# Natural Toxic Background in the Food of Man and His Animals

Donald G. Crosby

Food is only a mixture of chemicals, and not all of them are dietarily beneficial. Certain types of spoiled food, legumes, and seafoods long have been known to contain substances harmful to human health, and poisonous feed and forage represent classical problems in animal husbandry. Natural toxicants may be intrinsic to foods, arise from microbial infestation, or be formed from less toxic precursors by enzymatic action or food processing. Man and his domestic animals usually avoid the most extreme dietary poisons, but the present concern over traces of manmade chemicals in food must be considered in relation to the possible toxic effects of long-term exposure to minor food constituents of natural origin.

Food has been defined as "nutritive material taken into an organism for growth, work, or repair, and for maintaining the vital processes" (Neilson, 1938). This objective definition, although strictly correct, is hardly what most of us think of when we are hungry. In our omnivorous, holozoic way, we and our domestic animals seek out and consume available, independently living organisms which happen to gratify our immediate tastes.

Like ourselves, these plant and animal victims represent complex mixtures of chemicals, some of which we can utilize for "growth, work, or repair." As nutritional sciences developed, it was found that our bodies indeed are composed of and regulated by compounds (or their transformation products) originating in what we eat and drink, and that certain food constituents were absolutely necessary to us. Food value could be compared on the basis of proximate analysis (Table I), and the tables of food composition derived in this way conveniently were arranged to total 100%. However, the many nonnutritional minor constituents eliciting the positive physiological and psychological responses in us which actually spell "lemon-ness," for example—bright yellow color, fragrance, and astringent taste—were not represented. Possibly deleterious constituents generally were not even considered.

In their plant diet, animals and humans perennially have consumed deleterious constituents along with the beneficial ones. Toxicity is determined not only by intrinsic properties of the toxicant and the exposed individual but also, importantly, by the level and duration of exposure; while most plant species undoubtedly contain potentially toxic compounds, the low level of exposure generally precludes intoxication. Animals are attracted to their food by taste, odor, and texture. While it is true that some of the most toxic plants usually are repellent to all but very hungry animals, others, such as the fatally poisonous (cyanogenic) Johnson grass (*Sorghum halepense*) and Sudan grass (*Sorghum vulgare*), are eaten readily by cattle, and harmful species of *Astragalus* ("locoweed") actually may be sought preferentially by horses, with devastating results (Radeleff, 1964).

Department of Environmental Toxicology, University of California, Davis, Calif., 95616

Early man became able to recognize by sight and remember those plants and animals which had proved obviously unsatisfactory as food. As agriculture developed, he adapted to his use those native food organisms which combined acceptable organoleptic qualities with maximum harvest, and he attributed to the supernatural the occasions on which his fellows suddenly were stricken after eating what appeared to be their usual food.

Certain of these accidents were due to man's own genetic peculiarities: the early mathematician Pythagoras met his death at the hands of the emperor Dionysius' soldiers rather than cross a field of broad-beans to which he was, by race, allergic (Marcus and Cohen, 1967). In other instances, such as grain infected with ergot (*Claviceps purpurea*) or shellfish carrying *Gonyaulax catenella*, poisoning was due to the often unpredicted presence of microbial toxins. Other foods actually were recognized as potentially harmful (Table II), but were eaten, nevertheless, as delicacies, or in times of famine, or even because of the limited intoxication they could provide. These and other interesting examples have been discussed in considerable detail in recent reviews (Kingsbury, 1964; Mateles and Wogan, 1967; Mickelsen and Yang, 1966; National Research Council, 1966; Strong, 1966a).

