Paradoxical effects of chemicals in the diet on health

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In 1992, Block *et al*. [1] published a summary of 200 epidemiological investigations which indicated that a diet that was high in fruit and vegetables cut cancer risks approximately in half. These investigations used conventionally farmed produce that contained traces of synthetic pesticides and mycotoxins as well as an estimated 10 000 secondary products (i.e. natural pesticides). Dietary consumption of fruits and vegetables also reduces risks of cardiovascular disease, cataracts and brain dysfunction. Before genetic manipulation is undertaken to elevate or diminish any individual constituent of fruits and vegetables, the contribution of each of these constituents to health must be better understood, as in many cases their effects on health can be paradoxical.

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Abbreviations
EPA Environmental Protection Agency
MTD maximum tolerated dose

Introduction

Ever since the discovery of vitamins, there has been intense interest in the effects of food constituents on human health. The requirements for health of a protein balance containing all the essential amino acids, some unsaturated lipids, minerals and carbohydrates were established early on. But food also contains large numbers of other small molecules, plant secondary products, agricultural and food-processing synthetic chemicals and fungal by-products. With one third of premature human cancers seemingly related to diet [2], intense investigation is now focussing on the health effects of some of the small molecules in our diets. This short review focuses on the increasingly complex situation that is emerging in which even the concept of toxins, long established in the toxicology literature, is likely to undergo a paradigm shift. Many compounds have both health-improving and health-debilitating effects depending solely on the dose.

Natural carcinogens (pesticides)

Fruits and vegetables synthesise a great variety of secondary products that have evolved to control pest damage. Environmental conditions and/or predation can increase the synthesis of these secondary products. Of the 127 plant secondary products that have been tested in rodents (out of an estimated total of 10 000 in plants), more than half are carcinogenic at the maximum tolerated dose (MTD) [2]. However, some of the compounds that have been identified as carcinogenic have very different effects at lower concentrations. For example, quercetin is now recommended as a potent antioxidant that has anticancer properties [3,4]. Limonene and perillyl alcohol are now recognised anti-cancer agents [5]. Caffeic acid at normal levels of human consumption reduces cancer rates to below those in controls [6]. Allyl isothiocyanate is a potent inhibitor of tumour development [7]. And, in moderation, alcohol reduces cancer rates [8].

Arsenic and cadmium are potent human carcinogens that are found in soils, plants, and drinking and natural waters world-wide. However, arsenic is effective in treating leukaemia [9], and low concentrations of cadmium reduce cancer rates to below those in controls [10]. Benzene is a potent human carcinogen but is a natural constituent of roasted coffee [2].

Rodent bioassays that are based on MTD provide misleading predictions of the effects of natural carcinogens on humans at the low concentrations found in food and water. About one-half of all tested synthetic chemicals are also carcinogenic in rodents at MTD [2]. Thus, the identification of such synthetic chemicals as potential carcinogens at the low concentrations normally found in food must be as uncertain as the categorisation of low concentrations of naturally occurring products as harmful. Ames and Gold [11] suggest the rodent test is misleading because high concentrations of many chemicals invariably induce cell division. There is a strong correlation between the induction of cell division at MTD and the subsequent development of cancer, a correlation exemplified by isomers of supposed mutagens in which only the mitogenic isomer induces cancer.

Despite consuming natural carcinogens for thousands of years, humans are not adapted to them. For example, environmental conditions or plant-breeding accidents caused the overproduction of solanine (a fat-soluble nerve toxin) in two lines of potato and of cucurbitacin (now used as an organic insecticide) in organic courgettes. Those that ate the produce experienced intestinal problems and sickness [12,13]. Likewise, the over-production of

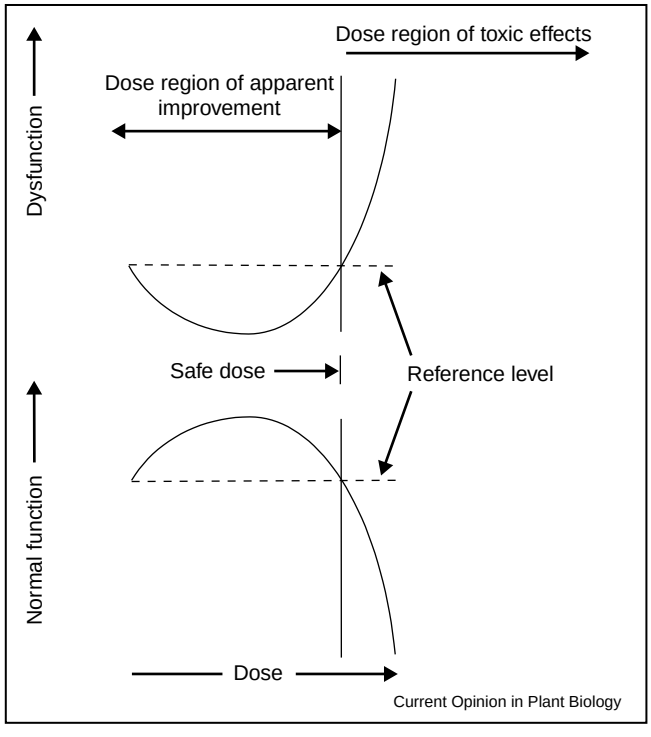
psoralen in celery caused extensive skin burns in those who harvested this crop [2].

