Coulombe 931

PERSPECTIVES IN BIOLOGY AND MEDICINE
Volume 24 · Number 1 · Autumn 1980

HERBAL TEAS AND TOXINS: NOVEL ASPECTS OF PYRROLIZIDINE POISONING IN THE UNITED STATES

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This article reviews the discovery of pyrrolizidine alkaloid poisoning in the United States caused by the drinking of herbal tea and describes some of the difficulties involved in establishing a causal relationship between exposure to these alkaloids and the delayed appearance of toxic symptoms. In addition, some of the more general problems presented by the widespread use of herbs in various forms are addressed. First, however, a brief overview is given of the toxicity of this class of alkaloids.

Occurrence and Toxicity of Pyrrolizidine Alkaloids

Pyrrolizidines occur in many plant families, including Boraginaceae, Compositae, Gramineae, Leguminosae, Orchidaceae, Rhizophoraceae, Santalaceae, and Saptoaceae. Part structures of these alkaloids are illustrated in figure 1. Toxic alkaloids contain an unsaturated ring. These alkaloids, and the plants in which they occur, are hepatotoxins, producing veno-occlusive disease, hepatomegaly and—with some alkaloids—liver cancers [1].

There is good evidence that the mechanism of toxicity involves a "lethal synthesis" in the liver whereby the alkaloids are metabolized to pyrroles (fig. 1). Pyrroles are chemically active and serve as biological alkylating agents by the mechanism shown in figure 2, in which groups *X*

The author thanks Charles Mason, Curator, University of Arizona Herbarium, for plant identifications. Laboratory work supported by USPHS grant HL-20087.

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and *Y* represent nucleophilic portions of proteins or nucleic acids, such as sulfhydryl groups [2]. Alkylation is a widespread mechanism of toxicity and takes place with many mutagens and carcinogens apart from pyrrolizidines.

Human Exposure to Pyrrolizidine Alkaloids

Pyrrolizidine alkaloid poisoning is a public health problem in many areas of the world. This is partly due to the wide botanical and geo-

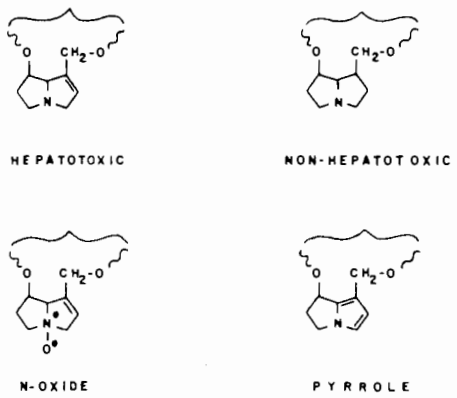

FIG. 1.—Pyrrolizidine part structure. The omitted portion of the structure is usually a cyclic diester grouping (– CO.R.CO –). Toxic alkaloids are metabolized to N-oxides and pyrroles. The cyclic diester may also be metabolically hydrolyzed.

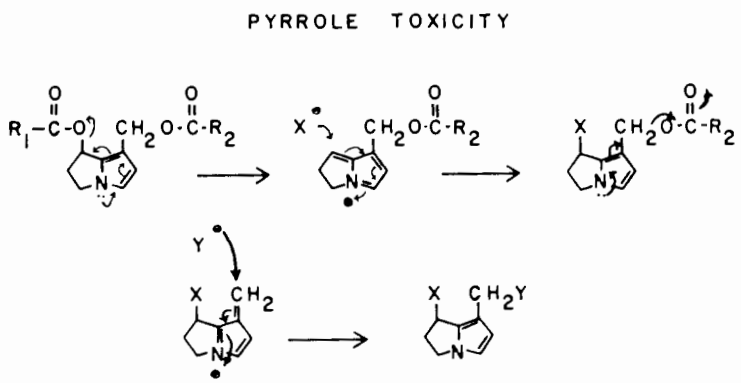

FIG. 2.—Pyrrole toxicity. Pyrroles formed in the liver are postulated to be toxic because of their ability to alkylate nucleophilic groups, such as sulfhydryl (X,Y), on cell macromolecules. Based on a proposal of Mattocks [2].

