Civilized man is capable of controlling many aspects of his environment and thereby eliminating or at least diminishing some of the potential threats to his life and health. The absolute necessity of nutrition for continuance of life points to his foods as critical substances that must be maintained free from significant levels of toxicants. Fortunately man is less frequently the target of food intoxications than are domestic animals simply because in most societies greater selective care is given to human foods. Man consumes many of the same basic dietary items as animals, however, and on rare occasions may ingest toxicants contained in the meat or milk of livestock that were allowed to eat toxin-laden feed or to graze toxic plants.

So-called “natural foods” consist of “chemicals” any one of which can be deleterious to health if ingested in excessive quantities. Some of the more potent toxic metabolites of animals and plants used as food are formed during their normal course of metabolism and growth. Others, such as toxic phytoalexins, may be acquired under conditions including microbial infection, mechanical and chemical injury, and insect parasitism. A third group can be attributed to toxic metabolites of food-contaminating microbes such as bacteria, fungi and algae.

Microbial Toxins

Microbial toxins related to food intake are usually produced prior to food ingestion. In the case of exotoxins of Clostridium botulinum and Clostridium perfringens bacterial proliferation also can occur in the intestinal tract with further toxin elaboration in vivo. Gram-negative organisms, belonging to such genera as Salmonella, Yersinia and Vibrio, among others, are disease-producing primarily because of their ability to establish intestinal infections. Toxicity in such cases usually is associated with endotoxins of the bacterial cells. Several strains of intestinal pathogens have in recent times acquired marked antibiotic resistance. Similarly, diarrheal disease also results from infections with animal parasites such as Endamoeba histolytica and Giardia lamblia and by intestinal virus groups.

In the following brief discussion only a few food-borne human diseases due to well-defined microbial toxins are mentioned. In each case the toxin, or toxins, are likely to be preformed in contaminated food in which the microbes are able to proliferate under suitable incubation conditions.

The first of these are enterotoxins from Staphylococcus pyogenes, a common infectious bacterium frequently carried on the skin and in upper respiratory passages of food handlers. They are gram-positive, facultative anaerobes that can form many other toxins in
addition to enterotoxins. At present six types of true enterotoxins are recognized, but undoubtedly others remain to be discovered. They are designated A, B, C₁, C₂, D and E. These potent exotoxins are antigenic simple proteins of about 30,000 molecular weight which are relatively heat-resistant. They exert a variety of adverse effects on several body organs in addition to the intestinal mucosa. Fortunately, staphylococcus food poisoning has a low mortality rate even though the short illness consisting of extreme nausea, vomiting, diarrhea and dehydration may be severe and quite incapacitating.

*C. perfringens* type A is an anaerobic, gram-positive, spore-forming bacillus found in the intestinal tract of humans and animals, in soils and several other places in the environment. It is also an infectious organism that may cause gas gangrene in traumatized tissues. Food poisoning due to this organism is usually of short duration and consists mainly of severe diarrhea with cramping. The specific enterotoxin is a low molecular weight protein associated with sporulation of the organism and has been shown to be a structural component of the spore coat. In experiments using isolated segments of rabbit intestine the ileum showed maximum response to the enterotoxin with net secretion of fluid and sodium, inhibition of chloride and glucose uptake, and substantial sloughing of epithelial cells. In recent studies administration of a few milligrams of purified toxin to human volunteers caused typical symptoms a few hours after dosing.

Botulinum neurotoxins are heat labile immunogenic proteins with molecular weights of more than 100,000. Seven types (A, B, C, D, E, F and G) have been identified each of which stimulates formation of type-specific antitoxin. Types A, B and E have caused most of the outbreaks in man.

The disease botulism is most often contracted through ingestion of anaerobically preformed toxin in foods, but on occasion is the result of wound infections with the organisms. Recently, it also has been identified in infants who apparently ingested spores of the bacterium (perhaps from honey) which led to intestinal toxin production and absorption.

Botulism is a neurological disease which, unless diagnosed and treated promptly, is likely to prove fatal. The toxins act to inhibit release of acetylcholine in cholinergic synapses and at motor end plates resulting in muscular weakness or paralysis and possible respiratory failure.

Among several seafood intoxications of man is that due to paralytic shellfish poison produced by the plankton *Gonyaulax catanella* and other marine microorganisms. This "red tide" dinoflagellate is ingested in large numbers by mussels and clams (and probably other seafood animals) where the toxic metabolite known as saxitoxin (Figure 1) becomes concentrated in the gills and hepatopancreas of the shellfish. This toxin is one of the most potent low molecular weight poisons known.

