Biotransformation, Cancer, Minerals, Oxidants, Toxicity

Living in a Chemical World, the 1988 publication of the symposium sponsored by the New York Academy of Sciences (Maltoni and Selikoff 1988) could easily be retitled *Living in a Toxic World.* In this volume of over 1000 pages, mainly related to cancer, only three short pages were devoted to the possible effects of diet. Toxic agents found in the general environment and from many industries have been adequately documented. More recently, publications have described toxic agents naturally found in some foods (Hathcock and Rader 1999; Gold, Slone, and Ames 1997; Grasso 1984; Kapadia 1982). Notably among these are various hydrazines in mushrooms (Toth 2000). These toxins are in addition to the intentionally applied pesticides that cause a concern in a large segment of the population (Mattisson 2000). All this implies that we live in a sea of chemicals, many of which are carcinogens. To obtain a better understanding of this world of chemicals, it is also important to examine the effects of nutrition on chemical toxicity.

In the main, single entities will be discussed. However, multiple chemical exposures are becoming more important in our environmental solutions (Kumar 2001).

A number of government agencies are concerned with protecting the health of the general public. Laws are proposed and passed to limit the amount of exposure to specific chemicals in or on the fruits and vegetables sold in the market, or limit the use of pesticides on the original crops. In spite of the attempts to clean the environment, and in spite of the fact that contamination is all around us, the majority of cancer rates are quite steady over the years. Only in some specific organs are the rates slowly rising (this is in contrast to the popular notion that there is an epidemic of cancer). Why then is life expectancy increasing? Of course, the reduction of infant mortality is a contributing factor, but this is not the only one.

To a large extent, the food we eat is a major contribution. Can foods affect toxins? The logical answer must be, *Yes*. This discussion will address this question. Three aspects will be discussed,

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in which in parts one and two there appears to be adequate information to explain the general protective action of foods against the toxic world and, in some cases, cancer. In part three, the major unknown sections are what components of food are the real protectors, and what the biochemical explanation needed to explain the protection is.

ESSENTIAL VERSUS TOXIC MINERALS

The first aspect of this review is concerned with minerals. A few toxic heavy metals are often encountered in our daily life. For the majority of these, there are essential trace metals that are able to antagonize the toxic ones. This is not necessarily true of workers exposed to "high" concentrations of these toxic metals. From the industrial point of view, the constant exposure to metal dusts, fumes, and compounds requires medicinal intervention, such as specific or general antidotes, and chelating agents. This aspect of metal exposure is not part of this paper. Three examples as representative chemicals and their interactions with antagonists are discussed. The mechanisms of actions can be the topic of another review.

Lead toxicity is a perennial problem. Calcium is an antagonist of lead absorption. For those who are lactate intolerant, milk would be the food of choice to counteract lead toxicity. In some way, aluminum has been linked to Alzheimer's disease; yet the true nature is not clearly known. Calcium can interfere with aluminum absorption. In a few foodstuffs, cadmium can be detected and this is especially true of vegetables that are grown in soils that have appreciable levels of cadmium. Cadmium in soils can be the natural result of volcanic action. Other sources of cadmium in the soil are from the cadmium impurities in fertilizers. Some leafy vegetables are so-called cumulater plants and do concentrate toxic metals as they grow. Zinc is a common antagonist to cadmium, and this essential trace element is found in some foods and in nuts.

Mercury has been detected in a variety of fish species and swordfish is often found with relatively high mercury levels. Different bays in the world have been found to be contaminated by mercury. In the United States, fish in the San Francisco Bay have been found to contain mercury at levels of health concern, with sources of mercury originating from the tailings of the mercury mines nearby. Selenium is an excellent antagonist of mercury poisoning. Precaution is important in relation to selenium intake, because, unlike zinc where the therapeutic and toxic levels are far apart, that range for selenium is quite narrow. Therefore, the amount of selenium that should be consumed should not exceed 400 mcg. There are a few plants that contain sulfur, and hence, selenium. Table 1 presents the three "trace" metals, the metal antagonists, and the food sources that contribute to the antagonistic action (Sandström and Walker 1996).