graphical distribution of pyrrolizidine-containing plants. There are two major sources of human exposure: accidental contamination of foodstuffs and the deliberate use of pyrrolizidine-containing plants in herbal preparations. Accidental contamination falls into two categories: that of continuous low-level contamination that may last for many years and epidemic poisoning caused by occasional massive contamination of foodstuffs. Recent examples of the latter occurred both in Afghanistan and in India in 1976. These epidemics were caused by *Heliotropium* and *Crotalaria* species contaminating fields of wheat and being harvested along with the grain to make bread. Wheat from the affected area was found to contain about 300 mg of *Heliotropium* seeds per kilogram of wheat. The Afghanistan outbreak involved approximately 1,600 cases of veno-occlusive disease of the liver [3]. Many of these patients died. The true scope of the epidemic may have been much larger however, due to the fact that the outbreak occurred in a primitive area where health care is uncertain and hard to obtain. Furthermore, many exposed persons may have suffered long-term deleterious consequences that did not result in an immediate clinical picture. The Indian epidemic involved fewer people. However, of the 67 recorded cases, 28 died [4].

Chronic contamination of foodstuffs has been a problem in South Africa. Here the major offending species appear to be *Senecio* and *Crotalaria,* and the usual route of exposure is that of these plants contaminating grains used to prepare food [5]. Senecio poisoning by this route has been thought to be responsible for the high incidence of primary liver carcinoma in black Africans. This type of exposure no longer occurs in the advanced industrialized nations due to the widespread use of chemicals for controlling unwanted plants in grain fields. Twenty-five years ago, it was not an uncommon sight in the English countryside to see fields of grain speckled with bright red poppies and blue cornflowers. However, this bucolic picture can be seen no more.

The intentional consumption of plants that contain pyrrolizidine alkaloids is a major public health and cultural problem in many areas of Africa, South and Central America, and, in particular, Jamaica. There is no intent, of course, to poison oneself and others, and the behavior is based on folklore and lack of knowledge. Pyrrolizidine-containing plants are used to prepare medications, teas, and other ingestible preparations. In Jamaica, for example, an indefinable "bush tea" is prepared by a person going into the scrubland that dominates the flora of much of the island and collecting leaves, which are subsequently infused, from a wide variety of plants. *Crotalaria* species are the major source of pyrrolizidines in bush tea. Pediatric veno-occlusive disease has been of almost epidemic proportions in Jamaica, and the medical description of this entity originated there [6]. The toxic sequelae of this habit are exacerbated by poor nutritional status and by the simultaneous consumption of other toxic

plants. Another major source of poisoning in Jamaica results from the consumption of the unripe fruit of the ackee plant (*Blighia sapida*). The name derives from a confusion with the breadfruit plant (*Artocarpus altilis*) that Captain Bligh of the *Bounty* was carrying to Jamaica from its original habitat in the South Seas at the time his crew mutinied. The unripe ackee fruit contains an agent, hypoglycin, which blocks gluconeogenesis in the liver. The resulting illness is known as Jamaican vomiting sickness [7]. This points to a general problem in herbal poisoning in that the victim has rarely been exposed to one toxic chemical. Often, he has been exposed to a variety of plants which modify the toxic action of each other, he may be suffering from parasitic diseases and poor nutritional status, and the toxicological action of a plant may differ quite substantially from that of a purified active principle isolated from the plant. One cannot expect pyrrolizidine poisoning produced by ingestion of a plant to mimic the disease caused by administration of a purified alkaloid in a laboratory setting.

Both *Senecio* and *Crotalaria* species are used to prepare teas in Africa. Extracts of *Senecio* have even been used in a commercial preparation sold to treat conditions as opposed as amenorrhea and menorrhagia [5].