Although most of our present-day food plants long have been bred to enhance their desirable characteristics, many actually retain a close botanical and chemical similarity

**Table I. Proximate Composition of Lemon Juice**[a]

| | |
|---|---|
| Water | 91 gm./100 gm. |
| Protein | Trace |
| Fat | Trace |
| Carbohydrate | 9 gm. |
| Vitamins | |
| A | Trace |
| $B_1$ | 0.04 mg. |
| $B_2$ | 0.02 mg. |
| Niacin | 0.15 mg. |
| C | 65 mg. |
| Minerals | |
| Ca | 15 mg. |
| Fe | 0.3 mg. |

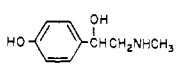
[a] Watt *et al.*, 1959.

to their wild predecessors. Wild lettuce (*Lactuca virosa*), for example, provided a medicinal extract known as "lactucarium," used well into this century as a sedative for coughs; throughout history, its cultivated progeny also have received attention for their purported ability to induce sleep (Crosby, 1963). Our preoccupation with the improvement of desirable chemical characteristics of our food may have made us unmindful that it is simply a mixture of chemicals, not all of which necessarily may be expected to be beneficial. Lest one think of food poisons as something exotic, it is the purpose of the present review to offer brief, selected examples which typify the natural toxic background existing in the food of man and his animals.

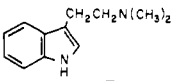
Natural food toxicants may be derived from a number of sources. Food constituents may exert a toxic effect directly; toxicants may be formed from nontoxic precursors by enzymatic action; the presence of microorganisms may induce the formation of toxicants not otherwise present, or present at nontoxic levels; microorganisms inextricably associated with food may elaborate toxic substances; or toxic substances may be formed in food by processing, storage, or cooking. The direct effects of food constituents probably are the most usual, and the lemon, which provided an example of proximate analysis, can represent a starting point.

## INTRINSIC TOXICANTS

The drug Synephrin (I) and its close relative, Neosynephrin, have received wide use as dilators and decongestants for relief from symptoms of the common cold. In 1964, Synephrin was reported to occur naturally in lemon juice, together with the related pressor amine, octopamine (Stewart and Wheaton, 1964). A variety of other sympathomimetic amines also occur in food; norepinephrin in bananas, tyramine in Camembert cheese, tryptamine in Stilton cheese, histamine in wine, and serotonin in many fruits (Strong, 1966b). The amounts may be quite large in relation to the usual serving—e.g., 200 mg. of tyramine per 100 grams of cheese—and have led to pronounced complications and death when the particular food was eaten by persons under medical treatment with tranquilizers (Asatoor *et al.*, 1963). The amounts of pressor amines occurring in lemon juice undoubtedly never reach so high a level, but total amine intake may be very large if diets are restricted to amine-bearing foods, such as bananas or plantains. Certain heart diseases commonly thought to be congenital may actually be due to a high-amine diet (Crawford, 1962).




I




II

One mechanism which controls the levels of such amines in the body is oxidation catalyzed by the enzyme, monoamine oxidase (MAO). Inhibition of this enzyme, then, is roughly equivalent to increased doses of amine; certain anti-depressant drugs, such as the tranquilizers mentioned above, act in this way. Several MAO inhibitors have been responsible for heart failure and other symptoms produced in livestock feeding on the pasture grass, *Phalaris* (Culvenor *et al.*, 1964), and include *N,N*-dimethyltryptamine (II) and its relatives. A closely related alkaloid, *N*-methyl-2-phenethylamine, is the toxic principle of guajillo (*Acacia berlandieri*), responsible for an ataxia known as "limber leg" which has resulted in extensive livestock losses (Camp and Lyman, 1956). Highly poisonous alkaloids are responsible for the toxicity of some of the most troublesome range plants (Table III) and are suspect in a number of other instances. The range problem is compounded by the accidental harvesting of small and very toxic plants, such as *Senecio* species, along with hay fed to farm animals.