TABLE 1
Toxic minerals and their antagonists found in various food sources

Toxic:	Pb	Hg	Cd
Antagonist:	Ca	Se	Zn
Sources:	Milk	Poultry	Oysters
	Tofu	Seafood	Meat
	Sardines	Whole grain	Liver
	Salmon	Onions	Cereals (fortified)
	Kale	Garlic	Sunflower seeds
	Broccoli	Nuts (hazel)	Brewer's yeast
		Tuna	

OXIDANTS AND ANTIOXIDANTS

How foods are important protectors is the second section.

Certain foods play an important role in preventing and counteracting the cellular and cell membrane damages caused by reactive oxygen species (ROS). There are adequate references detailing the chronic diseases related with the destructive action of the ROS. At the present time, a variety of cancers, some role of atherosclerosis, and many negative aspects of aging are associated with exposure to ROS.

The origin of ROS is very well known. Oxygen, which is essential for life, contains a very small percentage of a very destructive form called singlet oxygen (free radicals). Other sources of ROS are generated endogenously during metabolism. Some singlet oxygen is normally part of the process. A third source results when foreign particles are inhaled. The lungs invoke a mechanism for self-protection. Almost immediately, there is a mobilization of very large scavenger cells called macrophages that assemble to engulf or otherwise neutralize the foreign bodies. During the process of destroying the foreign bodies, singlet oxygen is liberated. This is especially true if the foreign inhaled particles are cytotoxic and kill the macrophages. In this latter situation, lung cells are destroyed.

Also well known is that free radical oxygen can induce other free radicals from lipids. These are often more destructive than the original singlet oxygen itself. Nitrogen oxides are also implicated in free radical reactions and add to the destructive action of cells and membranes (Halliwell et al. 1995).

Many plants are also exposed and attacked by singlet oxygen and free radicals. A number of these plants have evolved a special protective mechanism against ROS. One class of protectors is a series of phytochemicals called carotenoids (Krinsky 1993). There are about 600 carotenoids, most of which, but not all, are edible. These are usually long chains of conjugated double bonds and are highly colored with strong absorption in the ultraviolet region. These carotenoids destroy the ROS and quench the free radicals. The general term applied to these properties is *antioxidant* (Krinsky 1989).

These carotenoids not only protect the plants, but when they are ingested by humans, they are the best protectors against different types of cancers and other age-related diseases. Carotenoids are effective in enhancing the immune system (Bendich 1989). At the present time, not only are carotenoids suggested to counteract ROS, but some are now being investigated as protectors of specific organs in the body. For example,

TABLE 2
Antioxidants (carotenoids) found in various fruits and vegetables of different colors

Dark green	Yellow	Orange	Red
Kale	Carrots	Sweet potatoes	Tomatoes
Collard green		Pumpkins	Red pepper
Swiss chard			Pink grapefruit

lycopene, especially from tomatoes, is considered a protector of the prostate gland in men (Rao and Agarwal 2000), and the xanthophylls, leuten, and zeaxanthin are suggested as protectors against the destructive macular degeneration of the eye (Moeller, Jacques, and Blumberg 2000).

The U.S. Department of Agriculture recommends that one should eat five to nine helpings of fruits and vegetables a day. A major portion of these should be the highly colored plants that are mainly dark green, red, orange, and yellow. Table 2 gives representative examples of carotenoid-containing vegetables. Recent reference intake values for carotenoids have been published by the Institute of Medicine (IOM 2000).