![Structure of saxitoxin](Figure 1: Structure of saxitoxin)

Since saxitoxin is fairly heat resistant, it survives ordinary cooking procedures. Gastrointestinal and peripheral neurological symptoms of intoxication occur shortly after ingesting toxic shellfish, and the intoxication may prove fatal in a small percentage of afflicted persons.

Included as microbial toxins are the mycotoxins of toxigenic molds that contaminate various foodstuffs, especially animal feeds, at various stages of production and storage. Fortunately not all contaminating fungi are toxin producers, and not all foods serve as suitable substrates for formation of specific toxins.

The first mycotoxicosis recorded was ergotism (St. Anthony's fire) which made an impact on human history as a disease of people who consumed cereal grain infected with the parasitic fungus, *Claviceps purpurea*.

During the last twenty years hundreds of potential mycotoxins have been isolated and structurally identified. Their effects in animals have been documented either from outbreaks
of diseases in domesticated animals or by their experimental administration to laboratory animals and livestock. Many foods have been shown to contain mycotoxins, and several species of animals, including man, are susceptible to one or more of them.

In experimental animals the mycotoxins may affect several different tissues or organs. In attempts to group them by categories of toxic activity (such as carcinogens, radiomimetic agents, dermotoxins, hepatotoxins, neurotoxins, etc.), a single compound may be classified under more than one heading.

Since toxigenic molds are widespread in the environment, food contamination can occur easily. Optimal growth and toxin formation usually take place around 25°C, although a fairly wide latitude exists for certain organisms. The principal factor limiting mold growth on foods is moisture. Maintenance of dryness during storage is of considerable importance in preventing growth and toxin production.

Three genera of common fungus food contaminants, Aspergillus, Penicillium and Fusarium, are responsible for most of the recognized mycotoxins. Only a few examples can be mentioned in this brief review. Toxic mushrooms are omitted since their ingestion can be considered as accidental.\textsuperscript{13}

Undoubtedly, the best known mycotoxins of filamentous fungi are the aflatoxins, metabolites of the common molds Aspergillus flavus and Aspergillus parasiticus. A. flavus also is capable of synthesizing several other toxic metabolites. Perhaps the best known aflatoxins are the first four that were isolated from peanut meal, B\textsubscript{1}, B\textsubscript{2}, G\textsubscript{1} and G\textsubscript{2} (Figure 2).\textsuperscript{14} B\textsubscript{1} is the most toxic and often has been selected for experimental toxicity studies. In fact, it is the most potent carcinogen known at the present time and is a mutagen and an acutely hepatotoxic agent for the more susceptible species of experimental animals.

Aflatoxins have been detected as naturally occurring contaminants of many foods and have been produced experimentally on several others. Peanuts and corn are foods frequently contaminated.\textsuperscript{15}

Literally thousands of scientific publications featuring properties of the aflatoxins have appeared since their discovery in 1960. Many reprints have dealt with analytical methodology and studies on the molecular mechanism of toxic action. As regards the latter, evidence has been accumulating which indicates that B\textsubscript{1} is activated by microsomal mixed function oxygenase enzymes to form a 2,3-epoxide at the terminal furan position. This postulated form is instrumental in ultimate covalent binding of the molecule to nucleic acid of DNA. Acute toxicity may be related to other metabolic pathways.\textsuperscript{16,17}

In addition to intoxication of domesticated animals such as pigs, dogs, cattle and poultry, aflatoxin apparently has been implicated in human diseases in Thailand, India, Philippines and several African countries. The results of extensive sampling and analysis of native foods in certain regions along with tabulation of incidence of human liver cancer, suggest a correlation between aflatoxin intake in foods and the relatively marked incidence of hepatoma in the surveyed populations. In India and a few other countries acute hepatotoxic and hemorrhagic manifestations in ill persons have been attributed to relatively heavy contamination of a dietary item with aflatoxin.\textsuperscript{18}

Different species of Penicillium produce a variety of mycotoxins, some of which have caused outbreaks of disease in farm animals. Some of the most potent and unusual metabolites are neurotoxins collectively termed tremorgens. The tremorgens cause sustained whole body tremors in animals dosed parenterally or intragastrically with small doses. Increasing the dose will cause initial tremors to progress rapidly to convulsive seizures that may either terminate fatally or regress, after a
few hours, to a sustained tremor lasting several hours to several days.

The first tremorgenic mycotoxin, now called aflatrem, was isolated from the mycelium of a strain of A. flavus which also produced aflatoxins. Penicillium crustosum and a few related species of common food contaminants form three metabolites that were given the trivial names penitrem A, B and C. Penicillium isolates from which penitrem A was first obtained came from feeds causing fatal outbreaks of neurological disease in livestock.