Mexico is another area where there is widespread reliance on herbal medications. A highly readable description of the theory and therapy of sickness as practiced by Mexicans in a border community has recently appeared [8].

Until recently, pyrrolizidine poisoning had not been thought to be a public health problem in industrialized nations. The occasional case has been reported from England, usually involving a recent immigrant to the country from areas of the world where use of herbs is more common [9, 10]. In such cases, it is often difficult to obtain botanically identifiable samples. One case of veno-occlusive disease was ascribed to drinking Maté, or Paraguay tea (*Ilex* species). Such tea is used extensively. Indeed, it may be considered to be a national drink of Brazil and the neighboring states. There is no evidence that *Ilex* species contain pyrrolizidine, and it is more likely that the patient in this case had been poisoned by pyrrolizidines but the plant source was misidentified. The only case of pyrrolizidine poisoning reported in the United States involved a recent immigrant from Ecuador who had been exposed to herbs presumably containing pyrrolizidine alkaloids before she had entered this country. After her arrival, she developed veno-occlusive disease. However, no sample of the herb was obtained for confirmation of the diagnosis [11].

Pyrrolizidine Poisoning by Herbal Teas in the United States

The complacent attitude regarding the public health problem of pyrrolizidine alkaloids in the United States has been shaken within the past

2 years. Pyrrolizidines are a major cause of livestock poisoning in the Northern Pacific States. The offending plant is a European import—*Senecio jacobea*—which has spread over many square miles of pasture land. There are increasing indications that pyrrolizidine alkaloids can enter the food chain and thus create a potential source of exposure [12, 13]. In addition, we have documented cases of pyrrolizidine poisoning in children in Arizona. Clinical descriptions of two of these cases have been provided elsewhere, so only a synopsis will be given here.

Once case involved a 6-month-old Mexican-American female, admitted to the hospital with a diagnosis of a typical hepatitis [14]. An astute gastroenterologist, Dr. Alfred Stillman, was puzzled by the clinical presentation. Questioning of the mother revealed that the child had been given a herbal tea, known as gordolobo yerba, over a 2-week period prior to admission. The remainder of this herb was obtained, given to me, and identified as *Senecio longilobus*. This plant, which is probably identical with *Senecio douglasii*, had been shown by Adams and Govindachari [15] to contain a mixture of four pyrrolizidine alkaloids in a total concentration of about 0.24 percent of dried plant weight. Our analysis of the actual sample to which the patient had been exposed revealed an alkaloidal content of 0.3 percent, in good agreement with the earlier workers. In addition, however, we found 1.0 percent by weight of the nonbasic and nonextractable pyrrolizidine N-oxides (fig. 1) [16]. There is some dispute as to the toxicity of N-oxides, but they are probably equally as toxic as the free alkaloids. The contaminated grain that caused the Afghanistan outbreak contained largely N-oxides [3]. Thus this plant contained four times the total alkaloids detected by the original workers. The alkaloid fraction was largely riddelliine, and the N-oxide fraction was largely retrorsine N-oxide plus the N-oxides of seneciphylline and senecionine [17].

Based on the mother's recipe for preparing tea, we calculated that an amount of tea equivalent to 147 mg total alkaloids had been fed to the child. We prepared some tea in the laboratory by the mother's recipe following a conservative procedure. Water was brought to the boil, removed from the source of heat, and the correct quantity of herb added and stirred in. The tea was allowed to cool to room temperature, filtered, and analyzed for alkaloidal content. Under these conditions 48 percent of the alkaloids present in the sample were extracted. Boiling the tea increases the extraction efficiency. On the basis of this demonstration, we calculated that the child had received a minimum of 70 mg of alkaloid and a maximum of 147 mg over a 2-week period. Calculations of toxicity are complicated by the chronic effect of these substances. Some indication of relative toxicity, however, is given by the LD50 in rats over a 72-hour period, following a single intraperitoneal injection: senecionine 85 mg/kg, seneciphylline 77 mg/kg, and retrorsine 35 mg/kg [1]. The minimum dose ingested by the child of 70 mg of a retrorsine-

rich mixture is, therefore, clearly a toxic amount, especially when it is considered that the young of all species are more susceptible to the toxic actions of pyrrolizidine alkaloids. The child developed cirrhosis, but survived.