Other groups of antioxidants, of which there are over 1000, are the bioflavonoids and some closely related compounds such as elegic acid (Mimoto et al. 2000). These compounds are mainly in the class of polyphenols (Table 3) (Bravo 1998) and include (a partial list) flavones, catechins (flavonols), anthrocyanins, and proanthrocyanines (Rice-Evans, Miller, and Paganga 1996). They are found in a variety of foods, including regular, but not herb, teas (Table 3). These are not necessarily colored, but they too quench free radicals efficiently. As a result, they are excellent antioxidants (Kuhnau 1976). Flavonoids appear to be essential for the growth of lower stages of animal life, but they have not been proven for animals higher in the phylogenetic scale. These antioxidants are ubiquitous and are effective cell protectors in both lipid and aqueous biological environments. The antioxidant effect is enhanced as the numbers of hydroxyl groups are increased. Flavonoids in a variety of foods (Miller et al. 2000) are the best protectors against deterioration of foods. (Personal Note: I receive many advertisements for supplements. Included are "new" vitamins that do not exist. Also products that are more than 1000 times more active than vitamin C. No scientific data are presented. Thus, it should be noted that there are products sold as "antioxidants" made from a variety of nonfood sources, some of which carry outlandish claims about their antioxidant activity. These advertisements should be ignored.)

TABLE 3
Antioxidant bioflavonoids (polyphenols) in certain foods

Food	Antioxidants
Grapes (red wine)	Quercetin
Tea (not herbs)	Green > Black
Cherry	4-Oxoflavonoids
	Quercetin
	Genistein

FOODS: TOXINS AND ANTITOXINS

The third part is the major challenge to learn and then to elucidate the means and the mechanism of action as to how foods protect us from toxic agents. Why is not the majority of the population chronically poisoned or afflicted with cancer? If we look at the down side, we are living in a polluted world. The foods we eat do contain additives, and most contain some residues of pesticides. These two categories of substances are, in the main, regulated as to the maximum amounts permitted in foods that are consumed by those living in so-called civilized countries. What overshadows human exposures to these, however, are the natural toxins already present in foods. More troublesome are the carcinogens generated during the preparation or cooking processes. These natural toxins are ubiquitous.

Some examples of natural carcinogens are the general class of hydrazines that are indigenous in different species of mushrooms. Some of these are experimental carcinogens (Toth 2000). Bracken fern (*Pieridium aguilinum*) is used for food by certain populations and was found to induce urinary cancer in rats. The chemical structure is known but the mechanism of action is not (Evans and Mason 1965). The basic chemical unit, azoxymethanol, is found to be an animal carcinogen. This class of compounds is also found in *cycad*, a plant grown in tropical countries. Some island people use this as a source of starch. There are many other examples of carcinogens normally associated and found in foods used by various populations. The National Cancer Institute has published *Oncology Overview*, containing abstracts on natural carcinogens found in foods (Kapadia 1982).

It is not necessary to go to exotic foods for an exhaustive list of natural toxins. Hydrogen peroxide is found in cherry tomatoes, aniline in carrots, furans and psoralen in celery, and ethyl carbamate in beer. These are examples. A more complete list is found in Table 4. The American Council on Science and Health

TABLE 4
Natural toxicants in various foods

Food	Toxicants
Potato	Glyco alkaloids solans
Grapefruit	Bergamottin (P450 inhibitor) (CYP3A4)
Wheat	Mycotoxins
Soy	Phytoestrogens, coumoestrol
Mushroom	Hydrazine
Carrots	Aniline
Eggs	Benzene
Roast meats	Heterocyclic amines
Pumpkin	Benzo(α)pyrene
Apple pie	Acetaldehyde
Wine and Beer	Ethyl carbamate

in New York supplies a more complete list. The description above can be summed up by a quote, "No human diet can be free of naturally occurring chemicals that are carcinogens. Of the chemicals that people eat, 99.9% are natural" (Gold, Slone, and Ames 2000).

Many other toxins have been identified in foods. Some as a result of natural contamination like aflatoxin (Wogan 1992) in susceptible foods like peanuts. Some contaminants come from the soil. Some plants are cumulators. Mercury, lead, cadmium, and selenium are found in vegetables. Some ordinary foods such as spinach and rhubarb contain oxalates; corn contain phytates and cabbage, cauliflower, brussel sprouts, and broccoli contain goitrogens. Protinase inhibitors are found in legumes, peas, peanuts, and sweet potatoes.