The concept of hormesis

Hormesis is an unanticipated or paradoxical effect of a toxic chemical(s) or of radiation at low doses. Hundreds of chemicals that have damaging effects at high concentrations paradoxically have beneficial effects on growth, reproduction or longevity, or potentiate immune responses, at low concentrations [14•,15••,16••]. Surveys of both past scientific literature [17] and more recent literature [18] have turned up many hundreds of hormetic dose–response curves. These responses — which are found in plants, animals and bacteria — are commonly described as U- or J-shaped (Figure 1) and are invoked by chemicals that range from toxic metals, insecticides (pesticides) and fungicides, to herbicides and petroleum fractions [16••,17,18]. Clearly the natural carcinogens described above are producing hormetic responses.

At low concentrations, environmental dioxins reduce the incidence of human cancers [19]. Contaminated sea-water or diluted factory effluent containing, for example, cadmium and mercury can substantially promote hydroid and algal growth, but only when these elements are present at low concentrations [16••,20]. Both selenium deficiency and selenium excess can promote tumour growth, but selenium is an essential element for human health at the correct concentration [21]. Many other essential minerals and vitamins have similar dose–response characteristics.

Figure 1



J-shaped dose response curves illustrating an apparent reduction in dysfunction (such as cancer rate) or an improvement in function (such as growth or reproduction) at low doses.

Hormesis is considered to be an over-compensation for a disturbance to homeostasis [22,23]. In analogy, very low UV stress (sunshine) beneficially increases essential vitamin D synthesis; whereas greater, but limited, UV stress stimulates an over-compensation of melanin formation, thereby protecting against subsequent longer UV exposure. UV over-exposure without protection is, however, extremely damaging, causing serious inflammation, accumulations of oxidants and sometimes initiating skin cancer. In the same way, the immune system and DNA-repair systems are potentiated to over-compensate by low levels of chemical stress. In turn, a potentiated immune system contributes to lower cancer rates. Nevertheless, high levels of chemical stress overwhelm homeostasis and induce inflammation, cell division and eventual cancer.

Hormesis brings current US Environmental Protection Agency (EPA) regulatory assessments of synthetic agricultural chemicals [11,24,25] into serious question as low doses can be beneficial to health [15••,16••]. Hormesis strikingly contradicts EPA assumptions of 'no safe dose' for synthetic chemicals. Not unsurprisingly, early human ancestors evolved a generalised defence mechanism against low levels of 'toxic' chemicals to enable their consumption of many different plants containing variable levels of natural carcinogens without subsequent ill-health. Traces of synthetic pesticides (and perhaps mycotoxins) together with the natural pesticides (carcinogens) that are found in fruit and vegetables may potentiate the immune system, helping to protect against cancer. Attempts to clean food of all synthetic chemicals may be counterproductive.

'Antioxidants' in fruit and vegetables: protection against the accumulation of mutations

In human adults, superoxide, hydrogen peroxide and hydroxide radicals (produced by some 10^{10} free radicals per cell per day) cause in the order of 10^{6} mutational alterations of DNA per cell each day. The activities of these mutagens are countered by 'antioxidants', DNA repair, the removal of persistent alterations by apoptosis, differentiation, necrosis and the immune system so that only about one mutation per cell per day persists [25]. Ageing and its associated degenerative diseases — cancer, cataracts and circulation disorders — result in part from oxidative damage to DNA, lipids and proteins. Radiation and serious inflammation also increase oxidant production. By old age, many mutations have accumulated because the repair system is not perfect. The question is not why cancer occurs, but why it occurs so infrequently.