The other case involved a 2-month old Mexican-American male admitted to the hospital with a diagnosis of Reye's syndrome [16]. The patient died 5 days later. Two weeks prior to admission, he had been given gordolobo. This had been sold in popcorn packets as a sore-throat remedy by a pharmacy (fig. 3). We obtained the material, identified it as *Senecio longilobus,* and demonstrated the presence of pyrrolizidine alkaloids. This sample was slightly richer in total alkaloids, containing 1.0 percent N-oxides and 0.5 percent free alkaloids. The sample contained fewer woody stems than the one fed the first patient, which may account for the higher alkaloid content. Coincidentally, based on the mother's recipe, we calculated that this patient had consumed almost identically the same quantity of alkaloid as had the first patient. The most likely quantity ingested was 66 mg, albeit over a shorter period and by a lighter infant.

In one sense, both these cases were correctly diagnosed by chance. Confirmation of pyrrolizidine poisoning was achieved in these cases because herbal samples were available for chemical analysis. Usually, in cases of poisoning not involving pyrrolizidines an association can be made between symptomatology and blood levels of the toxin. However, with pyrrolizidine alkaloids no analytical method has yet been made available for the analysis of body fluids or tissue samples. Pyrrolizidine alkaloids are largely excreted within 24 hours of exposure, yet

FIG. 3.—The deadly clown. This packet of herbal tea killed a young child.

symptomatology may not appear for days, weeks, or even months. This means the diagnosis of pyrrolizidine poisoning must be made on circumstantial evidence. In practice, this reduces to (i) liver symptoms indicative of pyrrolizidine poisoning (especially veno-occlusive disease), (ii) analysis for the presence of pyrrolizidine alkaloids in samples of herbs or foods the patient has taken, and (iii) pathognomonic changes in liver architecture. This is limited to autopsy or biopsy material.

In the light of the difficulties of diagnosis, we may ask the question as to how widespread pyrrolizidine poisoning is in the United States. This point is discussed further in the following sections. However, we may say that we have come across a number of cases in Arizona of suspected pyrrolizidine poisoning. No definite confirmation is possible. Typical examples of some of these cases are briefly described.

A 2-year-old Mexican-American girl was admitted to the hospital with jaundice and hepatomegaly. Liver-function tests were markedly abnormal. An open liver biopsy revealed centrilobular necrosis. For several weeks prior to admission, the child had been given gordolobo yerba.

A 4-month-old Mexican-American girl (weight 4.5 kg) was admitted with pneumonia, nephritis, and liver disease initially diagnosed as Reye's syndrome. She had been fed a herbal tea on a regular basis for the month before admission. A sample of tea obtained from the parents contained a mixture of plant species, including some composites (the family that contains *Senecio*). However, analysis did not unequivocally reveal the presence of pyrrolizidines.

A 62-year-old Mexican-American female died of complications of portal hypertension, cirrhosis, hypertension, and hepatic encephalopathy resulting from the portal hypertension. The patient had not consumed alcohol. For the 6 months prior to death she had consumed several cups a day of tea prepared from gordolobo.

A 2-month-old Mexican-American boy was admitted to the hospital with jaundice and hepatomegaly. He did well in the hospital and was released. He was readmitted a short while later with fulminant hepatic failure and died. No genetic, infectious, or metabolic cause for the illness could be found. A year later, a 2-month-old brother was admitted with hepatomegaly. This boy died of hepatic necrosis. The mother had fed herbal teas to the children, but no samples could be obtained. A pattern of improvement in the hospital followed by relapse at home suggests a factor—such as herbs—in the home environment as a precipitant of ill health.