People eating a "good" diet, that is, eating mostly fruits and vegetables, are usually spared from the toxic symptoms. The question remains, how do these foods act to protect us?

Of greater concern is the different toxic and carcinogenic compounds generated during the preparation of food for consumption. A well-known example is the experimental carcinogen benzo(α)pyrene, generally found on the surface of the cooked food. These polycyclic hydrocarbons are generated from smoking, roasting, grilling, broiling, and frying—especially over open fires—resulting from the pyrolysis of lipids, proteins, or carbohydrates.

The carcinogenic heterocyclic amines formed from the pyrolysis of amino acids (especially tryptophan) have been extensively studied. There are about 19 variations on this theme (Figure 1) (Sigimura and Wakabayashi 1999; Sigimura, Nagae, and Wakabayashi 2000). They are excellent prototypes to discuss the science of biotransformation as a means of protection. In the main, these heterocyclic amines are from the following basic rings: carbolines, quinolines, and quinoxalines. Most studied are the quinoline derivatives, designated as IQ and MeIQ as well as the quinoxaline, $MeIQ_x$ (Figure 1). Specifically, the chemicals are:

IQ = 2-amino-3-methylimidazo[4,5-f]quinoline
MeIQ = 2-amino-3,4-dimethylimidazo[4,5-f]quinoline
$MeIQ_x$ = 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline

In summary, we are living in a world full of chemicals. A large number of foods we consume have detectable amounts of toxic agents that are indigenous to the plant of origin. In spite of this, life expectancy has increased. The number of living centenarians has markedly increased in this country. It is true that the air is now cleaner and the water purer. Also, the decrease of infant mortality does make a real contribution to the increase of life expectancy. Other contributors are the improvement of refrigeration and the introduction of antibiotics. The difference, however, between those who live long and those who do not, and the difference between those who do or do not become victims of age-related chronic diseases, will no doubt be related to the difference of diet.

Consumption of fruits and vegetables containing specific nutrients, namely, carotenoids and flavonoids and including the class of cruciferous vegetables, are the best ways to guard against chronic diseases (Walker 1996). The challenges, again stated, are to find the specific chemicals or family of chemicals that are responsible for the positive effects, and to determine the biochemical mechanism of action. A bibliography exists detailing some compounds found in foods (Weisburger 1982), but it does not include references on how these components react with toxic materials. Parke and Loannides (1994) did relate nutrition to toxic chemicals without detailed mechanisms.

It is not necessary to invoke new hypotheses to explain the phenomenon of protection. Standard toxicological detoxification (biotransformation) will be the basis of understanding the action (Glatt 2000). However, additional research is needed to relate the foods with the positive action. A comprehensive review is not available here. Two important topics will not be included as they are out of the scope of this essay. These are DNA repair (O'Conner et al. 2000) and DNA methylation (Nomparlen and Bovenyi 2000). A restatement of what is known about xenobiotic transformation will be useful. To convert a toxic agent to a derivative that is somewhat innocuous, and to eliminate it, a few biochemical transformations are necessary. If the compound has no special functional group, the cytochrome monooxidases come into play. The most extensively studied are the family of isoforms of P450 (Lewis 1996; Omura 1999). There are at least 200 identified now. These are called *phase I enzymes*. They act mainly to place a functional group on the toxic molecule. (Of course, there are other phase I enzymes that are involved