In New Zealand a syndrome known as grass staggers in sheep and cattle exhibits neurological signs identical to those resulting from penitrem A administration. The cause of the natural disease, however, has not been ascertained. Other neurological conditions of livestock including Bermuda grass staggers, ryegrass staggers and paspalum staggers are probably of fungus origin.

Reports from Nigeria and India suggest that certain endemic neurological afflictions of natives may be due to tremorgen-contaminated food or to other dietary items containing tremorgenic substances.

Since the discoveries of aflatrem and the penitrems, about 15 additional tremorgenic mycotoxins have been isolated from various species of Penicillium, Aspergillus and Claviceps. The chemical structures in some instances have been established by x-ray spectroscopy. The formulas are given below (Figure 3) for verruculogen (I) from Penicillium verruculosum, fumitremorgen A (II) from Aspergillus fumigatus and paspalinine (III) from Claviceps paspali. The indole structure is common to all tremorgens whose structures have been elucidated.

The precise mechanism of neurological action for these compounds remains to be determined, but preliminary studies on penitrem A suggest it may act both centrally, through inhibition of inhibitory interneurons of the spinal cord, and peripherally by potentiating neural transmission at the motor end plate.

The genus Fusarium contains many toxigenic species of fungi that frequently contaminate food of man and animals. One group of potent compounds consists of 12, 13-epoxy-trichotheccenes (as exemplified by T-2 toxin, Figure 4) which are dermotoxins, bone marrow depressants and carcinogenic agents.

Viewed in retrospect one or more of the trichotheccenes were undoubtedly responsible for the endemic alimentary toxic aleukia (ATA) affecting Russian populations during World War II.

Another toxic disease of livestock, known as estrogenism, is caused by zearalenone (Figure 5), a product of Fusarium graminearum and other Fusarium species. This compound has received considerable study because of its uterotrophic and anabolic properties, especially in swine. Fusarium moniliforme, a frequent contaminant and infectious agent of corn and other plants, produces an unidentified factor causing cerebral malacia in equines.

In another biogenic category of naturally occurring toxicants, Fusarium solani and closely related species are responsible for inducing toxic stress metabolites in the sweet potato (Ipomoea batatas). In this toxigenesis one is not dealing with a mycotoxin in the usual sense of that word. Instead the infecting fungus first
serves as a stressing agent for host tissues which react with altered metabolism to form several hepatotoxic furanosesquiterpenes. Continued biochemical activity by the fungus is responsible for conversion of at least one of the hepatotoxic compounds to three or four C9, 3-substituted furans having considerable selective toxicity for the lungs of susceptible animals.

Among hepatotoxins formed by the injured sweet potato, ipomeamarone (Figure 6) is usually the most abundant. In addition to invasion of the host root tissue by *F. solani*, infection by fungi such as *Ceratocystis fimbriata* (black rot agent) and contact with various exogenous stress factors such as certain chemicals, insect infestation and mechanical injury also may lead to furanosesquiterpene production. Biosynthesis of lung toxins, however, seems to be related uniquely to infection with the *Fusarium* organisms.28

![Fig. 6: Ipomeamarone (I ngaione)](image)

The bovine is susceptible to pulmonary disease caused by eating sweet potatoes containing the lung toxins 4-ipomeanol (IV), 1-ipomeanol (V), and 1,4-ipomeadiol (VI) (Figure 7). As little as 6 mg per kilogram body weight of synthetic 4-ipomeanol given intrarumenally can cause respiratory distress and 9 mg per kilogram is likely to be fatal.28 Several laboratory rodents also react to 4-ipomeanol by developing pulmonary edema and other manifestations of acute pulmonary toxic disease.50

![Fig. 7: 4-ipomeanol, 1-ipomeanol and 1,4-ipomeadiol](image)

P-450 enzymes of the lung activate 4-ipomeanol to an unknown chemical species capable of covalent binding to lung microsomal protein. Clara cells of the bronchioles, which contain prominent endoplasmic reticulum, bind activated toxin shortly after injection and soon afterward undergo necrosis.31 These phenomena are followed by perivascular, peribronchial and intra-alveolar edema which often are fatal to the animal. As yet no definite evidence links sweet potato stress metabolites with diseases among people consuming large quantities of sweet potatoes.