Pyrrolizidine-containing Plants in Arizona

Pyrrolizidine-containing plants known to occur in Arizona are listed in table 1. We have added two plants, *Baccharis pteronoides* and *Astragulus*

TABLE 1

NAMES OF ARIZONA SPECIES THAT CONTAIN PYRROLIZIDINE ALKALOIDS

Scientific	Synonyms	Common	Grazed
Amsinckia intermedia	*A. echinata*	Fiddleneck	*
A. tesselata	...	...	...
Crotalaria pumila	...	Rattlebox	*
C. sagittalis	...	Rattlebox	*
Eupatorium maculatum	*E. bruneri*	Bruner's trumpet weed	...
Heliotropium curassavicum	...	Quail plant	†
Senecio bigelovii	...	...	...
S. jacobea		Tansy ragwort	*
S. longilobus	*S. douglasii*	Thread-leafed groundsel	*†
S. spartoides	...	Broom groundsel	*
S. vulgaris	...	Common groundsel	...
Novel species:‡			
Baccharis pteronoides	*B. ramalosa*	Yerba de pasmo	*†
Astragulus lentiginosus	*Cystium lentiginosum*	Milk vetch, loco weed	

*It has been documented that stock graze on these species. The other species are probably grazed also, however.
†These species are used medicinally by Indians or other groups.
‡From the author's laboratory.

lentiginosus, to this list based on the results of the Ehrlich color test in our laboratory. *Baccharis pteronoides*, under the herbal name of yerba de pasmo, is widely used as a cold remedy and as a veterinary remedy by Mexican-Americans and rural populations throughout the southwest. *Astragulus lentiginosus* is known locally as "loco weed." It has long been known to be poisonous to stock, although the toxin had not previously been identified. It had been suggested that selenium accumulation, nitrate formation, or an uncharacterized alkaloid "locoine" were responsible for the toxin. Our analyses indicate that this plant contains toxic pyrrolizidine alkaloids, although it may also contain other toxic agents. Any of the plants listed in table 2 could pose a health problem as a result of consumption by stock, or as a result of direct use by humans. *Senecio longilobus* is extensively used by at least one Indian tribe in Arizona [18]. Another *Senecio* plant, *S. monoensis*, is used by the Seri Indians [19]. A tea is made by boiling the roots and is taken as a remedy for a cold. This plant has not been reported to contain pyrrolizidine alkaloids, but it is very likely that it does.

The use of pyrrolizidine-containing plants is probably widespread in many groups, even in the industrialized nations. I have seen such plants, for example, in a demonstration herb garden in Quebec.

TABLE 2

NONEQUIVALENCY OF HERBAL AND LINNEAN NAMES

Herbal	Linnean
Gordolobo yerba	*Senecio longilobus, Gnaphalium Macounii, Verbascum thapsus*
Mullein	*V. thapsus*
Manzanilla del Rio	*G. Macounii, G. Wrightii*
Punchon	*V. thapsus*
Tobaco cimarron	*V. thapsus, Nicotiana tabacum*
Candelaria	*V. thapsus*
Verbasco	*V. thapsus*

NOTE.—The plants in the right-hand column have been documented as being sold under the herbal names in the left-hand column, e.g., at least three plants have been sold as gordolobo; and *V. thapsus* has been sold under at least six herbal names.

Long-Term Effects of Pyrrolizidine Consumption

In older children, or adults, disease caused by pyrrolizidines would be expected to be cryptic, not resulting in clinical symptoms for months or years after exposure. One end result would be liver cirrhosis. The appearance of cirrhosis in an adult would probably be attributed to other aspects of life-style than herbal-tea drinking. It is of interest to observe that mortality rates from cirrhosis in Arizona are consistently higher than the national average. For the years 1970–1975, rates were 14, 12, 41, 3, 3, and 8 percent over the national rate. It is possible that exposure to pyrrolizidine alkaloids is at least one contributory factor to this.