Alkaloids usually have not been recognized as common constituents of normal human food. However, the glycoalkaloid solanine and its aglycone, solanidine (III), which are responsible for livestock poisoning by horsenettle (*Solanum carolinense*), bittersweet (*S. dulcamara*), and other *Solanum* species, are present in the tuber of the ordinary Irish potato (*S. tuberosum*) and the fruit of the common eggplant (*S. melongena*) (Orgell *et al.*, 1959). These alkaloids generally occur to the extent of only a few parts per million in market potatoes, but "green" potatoes which have suffered exposure to sunlight, old tubers, and especially the small sprouts so common on stored potatoes may result in fatal poisonings (Kingsbury, 1964). One of the ways in which *Solanum* alkaloids exert their toxic influence is by effective inhibition of the enzymes which regulate junctional transmission of nerve impulses in many parts of the body, the cholinesterases, a mechanism which they share with a number of other alkaloids and with the synthetic organophosphorus and carbamate insecticides (Crosby, 1966).

Lemon juice, lemon oil, and other citrus products

**Table II. Some Toxic Constituents of Unusual Foods**

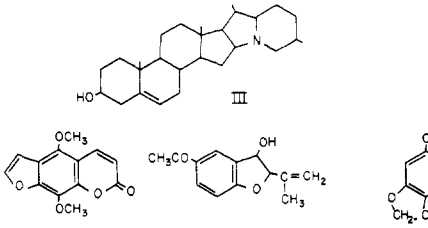
| Food | Location | Toxic Agent | Reference |
|---|---|---|---|
| Absinthe | France | Thujone | Balavoine, 1952 |
| Ackee | Jamaica | Hypoglycin | Hassal *et al.*, 1954 |
| Apple seeds | U. S. | Hydrogen cyanide | Kingsbury, 1964 |
| Bongkrek | Indonesia | Toxoflavin | Daves *et al.*, 1962 |
| Broadbean | Worldwide | Divicine? | Lin and Ling, 1962 |
| Cycad | Micronesia | Cycasine | Matsumoto and Strong, 1963 |
| Djenkol bean | Indonesia | Djenkolic acid | Van Veen and Hyman, 1936 |
| Kavakava | Polynesia | Dihydrokawain | Van Veen, 1939 |
| Polar bear liver | Arctic | Vitamin A | Rodahl, 1949 |
| Puffer fish | Orient | Tetrodotoxin | Woodward, 1964 |

**Table III. Alkaloids in Poisonous Range Plants**[a]

| Plant Source | Alkaloid |
|---|---|
| Death camus (*Zygadenus* sp.) | Zygadenine |
| Larkspur (*Delphinium* sp.) | Aconitine |
| Lupine (*Lupinus* sp.) | Lupinine |
| False hellebore (*Veratrum* sp.) | Cevadine |
| Groundsel (*Senecio* sp.) | Senecionine |
| Castor bean (*Ricinus Communis*) | Ricin |
| Rattlebox (*Crotalaria* sp.) | Monocrotaline |
| Poison hemlock (*Conium Maculatum*) | Coniine |
| Jimson weed (*Datura* sp.) | Hyoscyamine |
| Black nightshade (*Solanum nigrum*) | Solanine |

[a] Kingsbury, 1964; Manske and Holmes, 1950.

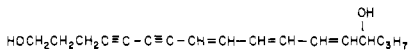
contain several members of the class of oxygen heterocyclics known as furocoumarins (Bernhard, 1958), of which isopimpinellin (IV) is typical. Although generally of only moderate oral toxicity, these compounds exert a photodynamic effect which results in sunburn or tanning when they come in contact with skin or upon ingestion (Fitzpatrick *et al.*, 1955). Furocoumarins and their close relatives are widely distributed in food plants, including celery, parsnips, and parsley, although their occurrence may be associated with microbial infection in some instances. Some of these same compounds exhibit herbicidal activity (Bennett and Bonner, 1953), and their photodynamic properties again are apparent in their bactericidal activity in the light but not in darkness (Fowlks *et al.*, 1958).