Dietary antioxidant defences are thought to reside in vitamins C and E, quercetin, zeaxanthin and carotenoids such as lycopene. Increased consumption of these antioxidants can reduce DNA oxidation [26]. Some large β-carotene supplementation studies have shown, however, that the incidence of lung cancer rose following increased intake of this antioxidant [27•,28]. Apoptosis may be induced by arsenic and *S*-allylcysteine, a constituent of garlic [29].

Many antioxidants influence other metabolic events. At high doses, vitamin C can be a pro-oxidant [30] but dietary supplementation of this vitamin has been reported to reduce the severity of cardiovascular disease [31•]. The antioxidant capsaicin (from chilli peppers) binds to a receptor in sensitive neurons, thereby elevating their permeability to calcium ions. Prolonged or repeated exposure to capsaicin leads to nerve damage and/or death [32]. The antioxidant glucosinolates (in *Cruciferae*) and their metabolites ([iso]thiocyantes, indoles, epithionitriles and dithiolthiones) exhibit not only anticancer properties but also antibacterial and goitrogenic activities [33,34]. These activities are possibly mediated by cytochrome p450 enzymes, which activate nitrosamines that alkylate carcinogens.

The more classical antioxidants — anthocyanins, procyanidins (tannins), flavonoids, hydroxy benzoic acid (HBA) derivatives and so on — inhibit the oxidation of low-density lipoproteins, transcriptionally reduce the synthesis of the vaso-constrictive peptide endothelin-1, and reduce platelet aggregation (by inhibiting cyclooxygenases and lipoxygenases) with a subsequent retardation of atherosclerosis [35,36]. Many classical antioxidants also exhibit the chelation of metal ions, thereby impairing mineral intake. Some flavonoids are reported to exhibit anti-ulcer/gastroprotective effects by inhibition of acid secretion and/or elevation of prostaglandin, leading to elevated duodenal bicarbonate secretion, and also have antibacterial action against *Helicobacterpylori* [36,37]. Whereas some flavonoids protect against some cancers [38], others (e.g. genistein) can negate the inhibitory effects of chemotherapy on cancerous growth [39]. Small phenolics, such as gallic, gentisic and salicylic acids, inhibit cancer in cell-line studies. The acetylation of salicylic acid to make aspirin greatly increases its uptake, changing its dose–response characteristics. The actual level of these compounds in the plasma may not, however, equate to their consumption level as the gut microflora are known to degrade other phenolics, such as cinnamates and flavonoids, to hydroxy-benzoic acids.

Other recently discovered natural products in foodstuffs, such as stanol esters, effectively lower serum cholesterol. These compounds do not accumulate in plasma themselves, but feruyolated stanols and sterols in corn oil may provide dietary benefits both by this effect on cholesterol levels and through antioxidant protection [40]. Soluble extracts of bitter melon or ginger rhizome inhibit mammary carcinogenesis [41] but the active chemicals remain unknown. The extent to which a diet that is high in any of these chemicals reduces oxidant damage to DNA has yet to be determined. The alternative, potentiation of DNA repair needs further investigation, particularly as cell oxidant concentrations may be homeostatically regulated.

Carcinogenic mycotoxins

The fungal mycotoxins aflotoxin, ochratoxin, patulin and fumonisin, and the tricothonenes, are produced by species of *Penicillium*, *Fusarium* and *Aspergillus* growing on a wide variety of foods. All these mycotoxins can act as carcinogens in either rodents or humans; in addition, they weaken the immune system, exposing damaged individuals to other diseases [42,43,44•]. Economic loss from the contamination of food by these mycotoxins is substantial: estimated to exceed ten billion US dollars in the US alone [45]. Aflotoxin is the most potent human carcinogen, inducing aflotoxicosis and liver cancer within several months; its effects on poultry can be detected in the parts per billion range. The consumption of all mycotoxins by humans is currently considered to be inevitable. It is thought that present 'safe' levels might induce cancer in a minority of individuals even in western countries [45]. If the dose response is hormetic, and this is currently unknown, then safe levels might actually improve health. A need for more research is clearly indicated.

