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

RICHARD W. DENT, M.D., Ph.D.

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, Erysiphaceae, Loganiaceae, Orchidaceae, Rhamnaceae, Santalaceae, and Sapindaceae. Part structures of these alkaloids are illustrated in figure 1. Tox alkaloids contain an unsaturated ring. These alkaloids, and the plants in which they occur, are hepatotoxic, producing veno-occlusive disease, hepsinomalgia 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 pyroloes (fig. 1). Pyroles are chemically active and serve as biological alkylating agents by the mechanisms shown in figure 2, in which groups X

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in the text.

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and Y represent nucleophilic portions of proteins or nucleic acids, such as sulphydryl groups [2]. Alkaloids are 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 and geo-

**Nephrotoxic**

**Hepatotoxic**

**Pyrole**

**Hydrolysis: Part Structures**

Fig. 1.—Pyrrolizidine part structures. The central portion of the structure is usually a cyclic diene grouping (= CO.COO =). Toxic alkaloids are hydrolyzed to N oxides and pyroles. The cyclic diene may also be metabolically hydrolyzed.

**PYRROLE TOXICITY**

![Pyrole toxicity diagram](image)

Fig. 2.—Pyrole toxicity. Pyroles formed in the body are postulated to be toxic because of their ability to alkylate nucleophilic groups, such as sulphydryl (SH), on cell macromolecules. Based on a proposal of Matrucka [2].

graphical distribution of major sources of foodstuffs, and the herbal preparations that of continental and epidemic foodstuffs. Recent and in India in 1974, **Crotalaria** species co- along with the grain found to contain all wheat. The Afghan veneno-isloworly can le, even the true scope of the epi- toms-certainty, the 1975 may have suffered by as in an immediate future.

**Chronic Contamination in Africa**

Here the in **Crotalaria**, and the u- tating grains as route has been thou- many lives can be caused to occur in the advance of chemicals for conti- years ago, it was not a path for grain cer-ers. However, this be.

The intentional or alkaloids is a major p. **Africa, South and The** no inept, of course, based on folklore and are used to prepare it.

In Jamaica, for exam- person going into the island and collecting a variety of plants. Coastal in bush tea. Pediatric proportions is Jamaic- nased there [6]. The 3 nutritional status and
graphical distribution of pyrrolizidine-containing plants. There are two major sources of human exposure: accidental contamination of foods 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 foods. Recent examples of the latter occurred both in Afghanistan and in India in 1975. These epidemics were caused by *Heliotropium* and *Crotalaria* species contaminating fields of wheat and being harvested along with the grain to make bread. When from the affected area was found to contain about 3000 mg of *Heliotropium* seeds per kilogram of wheat. The Afghan epidemic involved approximately 1500 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 disabilities consequences that did not result in an immediate clinical picture. The Indian epidemic involved fewer people. However, of the 67 recorded cases, 28 died [1].

Chronic contamination of foods and the problem has been a problem in South Africa. Here the major offending species appear to be *Senna* and *Crotalaria*, and the usual route of exposure is that of these plants contaminating grains used to prepare food [5]. Senna poisoning by this route has been thought to be responsible for the high incidence of primary liver carcinomas in Black Africans. This type of exposure no longer occurs in the advanced industrialized nations due to the widespread use of chelating agents 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 pyrrolizidines alludes to 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, a well-defined "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 this tea. Pyrrolizidine poisoning has been of almost epidemic proportion 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 substances.
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 bird-of-pye plant (Abrus precatorius) 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 entice ackee fruit contain 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 venoms have been exposed to one toxic chemical. Often, he has been exposed to a variety of plants which causes the toxic action of each other, he may be suffering from parasitic diseases and post-natal nutritional anemia, and the toxicological action of a plant may differ quite substantially from that of a poison, the poison principle is derived from the plant. One cannot expect poisoning poisoning produced by ingestion of a plant to mimic the disease caused by administration of a purified alkaloid in a laboratory setting.

Both South and Central America are used to prepare teas in Africa. Extracted Senna have even been used in a commercial preparation sold is treat conditions as opposed as anguina and menstruation [5].

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

Until recently, psychotropic 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 some cases, it is often difficult to obtain samples of identifiable samples. One case of venous-rectural disease was attributed to drinking Mate or Paraguayan tea (Ilex sp). 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 the species contain psychotropic agents. It is much more likely the patient in this case had been poisoned by psychotropics but the plant source was unidentified. The only case of psychotropic poisoning reported in the United States involved a recent immigrant from Brazil who had been exposed to herbs presumably containing psychotropics before she had entered this country. After her arrival, she developed vena-rectular disease. However, no sample of the herb was obtained for confirmation of the diagnosis [11].