III



IV V VI



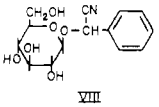
VII

Other intrinsic plant phenolics have been intimately associated with food-derived intoxication. For example, "milk sickness," which is said to have caused the death of Abraham Lincoln's mother, is due to transmission of the benzofuran toxol (V) (Zalkow and Burke, 1963) through the milk of cows which have eaten snakeroot (*Eupatorium rugosum*) (Kingsbury, 1964); the coumarin esculin (6,7-dihydroxycoumarin) is reported to be responsible for stock poisonings by buckeye (*Aesculus* species) (Macbeth, 1931); and the cottonseed pigment gossypol and other pigment-gland constituents have been recognized as toxic for over a century (Eagle, 1966). Of special interest in human diets, myristicin (VI) is hallucinogenic. Although myristicin s present in dill, celery, parsley, parsnip, and mint, nutmeg oil is the most prominent source; as little as 500 mg. of raw nutmeg may produce a detectable psychic response (Weil, 1965). Myristicin also acts as both an insecticide and an insecticide synergist (Lichtenstein and Casida, 1963). A related flavoring agent, safrole, no longer is permitted in food because of its reported carcinogenic properties (Long *et al.*, 1963).

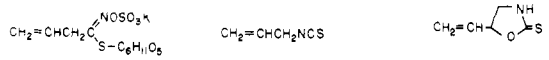
One of the most poisonous of all plant constituents is derived from species of *Cicuta*, or water hemlock. It is the acetylenic alcohol, cicutoxin (VII) (Anet *et al.*, 1953), and its high oral toxicity—the lethal dose for a laboratory mouse is about 4 $\mu$g.—has been responsible for the deaths of numerous humans and livestock. Ordinary garden carrots and celery contain a very similar acetylenic alcohol, "carotatoxin," which, although much less toxic, produces the same symptoms (Crosby and Aharonson, 1967). These symptoms also are reminiscent of those produced by acute exposure to DDT.

## TOXICANTS FORMED BY ENZYMATIC ACTION

In many instances, toxicants appear not to be present originally in a food item, but are formed enzymatically from nontoxic precursors after harvest or during digestion. Perhaps the best-known examples are the cyanogenetic glycosides found in apricot and peach stones, lima beans, and sorghum. These cyanohydrin derivatives are hydrolyzed in the presence of glucosidases to yield the aglycones which produce hydrogen cyanide spontaneously or by action of oxynitrilase. The prunasin (VIII) found in fruit stones is not toxic to mammals (Couch, 1934), but apricot kernels, for instance, release 275 mg. of HCN per 100 grams of pit (Hurst, 1942). Tropical lima beans may release as much as 300 mg. of HCN per 100 grams, although HCN content is legally restricted to 10 mg. per 100 grams in the United States (Kingsbury, 1964). Arrowgrass, chokecherry, sorghum, Johnson grass, and occasionally linseed meal or press cake, are the most common sources of cyanosis in domestic animals (Radeleff, 1964).



VIII



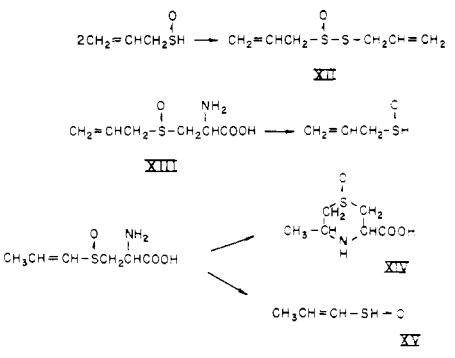
IX X XI

The enzymatic formation of toxic substances from the organosulfur constituents of foods is particularly prevalent. One of the best-known examples is the enzyme-catalyzed hydrolysis and Lossen rearrangement of the nontoxic thioglucosides, occurring principally in cole crops (Cruciferae), to isothiocyanates presenting pronounced physiological activity. For instance, the allyl thioglycoside sinigrin (IX) is converted by myrosinase to allyl isothiocyanate (X), which is responsible for the flavor of mustard and horseradish. Compound X is moderately toxic in laboratory animals (Jenner *et al.*, 1964); however, a lethal oral dose for dairy cows is about 10 mg. per kg., so that most plants which produce X are listed as poisonous to livestock (Kingsbury, 1964). The immediate effect on contact is an acute inflammation, which has been used for centuries in human medicine in the form of the "mustard plaster."