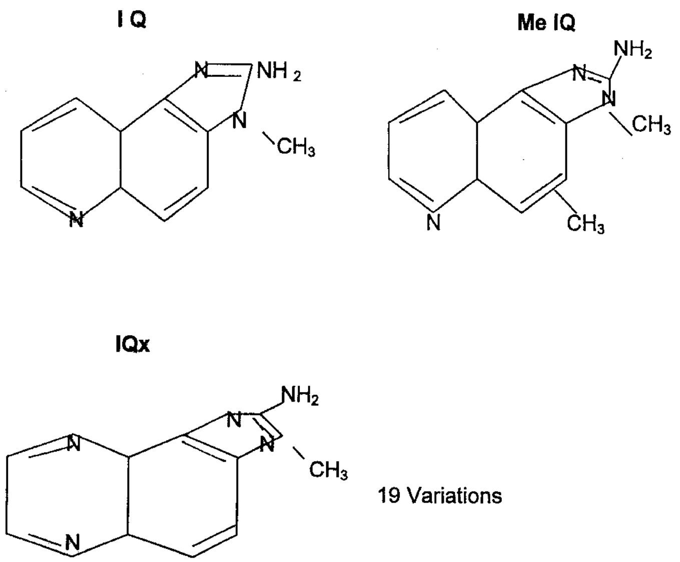

FIGURE 1
Carcinogenic heterocyclic amines formed from the pyrolysis of amino acids (especially tryptophan).

with processes like hydrolysis and reduction.) For example, an aromatic hydrocarbon compound devoid of functional groups will have one or more hydroxyl groups attached. This process only slightly increases the aqueous solubility or, as termed, hydrophilicity. The second step is to make the initially oxidized compounds much more polar. Phase II enzymes are then invoked. These assist in conjugating the oxidized (or compounds with other functional groups) with substrates that help excrete the "detoxified" compound more effectively via the urine or bile.

A few epidemiological studies have concluded that consumption of certain foods is positively related to cancer prevention or protection (Tomatis 2000), as well as heart protection and even rheumatoid arthritis and in some cases menopausal relief. Not all, but some, of these fruits and vegetables have been subject to analysis. Some specific compounds have been identified. These may be responsible for the cancer protection noted. For example, brasicca vegetables like cabbage, broccoli, brussel sprouts, cauliflower, and bok choy contain isothiocyanates. Sulfraphane is also a major component (Zhang et al. 1996). Will this class of compounds enhance phase I and/or phase II enzymes? This information is needed in order to explain the protective action against experimental cancer by detoxifying the toxic compound already in some foods. A biochemical explanation would be useful. This will help extrapolate the animal information to humans.

Some cruciferous foods contain indole-3-carbinol and even diindolemethane (Loub, Wattenberg, and Davis 1975). The same question applies here. Isoflavones, which are plant estrogens, are found in soy products. Genistein is a major compound here. It appears to reduce the cell intake of human estrogen that stimulates breast cancer. Are phase I or phase II enzymes involved? (Setchell 2000; Potter 2000).

Soy proteins have also been associated with cholesterol lowering, easing menopause hot flashed, and slowing postmenopausal bone loss. Do these proteins modify the critical detoxification enzymes, or are these actions only due to hormonal pathways? More research needs to be done. The carotenoid, lycopene, appears to protect the prostate gland. Is an antioxidant function the only explanation of this action, or are the enzymes involved? The same question can be raised for the other protective carotenoids like leutene. What in green tea is active against cancer? Are detoxifications involved?

Some facts are known about possible modes of action. For example, a diet low in selenium results in lower P450 enzyme reaction and an increase of lipid peroxidation. Grapefruit juice will also decrease the action of the P450 enzymes, resulting in some cardiac drugs to become more potent (Furst and Miller 1999).

The experimental carcinogenic heterocyclic amines, as mentioned, may play a much greater role in the induction of cancer in humans than previously suspected. Here, detoxifying foods, no doubt, will make the difference between who does develop a neoplasm and who will be spared. For these carcinogens can be deactivated by the actions of both phase I and phase II enzymes. The attacks will be on the free amino group. What will be helpful is to determine which of the isoforms of P450 enzyme is involved to modify the hydrogen on that free amino group. Then it will be helpful to know which of the conjugating enzymes continue the detoxification process. Schwab et al. (2000) added to our knowledge with a comprehensive review on this subject. Much more investigation is in order for there are still too many unknown aspects of the problem. When more is known about the components in fruits and vegetables that are the best protectors against cancer, this information can be transmitted to those involved in modifying seeds by genetic techniques.

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