Psychotropic Poisoning by Herbal Tea in the United States

The complaint made regarding the public health problem of psychotropics in the United States has been shaken within the past

[1] Paul J. Schulte - Herbal Teas and Poisons

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

One case involved a 12-year-old Mexican-American female, admitted to the hospital with a diagnosis of a typical hepatitis [14]. An acute gastroenterologist, Dr. Alfonso Sánchez, was called for the clinical presentation. Questioning of the mother revealed that the child had been given a herbal tea, known as gambó,缠lnam, over a 2-week period prior to admission. The remainder of the herb tea obtained, given to the child, identified as Smilax longifolia. This plant, which is probably identical with Smilax douglasii, had been shown by Adams and Gencokian [15] to contain a mixture of four psychodolea alkaloids in total concentrations of about 24 percent of dried plant weight. Our analysis of the actual sample to which the patient had been exposed revealed an alkaloidal content of 0.1 percent, in good agreement with the earlier workers. In addition, however, we found 1.0 percent by weight of the norbitter and nonextractable psychodolea N-oxide (fig. 11-16). There is some dispute as to the toxicity of N-oxides, but they are probably equally toxic as the free alkaloids. The contaminated ground caused the child to contract a severe fulminant hepatitis. The plant continued for years the total alkaloids detected by the original workers. The alkaloid fraction was largely gambólina, and the N-oxide fraction was largely a mixture of Smilax N-oxides of terrebelline and serpentine [15].

Based on the moxeter’s recipe for preparing tea, we calculated that an amount of tea equivalent to 1.7 g total alkaloids had been fed to the child. We prepared some tea in the laboratory by the mother’s recipe following a recovery 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. Ignoring the tea increases the extraction efficiency. On the basis of this demonstration, we calculated that the child had received a minimum of 20 mg of alkaloid and a maximum of 167 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 1500 mg L.D. value over a 7-hour period, following a single intraperitoneal injection: terrebelline 85 mg/kg, terrebelline 72 mg/kg, and serpentine 35 mg/kg [15]. The minimum dose imposed by the child of 20 mg of a terrebine

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rich mixture is, therefore, clearly a toxic amount, especially when it is
considered that the dosage of all species are non-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 ad-
mitted to the hospital with a diagnosis of Reye's syndrome [10]. The
patient died 3 days later. Two weeks prior to admission, he had been
given gordolobo. This had been sold to patient's parents as a sinut-remedy
by a pharmacy (fig. 5). We obtained the material, identified it as
Senecio longifolius, and demonstrated the presence of pyrrolizidine
alkaloids. This sample was slightly richer in total alkaloids, containing
1.6 percent N-oxides and 0.5 percent free alkaloids. The sample con-
tained fewer woody stems than the one lot 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 60 mg, which 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 be-
cause 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 bodily fluids or tissue samples. Pyrrolizidine-
alkaloids are largely excreted within 24 hours of exposure, yet

Fig. 5 - The death plant. The plant of loads for killed a young child.

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Pyrolozidine-containing Plants in Arizona

Pyroloidine-containing plants known to occur in Arizona are listed in table 1. We have added two plants, Barleria pyrolifera and Atriplex

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In Arizona, to this list based on the results of the Ethnobotany Field Guide in our laboratory. *Baccharis pensilis*, under the herbal names of *verde de madera*, is widely used as a cold remedy and as a tonic remedy by Mexican Americans and local populations throughout the southwest. *Aristolochia homalodes* is known locally as "boar weed," it has long been known to be poisonous to livestock, although the toxin has not previously been identified. It has been suggested that selenium accumulation, separate formation, or an uncharacterized alkaloid "bronze" were responsible for the toxicity. Our analyses indicate that this plant contains some pyrrolizidine alkaloids, although it may also contain other toxic agents. Any of the plants listed in table 2 could pose health problems as a result of consumption by livestock, or as a result of direct use by humans. *Senecio angulatus* is eventually used by at least one Indian tribe in Arizona [19]. Another *Senecio* plant, *S. novaezielandiae*, is used by the Micmac Indians [19]. A tea is made by boiling the roots and is taken as a remedy for cold. This plant has not been reported to contain pyrrolizidine alkaloids, but it is very likely that it does.