Mycotoxic fungi infect both grains and fruit; their growth is encouraged by poor storage conditions. Pre-harvest pest or mechanical damage to cereal grains, cobs and fruits enables fungal spores to enter the plant tissues, and these spores germinate when the crop is moist. Post-harvest fungicide treatments are used to control fungal infection but penetration may limit the effectiveness of these treatments. Furthermore, post-harvest pesticides are the major source of synthetic pesticide traces in food [46]. Early results indicate that expression of the *Bacillus thuringiensis* toxin (Bt) protein in corn, reduced both pre-harvest pest damage and contamination by fumonisin and aflotoxin by 5–30 fold [44•]. Harvesting in wet conditions and storage of seed at warm temperatures encourage fungal growth, and rapid drying is necessary to discourage contamination [47]. Small farms often lack the necessary expensive drying equipment, and this might contribute to the frequent reports of higher fumonisin contamination of organic wheat (e.g. [48–50]), as organic associations frequently emphasise the virtues of small farms. In dry years, fumonisin levels seem unrelated to the mode of farming [51]. Human vaccination against aflotoxin is being used to combat this problem [43], and the construction of crops that are transformed with fungal genes that degrade fumonisin are an alternative solution [52].

Contamination of peanuts by aflotoxin is encouraged by severe drought followed by heat stress during fruit development, which compromise plant defence responses and increase the risk of infection [53]. Placing a battery of disease resistance genes under transcriptional control by abscisic acid or heat shock promoters might help reduce aflotoxin contamination. Fungal contamination of peanuts may also result in more serious aflotoxin contamination during the preparation of peanut products and in other nuts, such as walnuts, hazelnuts and so on, that are poorly dried during harvest.

Patulin is synthesised in contaminated apples that are infected by *Penicillium* species [54,55]. Even fruit with minor spots of infection or no apparent blemishes can be contaminated throughout, suggesting that *Penicillium* species may be endemic in apple trees because all are vegetatively propagated. Patulin concentrations have been reported to be higher in organic apple juice. The reasons for this are not clear [49] but the lack of use of effective fungicides might be responsible. At present, patulin contents generally appear to be within safety guidelines for consumption [56].

Deficiencies in diet

About 80% of US and 75% of UK citizens eat insufficient fruit and vegetables to provide minimal protection against cancer [2]. Sufficient, and sometimes excessive, calories are consumed but the diet is imbalanced as regards the necessary components from fruit and vegetables. Vitamin A deficiency in early childhood potentiates visual disorders and sensitivity to childhood diseases that can lead to death. Genetically modified vitamin-A-enhanced rice is currently being researched in field trials because rice gruel, a commonly used substitute for breast milk, is severely deficient in the vitamin A necessary to synthesise retinal, the dominant visual pigment. Many necessary nutrients exhibit a hormetic dose response, however, and vitamin A in excess can cause bone disorders and cancer. A common deficiency in folic acid reduces mitotic rates (particularly in bone marrow, leading to anaemia) and enhances the replacement of thymine by uracil during DNA replication, potentially causing chromosome breakage and eventual cancer [21]. Folate deficiency accelerates homocysteine accumulation, thereby damaging endothelial cells in culture, and is a risk factor for arterial endothelial dysfunction.

Conclusions

The inhibition of cancer, cardiovascular disease and other degenerative diseases is the biggest goal facing nutritional plant breeding [57]. The potential for genetic modification of dietary chemicals is substantial, but this short review indicates the difficulties of assuming that increasing the dietary level of any compound will necessarily improve health. Many plant secondary products and dietary contaminants seem to have paradoxical (hormetic) effects on these diseases that depend on their concentration and thus level of consumption. For the individual, the conclusion must be that everyone should eat more fruits and vegetables but must live with potential risks, particularly as there is likely to be variation amongst the human population in sensitivity to many of the natural and supposedly hazardous chemicals that these foods contain. More dramatically, the consumption of conventionally grown fruits and vegetables that containing traces of pesticides that have hormetic properties should involve lower health risks than the consumption of organic fruits and vegetables in which these products have purportedly been eliminated. This contradicts common assumptions about toxicity, such as those made by Baker *et al.* [46]. Organic food that is contaminated with varying amounts of the organic pesticides copper or rotenone provides further problems for the assumption that organic is necessarily better [58].

A change in EPA regulations with regard to chemicals that have pronounced hormetic properties must be a priority. Re-educating the public, who have been told for so long that a toxin is toxic, no matter the concentration, will not be easy but should be the goal of any scientist interested in the health of the community. A balanced conventional diet is currently the most promising route to healthy eating, particularly as the 200 investigations summarised by Block *et al.* [1] to indicate that a diet that is high in fruit and vegetables cuts cancer risks substantially used conventional fruits and vegetables rather than organic ones. For the food scientist, there is a clear need to generate detailed information on the metabolomics of both fruits and vegetables that have been grown and stored under many different conditions, and to produce hormetic dose–response data for many of the compounds contained in these foods. The manipulation of dietary constituents by genetic modification can then proceed with confidence.

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