Many other isothiocyanates are formed analogously (Kjaer, 1960), and many have antimicrobial properties (Virtanen, 1962). 2-Hydroxy-3-butenyl isothiocyanate, formed from a thioglucoside (progoitrin) that is widely distributed in the edible parts of cabbage, turnip, and rutabaga, undergoes spontaneous ring closure to provide goitrin (L-5-vinyl-2-thiooxazolidone, XI) (Greer, 1956). The compound is moderately effective in causing thyroid enlargement and has been thoroughly reviewed elsewhere (Kingsbury, 1964; Wills, 1966). Thioglucosides also may be converted enzymatically to organic thiocyanates and to the thiocyanate ion responsible for goiter in some areas (Virtanen, 1962).

The curative effects of garlic and onions have been recorded for centuries, "being a remedy for all diseases and hurts" (Culpepper, 1869). Dry garlic has little or no odor, but the addition of water causes the almost immediate development of both the characteristic smell and a high degree of antibiotic activity. The structure of one of the antimicrobial substances, allicin (XII), has been determined (Cavallito *et al.*, 1945), and mechanisms for its

enzymatic formation from the natural, physiologically-inactive precursor, alliin (XIII), have been proposed (Stoll and Seebeck, 1949; Virtanen, 1962).



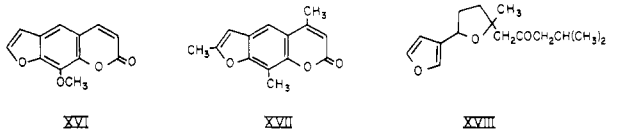
The corresponding methyl and *n*-propyl thiolsulfinates have been reported in onion. A comparable series of reactions, starting with the allicin analog, 1-propenyl-cysteine sulfoxide, known to occur in onion, leads in part to cycloalliin (XIV), which is found at levels up to 0.25% of the fresh weight; the enzymatic decomposition of XIV results in the toxic 1-propenylsulfenic acid (XV), the lachrymator so readily recognized in onions (Spare and Virtanen, 1963). Except for the tear-producing effect and the common experience of "stomach upsets," no other definite toxicological reports about the onion appear to exist. However, the great herbalist Culpepper (1869) remarks that "its heat is very vehement . . . [it will] send up strong fancies, and as many strange visions to the head."

The consumption of seeds or seed meal from several species of pea-like legumes known as vetches (*Lathyrus*) produce an ancient human neurologic disease known as lathyrism (Kingsbury, 1964; Liener, 1966). Although apparently no longer a serious health problem, lathyrism earlier caused many deaths and disabilities throughout Europe, India, and Africa. Prolonged inclusion of *Lathyrus* or *Vicia* seeds as a major part of the diet apparently leads to two diseases—the human neurolathyrism, and a deformity of bones and connective tissue in laboratory animals known as osteolathyrism. Although the relationship of the toxic agents to the diseases still presents a confused picture, a group of structurally related vetch constituents surely are involved: β-aminopropionitrile (Dasler, 1954), β-cyanoalanine (Ressler, 1962), α,γ-diaminobutyric acid (Ressler *et al.*, 1961), and β-*N*-oxalyl-α,β-diaminopropionic acid (Murti *et al.*, 1964). Part of the confusion may be due to the fact that β-aminopropionitrile and β-cyanoalanine commonly occur as the *N*-γ-glutamyl derivatives (Ressler *et al.*, 1963; Schilling and Strong, 1954) which must undergo enzymatic hydrolysis to the active agent.