The use of pyrroline-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

<table>
<thead>
<tr>
<th>Medicinal Herb</th>
<th>Scientific Name</th>
<th>Latin Name</th>
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</thead>
<tbody>
<tr>
<td>Coriandrum sativum</td>
<td>Coriandrum sativum</td>
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</tr>
<tr>
<td>Salvia officinalis</td>
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<tr>
<td>Lycium barbarum</td>
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<td>Echinacea angustifolia</td>
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<td>Echinacea angustifolia</td>
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<tr>
<td>Hypericum perforatum</td>
<td>Hypericum perforatum</td>
<td>Hypericum perforatum</td>
</tr>
<tr>
<td>Taraxacum officinale</td>
<td>Taraxacum officinale</td>
<td>Taraxacum officinale</td>
</tr>
<tr>
<td>Valeriana officinalis</td>
<td>Valeriana officinalis</td>
<td>Valeriana officinalis</td>
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</tbody>
</table>

**Note:** The plants in the right-hand column have been identified as being sold under the herbal name in the left-hand column. All of these plants have been sold with the appropriate medicinal use. "Hypericum perforatum" is not a well-known or accepted herbal name.

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**Long-term Effects of Pyrrolizidine Consumption**

In older children, or adults, disease caused by pyrrolizidine alkaloids would be expected to be cryptic, not resulting in clinical symptoms for many years after exposure. One end result would be liver cirrhosis. The appearance of cirrhosis among adults 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 period 1970-1975, rates were 14, 12, 44, 13, 8, and 8 percent over the national rate. It is possible that exposure to pyrrolizidine alkaloids is a 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 where 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 pyrrolizidine alkaloids into the bloodstream which are then delivered to the new organ in situ—the lung. Any toxins 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 erosion of capillaries and the production of a thrombogenic cell surface [21].

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Gordolobo Yerba and Pyrrolizidine Poisoning

The Arizona cases involved poisoning with tea prepared from *Seearia longifolia*, which has been sold under the herbal name of gordolobo yerba. *Seearia longifolia*, commonly known as thread-foot 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 exports herbs to many communities in southwestern Mexico. One may ask why a person would pay a dollar for 1/2 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, these appear to be a deep-rooted belief among some Mexican-Americans, and Mexican-Indian immigrants in this country, that plants from Mexico are more efficacious. There is a part religious, part magical belief that the closer the plant was collected to the home area of the person the more effective it will be. It was told by the importer that *Seearia longifolia* had been imported and sold by his company for 2 generations.

In the Mexican border town of Nogales, 60 miles from Tucson, we purchased a sample of gordolobo yerba which was identified as *Gomphostemma macrophyllum*. This plant contains no pyrrolizidine alkaloids and is similar in appearance to *Seearia longifolia*. Monitor and other *Gomphostemma* species are commonly used in a number of areas of northern Mexico under the cognomen gordolobo. Does this mean that the distribution of gordolobo yerba can be traced to locations in Mexico?
tributors of Serrio made an error and confused Serrio and Geophalium. 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 these 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 Linnæan and herbal names is obvious. According to Ford [23], Verbascum thapsus was being sold as gos-
dolobo in California in 1914. Gosdolobo 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 pinchun, 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 Linnæan 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, other problems: single misidentification by people collecting their own herbs. Professional herbalists and canneros (headers) 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 (sagebrush [Artemisia]) and killed themselves by drinking a tea prepared from it [24].

Relationship between Herb Use and Orthodox Medicine

Kay [8] has described the fundamental plan 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 vernal remnant of nineteenth-century Europeans medicine. Although these customs have a large extent died out in Europe, they still persist among Mexicans. For example, no Victorian book on medicine is complete without a description of chamomile (matricaria). This is a herb (Matricaria chamomilla) 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

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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” [22]. This comment reveals pre-Johnsonian dictionaries to which a dog is defined as an animal too common to require description. The quote continues, “It grows with many parts of England, and is a common object in almost every cottage garden, and recommends the plant for female complaints, tertials, diarrhea, cramps, and as a sedative.

A small number 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 unrecognized to a last-century physician. Many others, however, would be readily recognized. Some of the plants which are used both in nineteenth-century texts on pharmacy and materia medica and in Mexican herb stores are Amica, calumbia (Caulobus polyanthus), gentian, Lobelia, mahoe (marshmallow), candel—Althaea officinalis—was a common confection in England when I was growing up in the fifteen, quanita chico (Bezania), and sarsapalli (Sarsaparilla). 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 pyrrolizidine-—to 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 brocklehead sea [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 hallucinatory effects of the central nervous system. Barter totemism 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, barbarea, senec, buckhorn, and many other plants (e.g., see [25]).

**APPENDIX**

**BIBLIOGRAPHY OF HERBS**

This brief list provides further reading on various aspects of herbs.

- **Heron, E. A.** _Flower and Foliage Plants of the World_. New York: Dover, 1972. (Originally published 1910.)

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