**Poisons of Higher Plants**

The Ngaio tree of New Zealand, *Myoporum laetum*, and the Ellangowan poison bush, *Myoporum deserti*, of Australia, form a normal metabolite called ngaione which is the enantiomorph of ipomeamarone. Myoporone is another hepatotoxic metabolite common to both plants.32 Leaves of the Australasian plants are toxic to livestock, especially sheep, in which hepatic necrosis and occasionally pulmonary edema are produced.33

The purple mint plant, *Perilla frutescens*, is an imported Asian plant that apparently garden escaped some time ago and is now a common annual weed in the eastern half of the United States. Certain more highly pigmented varieties are cultivated as ornamental plants. During the course of its development in the spring and summer months *P. frutescens* synthesizes three closely related pungent oils which act as potent pulmonary toxins. These three toxins (Figure 8) are perilla ketone (VII), egomaketone (VIII) and isoegomaketone (IX). Their chemical similarities to the ipomeanols are evident and account for comparable pulmonary effects in both laboratory animals and livestock. Although perilla essential oil is produced in Japan as a food flavoring or condiment, no reports linking its use with pulmonary conditions of humans have as yet been noted. Outbreaks of acute pulmonary disease in cattle grazing the green or frost-killed plants, however, have been documented.34,35

![Fig. 8: Toxins of Perilla frutescens; Perilla ketone (IV) and isoegomaketone (VI)](image)

Many other plant foods commonly used by man are known to contain one or more natur-
ally occurring toxic constituents. In advanced societies such as the United States, however, with rare exception there is no evidence that moderate intake of these toxicants constitutes a threat to human health. Livestock, however, exposed to plants which are sufficiently toxic, may become ill and die.

Components of foods which are considered broadly toxic may be grouped into a variety of categories including allergens, carcinogens, hemolysins and hemagglutinins, vitamins and antivitamins, phenolics, and cyanogenic glycosides. The following examples are but a few toxicants of higher plants that can cause serious illness in man.

The white snakeroot, *Eupatorium rugosum*, and the rayless goldenrod, *Alopappus heterophyllus* are common weeds that may poison grazing cattle in areas of the United States. More importantly, the toxic component(s) is (are) secreted in the milk and can cause fatal milk sickness of man. Nancy Hanks Lincoln, the mother of President Abraham Lincoln, was a notable victim of the “milk sick” among many persons in pioneering families decimated by the disease. Although the toxic weeds still abound in several states, reports of human intoxications are rarely noted. A crude extract of the plants known as “tremetol” contains hepatotoxic properties, but the active chemical components have not been clearly identified.

Certain toxic *Senecio* alkaloids causing liver necrosis and tumors and sometimes lung toxicity in grazing animals have been identified and extensively studied. Natives of the West Indies and of South Africa also have suffered from hepatic venoocclusive disease from drinking bush teas and other medicinals made from these plants as well as using them as foods. Some of the pyrrolizidine alkaloids such as retrorsine are apparently activated by the liver to form toxic pyroles (Figure 9). In recent work it has been shown that bees feeding on the blossoms of tansy ragwort (*Senecio jacobaea*) can accumulate significant amounts of several toxic alkaloids in their honey.

The cyanogenetic glycosides are plant constituents that give rise to hydrogen cyanide when hydrolyzed by acid or by β-glycosidic enzymes. The liberated CN⁻ inhibits the respiratory enzyme cytochrome oxidase. Although hundreds of plants and some insects are cyanophoric, only a few are used for human food. Among these are certain varieties of lima beans, cassava and almond. The seeds of apple, apricot, peach, cherry, plum and quince also contain significant amounts of glycosides. The spurious cancer drug called laetrile is purported to be made from apricot seeds. Livestock may become intoxicated and die from eating sorghum or the foliage of the wild black cherry (*Prunus scrofa*) and other species.

In Western Africa in spite of the fermentation of cassava, which is designed to hydrolyze the glycoside, remove HCN and destroy β-glycosidase, the prepared food may have sufficient residual cyanide to cause certain endemic neuropathies or blindness in persons consuming appreciable amounts of the fermented products.

Many years of investigations on the toxic components of the pea, *Lathyrus sativus*, have led to isolation of toxic compounds possibly related to the human paralytic disease neuro-lathyrism. The amino acid, L-3-oxalylamino-2-aminopropionic acid (OAP, Figure 10) appears to be a possible causative agent. It is a competitive antagonist of L-glutamic acid transport in rat mitochondria. The significance of this finding relates to the fact that L-glutamic acid serves as a neurotransmitter in certain regions of the central nervous system. Recent studies have shown that OAP is neurotoxic to one-day-old chicks and to an inbred strain of mice by oral administration.
In summing up, it is readily apparent that “natural foods” may contain more than “natural goodness,” namely, naturally occurring toxicants. The full extent such substances play a role in human afflictions cannot be assessed at this time. Needless to say, nutritionists and toxicologists must be alert to the hazards inherent in many foods. Eating a wide variety of dietary items and avoidance of excessive intake of any one are good rules to be followed in human nutrition.

1. R.P. Novick, The Sciences 19: 14-17, 1979
12. A.F. Harthman, Sr., A.F. Harthman, Jr., M.L. Hartmann, Jr., A.F. Hartmann, Jr., M.L.