## TOXICANTS INDUCED BY MICROORGANISMS

Recognition that the infection of higher plants by certain species of microorganisms elicits a chemical response—the plant's form of disease resistance—has been very slow to develop. Although gross chemically-based changes such as loss of chlorophyll (chlorosis), pigmentation, deformation, and abscision in infected species formed much of the early body of observation in the science of plant pathology, the identification of toxic agents formed in response to the infection has come about only within recent years.

Scheel *et al.* (1963) investigated the cause of a painful photosensitized dermatitis which long had been prevalent among celery pickers. They reported that the disease resulted from exposure to celery plants which were infected with pink rot (due to *Sclerotinia* species), with subsequent formation of toxic levels of the photodynamic furocoumarins, 8-methoxypsoralen (XVI) and 4,5′,8-trimethylpsoralen (XVII). Although the furocoumarins could not be isolated from healthy celery, even slight infestations with *Sclerotinia*, asymptomatic in the plants, could be detected by the brilliant fluorescence of the induced toxicants under illumination with ultraviolet light (Scheel, 1964).



Ipomeamarone (XVIII) occurs along with other furans in sweet potatoes infected with black rot caused by the fungi *Ceratostomella fimbriata*, *Helibasidium morpa*, or *Thilavia basicola* (Akazawa, 1960). The compounds are not present in healthy tubers. Ipomeamarone inhibits the growth of a wide variety of fungi and bacteria (including the original infective agents) and is highly toxic to laboratory animals (Watanabe and Iwata, 1952). The substance is intensely bitter, which fortunately appears to limit the quantities normally ingested by humans, although domestic animals commonly have been poisoned by eating partially spoiled sweet potatoes (Hansen, 1928).

A number of other antifungal phenolic compounds form rapidly in infected vegetables and include phaseollin (French bean), pisatin (garden pea), 3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (carrots), and hydroquinone (pear) (Kuć, 1964). Umbelliferone (7-hydroxycoumarin) and scopoletin (6-methoxy-7-hydroxycoumarin) are formed at high levels in fungus-infected sweet potatoes (Minamikawa *et al.*, 1963) and virus-infected potatoes (Andreae, 1948).

Agents other than infective microorganisms apparently can bring about induction of antifungal substances. Dilute aqueous solutions containing heavy metal ions such as $Hg^{2+}$ or $Cu^{2+}$, as well as metabolic inhibitors including sodium fluoride or iodoacetic acid, cause the appearance of ipomeamarone in sweet potatoes (Uritani *et al.*, 1960) and the previously mentioned isocoumarin in carrots (Condon and Kuć, 1962). Scopoletin levels are cumulatively increased in plants treated with the herbicide 2,4-D (2,4-dichlorophenoxyacetic acid) (Fults and Johnson, 1950).

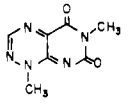
In some instances, such external influences as microorganisms seem to cause large increases in the levels of existing endogenous plant constituents. Indole-3-acetic acid (IAA) occurs in many common vegetables and fruits, and has been considered a natural plant growth substance of major importance (Bentley, 1958). Turian and Hamilton (1960) observed that infection of corn plants by smut (*Ustilago zeae*) caused a rapid 20-fold increase in the tissue level of IAA, and a similar phenomenon often may be responsible for disease symptoms in many other plant species. Although there is some question about the acute mammalian toxicity of IAA, subacute or chronic feeding of a few milligrams of the compound per day produced irreversible behavioral changes in rats (Sullivan and Strong, 1958). When IAA was fed during pregnancy, the animals gave birth to reduced numbers of offspring, and these were dead or grossly malformed at birth (Gottlieb *et al.*,

1958). Consequently, although IAA levels in plants generally are low, infection as well as climatic and nutritional factors could bring about drastic increases in its concentration and so induce unexpected long-term toxic effects in animals.

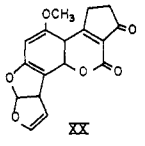
## TOXIC METABOLITES OF MICROORGANISMS

Microorganisms remain so intimately associated with our lives and, intentionally or not, with our everyday food, that distinction between the toxic effects of constituents of the parasite and those of the host often may be extremely difficult. For example, to what extent are the sympathomimetic amines mentioned as toxicants intrinsic to wine or cheese actually microbial metabolites?