A further cause for concern is that, in experimental animals, exposure to low levels of pyrrolizidine alkaloids results in the appearance of lung rather than liver lesions [20, 21]. These lung lesions progress to pulmonary arterial hypertension and right-ventricular hypertrophy. Again, the appearance of lung disease in middle age is unlikely to be attributed to prior exposure to herbal teas. Several reports of pyrrolizidine poisoning in humans state that lung disease also occurred [9, 22]. These lesions are probably caused by a similar mechanism to the one producing liver lesions. The liver releases small quantities of pyrrole metabolites into the bloodstream which are then delivered to the next organ in line—the lung. Any toxin passing through the circulation of the lung comes into intimate contact with the endothelial cells lining the lung capillaries. It is likely that the gross toxic manifestations in the lungs and right heart are a consequence of endothelial cell dysfunction, such as proliferation and occlusion of capillaries and the production of a thrombogenic cell surface [21].

The Arizona cases involved poisoning with teas prepared from *Senecio longilobus,* which had been sold under the herbal name of gordolobo yerba. *Senecio longilobus,* commonly known as thread-leaf groundsel, or woolly groundsel, grows wild throughout much of the southwestern United States and northern Mexico (fig. 4). In the case of the herb used by the first patient, the distribution could be traced. The plant was collected in Mexico and imported into this country by a major wholesaler. This importer is a major supplier of herbs in the western United States and even reexports herbs to many communities in northwestern Mexico. One may ask why a person would pay a dollar for ½ ounce of a plant imported from Mexico that grows freely in southern Arizona. Part of the answer is probably ignorance of which plant is which. However, there appears to be a deep-rooted belief among poor Mexican-Americans, and Mexican-Indian immigrants in this country, that plants from Mexico are more efficacious. There is a part religious, part magic belief that the closer the plant was collected to the home area of the person the more effective it will be. I was told by the importer that *Senecio longilobus* had been imported and sold by his company for 2 generations.

In the Mexican border town of Nogales, 66 miles from Tucson, we purchased a sample of gordolobo yerba which was identified as *Gnaphalium Macounii.* This plant contains no pyrrolizidine alkaloids and is similar in appearance to *Senecio. Gnaphalium Macounii* and other *Gnaphalium* species are commonly used in a number of areas of northern Mexico under the cognomen gordolobo. Does this mean that the dis-

FIG. 4.—Senecio longilobus growing in a typical Southwestern habitat

tributors of *Senecio* made an error and confused *Senecio* and *Gnaphalium*? I think this is too simple an answer. The identification of a species is based on morphological characteristics, whether one is a scientist or a herbalist. However, there is no more reason that there should be a one-to-one correspondence between herbal and botanical identifications than there is that a word in one language should have a precise equivalent in another. The sets of characteristics used to delineate species need not necessarily be the same in the value system of the herbalist and the value system of the botanist. This point might be seen by reference to table 2, in which the overlapping of Linnean and herbal names is obvious. According to Ford [23], *Verbascum thapsus* was being sold as gordolobo in California in 1947. Gordolobo sold in Chicago in September 1977 was also identified as *Verbascum thapsus*. When sold in this way, *Verbascum thapsus* is being used as a sore-throat remedy and is consumed in the form of a tea. When sold as punchon, it is used to treat asthma. In this case, it is either smoked or soaked in whiskey and drunk. Examples like this could be multiplied endlessly.

Furthermore, whereas Linnean names are the *lingua franca* of botany, and are used worldwide, the plants intended to be indicated by a herbal name may differ from user to user or region to region in a similar manner to the way the common names of plants vary in English.