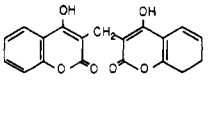
Although many classes of microorganisms now are recognized as producing toxicants in food and feed, perhaps the most widely suffered poisonings are due to bacterial toxins. An enormous body of information has accumulated on the biological and technological aspects of food poisoning by toxins of *Clostridium*, *Salmonella* and *Staphylococcus* species, but detailed information on the chemical nature of these toxic substances is meager. This is due in part to the apparent molecular complexity, and in part to the very small amounts which may be isolated and purified (Bergdoll, 1967; Boroff *et al.*, 1967). In some instances, at least, it may be that the structure of the toxic principle is not so complicated as we imagine. *Pseudomonas cocovenenans* occasionally brings about a fatal contamination of the common Indonesian food known as *bongkrek;* two extremely poisonous compounds have been isolated from pure cultures. One was the toxoflavin (XIX) (Daves *et al.*, 1962; Van Damme *et al.*, 1960), while the other, still not finally identified, was a highly unsaturated acid, $C_{29}H_{40}O_7$ (Nugteren and Berends, 1957).



XIX



XX



XXI

The algal (dinoflagellate) toxins which are responsible for the extremely poisonous character of certain shellfish foods during warm periods of the year ("months without an R") have received much recent chemical attenton. Saxitoxin, the violent poison from *Gonyaulax catenella* which mussels and clams accumulate, has been the subject of intense recent investigation (Schantz *et al.*, 1966), but the exact structure of this unusual nitrogen heterocyclic still is a matter of conjecture.

In addition to their ability to induce or stimulate the formation of certain metabolites in higher plants, fungi elaborate toxic compounds independently. The drastic and widespread effects of ergot poisoning, caused by grain infected with *Claviceps purpurea*, exerted a profound social influence in Europe during the Middle Ages, and the "side effects" of treatment with many fungal antibiotics such as chloramphenicol have presented continuing headaches for the pharmaceutical industry. In the past several years, however, common fungi associated with food finally have been recognized as responsible for many serious food and feed intoxications, and investigation of "mycotoxins" now is receiving world-wide emphasis (Feuell, 1966; Mateles and Wogan, 1967; Wilson, 1966).

To cite but a single example from this broad field, *Aspergillus* species are among the most common molds found world-wide on food. A number of them produce toxins, the best known of which are the aflatoxins, such as XX isolated from *A. flavus*. Like the fungus-induced celery toxins, aflatoxins are furocoumarins. While apparently not of extremely high acute toxicity to man, aflatoxin $B_1$ exhibits an oral $LD_{50}$ in the duckling of about 0.36 mg. per kg., or 18 $\mu$g. per animal. More important, perhaps, is the discovery that aflatoxins are carcinogenic in a wide variety of higher animal species (Miller, 1966).

Some fungi can convert preformed nontoxic plant substrates into substances toxic to animals. A classic example is the haemorrhagic (anticoagulant) principle of spoiled clover and alfalfa, dicoumarol (XXI), discovered by Link and his coworkers (Campbell and Link, 1941; Link, 1959). These and other investigators mistakenly attributed dicoumarol formation to the presence of coumarin in the hay. Recently, it has been established both on hay (Davies and Ashton, 1964) and in pure culture (Bellis *et al.*, 1967) that the green plants actually produce *trans*-2-hydroxycinnamic acid, which subsequently is converted by any of several fungal species to 4-hydroxycoumarin and then to the stock-killing toxicant.

## TOXICANTS FORMED DURING STORAGE OR PROCESSING

No doubt the most widely recognized examples of this type arise from microbial spoilage of food during storage, as discussed in the previous section. Man has developed fear and distaste for the results of certain microbial processes which he views as harmful to foods, while relishing others which actually may prove more dangerous to himself. True, many fish rapidly develop a "spoiled" odor in air due to formation of the innocuous trimethylamine *N*-oxide, and "ptomaine poisoning" long was ascribed to the weakly active but odorous and psychologically repulsive cadaverine (1,5-diaminopentane) and putrescine (1,4-diaminobutane). Yet, other "spoiled" foods, such as wine and cheese, may contain significant amounts of pressor amines, and the widely practiced fermentation of grains, followed by concentration and purification of the product, yields beverages rich in the common poison, ethanol, as well as the aldehydes, ketones, and phenols so well known to add extra dimensions to intoxication by alcohol.

The process of smoking meat, especially fish, for preservation has led to an unusually high incidence of tumors in populations where this type of food constitutes an important part of the diet—Iceland, for instance. However, any roasting process appears to provide the opportunity for the formation of carcinogenic hydrocarbons; roasted coffee contains 3,4-benzpyrene (XVIII) (Golberg, 1967), and Lijinsky and Shubik (1965) reported the presence of this and other polynuclear hydrocarbons in charcoal-broiled steak.

Oxidation is a continual problem in stored products, especially in its creation of rancid off-flavors in fats. Prolonged exposure of unsaturated fat to air produced lethal peroxides (Matsuo, 1962), while strong heating formed highly toxic cyclized products (Crampton *et al.*, 1953).

Potato tubers stored for long periods or exposed to sunlight may develop poisonous levels of alkaloids. Processing exerts the same effect. Kuć (1964) reported that fresh potato slices did not contain detectable amounts of solanine and its close relative, chaconine; after storage

at room temperature in the dark for three days, these toxicants had reached a concentration of 200 p.p.m. in some slices.

Chemical agents used as processing aids sometimes have caused severe problems through reaction with normal constituents of food (Campbell and Morrison, 1966). Especially notable were the formation of the extremely toxic (to dogs) methionine sulfoximine in white flour "agenized" (bleached) with nitrogen trichloride, and the reaction of soybean meal protein with trichloroethylene, employed as a defatting solvent, to produce 5-chlorovinyl-L-cysteine, which causes bovine aplastic anemia. Such practices have been discontinued or modified. However, research continues to uncover other examples; recently, Wesley *et al.* (1965) found that the widely-used fumigant, ethylene oxide, reacts rapidly with chloride ions in fruit tissue to produce potentially toxic levels of 2-chloroethanol, and the presence of sodium nitrite in food has led to formation of carcinogenic nitrosamines (Hedler and Marquardt, 1968).

## CONCLUSION

Discussion of other examples of real or potential toxicants occurring naturally in food could continue. Additional examples could be mentioned within each type; this review has all but ignored many very important groups, including estrogens, hemagglutinins, allergens, vitamin antagonists, inhibitors of proteolytic enzymes, minerals, oxalate, nitrates, excess vitamins and amino acids, etc. However, the point is obvious—food is a mixture of chemicals, and some of them can exert deleterious effects.

Most people are willing to accept the idea that the presumably less sophisticated in other parts of the world may suffer by eating poisonous cycads, drinking hallucinogenic potions, or pleasing themselves with the *fugu* fish. The thought that any of our unexplained diseases may be due to minor natural constituents of common food is hard to accept. We consider even smaller amounts of man-made chemicals undesirable, yet this review has referred to the natural presence of a common type of drug (Synephrin), a class of herbicides and fish poisons (furocoumarins), a plant growth regulator (indoleacetic acid), insecticide-like compounds in carrot and potato, a variety of fungicides, bactericides, antibiotics, and even the classical poison, cyanide.

We and our ancestors have been fairly successful in selecting food that is not acutely toxic. Our expanding capabilities for determination of chemical structure and for toxicological investigation promise a more scientific evaluation of the chronic hazards which we face in this toxic background of natural compounds which underlies our nutrition.

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