In addition to this cultural problem, there are, of course, also problems of simple misidentification by people collecting their own herbs. Professional herbalists and *curanderos* (healers) are often extremely knowledgeable about the plants they use and can unerringly select the plants they want. Less experienced people, however, in an attempt to collect the same material as the herbalist, may collect mixtures of species or totally different plants. This explains tragedies, such as one reported from Washington state in 1977 in which two people who thought they were collecting comfrey (*Symphytum*) in fact collected foxglove (*Digitalis*) and killed themselves by drinking a tea prepared from it [24].

Relationship between Herb Use and Orthodox Medicine

Kay [8] has described the fundamental place that use of herbs has in Mexican and Mexican-American populations. The herbs used are partly indigenous, being a holdover of folk customs developed over a long period, and partly a vestigial remnant of nineteenth-century European medicine. Although these customs have to a large extent died out in Europe, they still persist among Mexicans. For example, no Victorian book of medicine was complete without a description of chamomile (or camomile). This is a herb (*Anthemis nobilis*) which has been used since Roman times, and in fact was probably imported to England by the Romans. The following is a quotation from a four-volume Victorian

work on medicine and materia medica (i.e., a reputable book of medicine, and not a herbal): "The chamomile is too well known to call for any detailed description" [25]. This comment recalls pre-Johnsonian dictionaries in which a dog is defined as an animal too common to require description. The quote continues: "It grows wild in many parts of England, and is a common object in almost every cottage garden," and recommends the plant for female complaints, teething, diarrhea, cramps, and as a sedative.

Anthemis species, such as *A. cotula,* are widely sold as herbal teas in the Southwest under the European name of chamomile or the Mexican name of manzanilla. It is also known as mayweed or dog fennel. It is frequently given to babies or young children and is used for teething disorders.

In excess of 600 species of plants are imported into Arizona for sale as herbs. Many of these, and the uses they are put to, would be unrecognizable to a last-century physician. Many others, however, would be readily recognized. Some of the plants which are listed both in nineteenth-century texts on pharmacy and materia medica and in Mexican herb stores are *Arnica,* calumba (*Cocculus palmatus*), gentian, *Lobelia,* mallow ("marshmallows," candy flavored with mallow—*Althaea officinalis*—was a common confection in England when I was growing up in the fifties), quassia chips (*Picraena*), and sarsaparilla (*Smilax*). Many other examples of the endurance of nineteenth-century European pharmaceutical practices among Mexicans could be quoted.

Public Health Aspects of Herbal-Tea Consumption

The use of herbs appears to fall into a regulatory hole. They are not foods, and they are not drugs. There is no enforced requirement for demonstrations of efficacy or safety. This contrasts sadly with regulations applied to the drug industry. Any new drug has to undergo expensive and time-consuming tests, first to show that it will do what the manufacturer claims it will and second to show that it will do this safely—and that side effects fall within acceptable limits. No such tests are required to introduce a herb.

Does this lack of regulation indicate a serious public health problem? In the absence of detailed information, this is a hard question to answer. In cultures that have a tradition of herbal usage, such as Mexican-Americans or various American Indian groups, people are in general protected from plants that are obviously toxic because the community builds up a body of information on these plants. The risk here comes from plants—such as those containing pyrrolizidines—in which the toxic consequences do not follow immediately upon exposure to the plant.

Recently, there has been a tremendous interest in the use of herbs by groups lacking a cultural tradition of plant usage. This results in many poisoning cases each year. This may be because of misidentification, as in the case of the foxglove tea [24] or with a recent death due to drinking *Datura* by a group on a desert survival exercise. Death or illness may also result from the deliberate ingestion of a toxic plant in order to experience the disturbance of the central nervous system. *Datura stramonium* is commonly used for this purpose in the Southwest. In many cases of poisoning, the herb was purchased from a health-food store, as with recent intoxications for pennyroyal, pokeweed, *lobelia,* burdock, *aloes,* senna, buckthorn, and many other plants (e.g., see [26]).

APPENDIX

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