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Diagnosis and Treatment of Amanita Phalloides-Type Mushroom Poisoning

Use of Thioctic Acid

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The number of cases of mushroom poisoning is increasing as a result of the increasing popularity of "wild" mushroom consumption. Amanitin and phalloidin cytotoxins found in some Amanita and Galerina species produce the most severe and frequent life-threatening symptoms of Amanita phalloides-type poisoning. Delay in onset of symptoms, individual susceptibility variation and lack of rapid and reliable identification have contributed to the significant morbidity and mortality of this type of poisoning.

A rapid chromatographic assay for identifying the potent cytotoxins and apparently successful management using thioctic acid of two cases of A. phalloides-type mushroom poisoning are reported. All known cases of A. phalloides-type mushroom poisoning treated with thioctic acid in the United States are summarized.

THE GATHERING AND EATING of wild mushrooms is a popular pastime in the United States, partly owing to increased interest in "organic" foods and in the hallucinogenic substances found in certain species. Severe and life-threatening poisonings from the ingestion of wild mushrooms have increased in frequency. Of the 2,000 or so species of mushrooms known to exist, fewer than 50 are poisonous to man.[1] Many mushroom hunters believe that poisonous varieties can be identified easily[2,3] and many have the erroneous notion that some toxic species can be rendered harmless by cooking in a particular manner. As a result, even experienced mushroom seekers have been stricken when they harvested and ate poisonous varieties.

From 1957 to 1964, 30 deaths from ingestion of wild mushrooms were reported in the United States; 11 of these occurred in California.[2] From 1964 to 1974, 57 cases of mushroom poisoning, including eight deaths, occurred in California alone (Table 1); 18 of the poisonings and four of the deaths occurred in 1972.

The principal toxins of the most poisonous mushrooms are complex proteins containing

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TABLE 1.—*Summary of Known Cases of Mushroom Poisoning in California from 1964 to 1974 (57 Cases)*

No. of Cases	*Age(s) Sex(es)*	*California County Where Mushrooms Were Picked*	*Genus and Species of Mushroom*	*Date Ingested*	*Onset of Symptoms After Ingestion (hr)*	*Initial Symptoms**	*Treatment*	*Outcome*
17	10-60 ♂&♀	Los Angeles	Chloraphyllum molybdites	9-13-64	1½-2	GI, fever, headache, diaphoretic	Supportive care	Recovered
1	46 ♂	Marin	Amanita phalloides	11-?-68	Several	GI, shock	?	Died
2	50 ♂, 15-18 ♂	Sierra	?	6-?-68	?	GI, prostration	Atropine, supportive care	Recovered
2	78 ♂, 80 ♀	San Joaquin	?	9-?-68	1½-2	GI	Atropine, supportive care	Recovered
2	50 ♂, 80 ♀	San Joaquin	Boletus eastwoodii	3-?-69	1½-2	GI	Atropine, supportive care	Recovered
1	72 ♂	Marin	A. phalloides	12-?-70	Several	GI, shock	?	Died
1	59 ♀	Marin	A. phalloides	1-1-72	6-8	GI	?	Died
2	45 ♂, 44 ♀	San Francisco	?	5-9-72	?	?	?	Recovered
7	20-29 ♂&♀	Nevada	B. eastwoodii	1-22-72	1½	GI, prostration, cramps, bradycardia	Atropine, supportive care	Recovered
1	41 ♂	Santa Cruz	A. phalloides	11-5-72	12-24	GI, abdominal pain, shock	?	Died
4	14 ♂, 52 ♀ †	Santa Cruz	A. phalloides	11-5-72	6-12	GI, abdominal pain, shock	Supportive care, thioctic acid	2 recovered, 2 died‡
1	31 ♀	San Mateo	A. phalloides	11-12-72	12	GI, abdominal pain	?	Recovered
2	74 ♂, 74 ♀	Sacramento	A. phalloides	11-12-72	14	GI, abdominal pain, prostration	?	Recovered
1	63 ♂	Sonoma	A. phalloides	12-30-72	13	GI, abdominal pain, prostration, dehydration	?	Recovered
1	30 ♂	Fresno	A. phalloides	3-21-73	Several	GI, weakness	Supportive care	Recovered
1	32 ♂ §	Fresno	A. phalloides	3-2-73	12	GI, weakness, fever?	Thioctic acid, supportive care	Recovered
2	20 ♂, 30 ♂	Santa Cruz	A. phalloides	10-30-73	10-15	GI, shock, jaundice seizure	?	1 died, 1 recovered
2	20 ♀, 30 ♂	San Joaquin	A. phalloides	5-27-74	Several	GI, cramps	Supportive care	Recovered
1	21 mo. ♂	San Joaquin	A. phalloides	5-27-74	Several	GI, cramps	Supportive care	Died
3	40 ♂, 18 ♀, 39 ♀	Orange	Chloraphyllum molybdites	8-22-74	½-3	GI, cramps, weakness, abdominal cramps and pain	?	Recovered
1	23 ♂ ¶	Sonoma	C. molybdites	9-?-74	2	GI (no diarrhea)	Supportive care, thioctic acid	Recovered
1	33 ♂ **	Marin	A. phalloides	11-?-74	Several	GI	Thioctic acid, supportive care	Recovered
1	87 ♂ ††	Santa Clara	A. phalloides	12-16-74	22	GI, cramps	Thioctic acid, supportive care	Recovered

*GI = nausea, vomiting and diarrhea.
†One is Case No. 11 in Table 3.
‡Death in one who received thioctic acid.
§Case No. 1 in Table 3.
¶Case No. 4 in Table 3.
**Case No. 3 in Table 3.
††Case No. 2 in Table 3.

TABLE 2.—*Diagnosis of Mushroom Poisoning*

Cause	*Toxic Constituents*[1,10]	*Genus and Species*	*Comments*
Cellular Toxins	Amanitins Phalloidins	Amanita (Sp. phalloides, verna, virosa)	Found mostly in wooded areas, frequently during late summer and fall seasons. No obnoxious taste or smell. Gastrointestinal symptoms occur 6 to 24 hours after ingestion. A transient period of improvement is followed by metabolic disturbances and renal and hepatic impairment. Most fatalities occur within several days. As little as one third of a single cap can be fatal in a child. Mortality is 40 to 90 percent. These species of Amanita account for nearly 90 percent of all cases of severe mushroom poisoning.
	Amanitins	Galerina (Sp. autumnalis, marginata, venenata)	These species are found in the western and midwestern United States on lawns, meadows, and decaying wood. Symptoms are similar to those of A. phalloides-type poisoning. Despite absence of the phalloidin toxin, the mortality risk from ingestion of these species should be considered as significant as for A. phalloides due to presence of amanitin.
Enzyme Toxins	Monomethylhydrazine (Gyromitrin)	Gyromita (Sp. esculenta) Helvella (Sp. esculenta, underwoodii)	These species (except underwoodii) are not confined to any particular habitat or geographic region. These mushrooms produce symptoms similar to intoxication by amanitin but less severe, appearing 6 to 12 hours or more after ingestion. Symptoms are primarily gastrointestinal. Hemolysis and central nervous system effects are associated with these mushrooms. Certain people are resistant to their effects. Cooking may attenuate toxicity. Estimated mortality is 2 to 4 percent.
Neurologic Toxins	Muscarine	Inocybe (Sp. napipes) Clitocybe (Sp. rivulosa, trunicola, cerussata, olearia, dealbata)	Toxins produce "muscarinic" effects, e.g. salivation, lacrimation, nausea, bronchospasm, abdominal pain, vomiting, diarrhea, headache and miosis within 15 to 30 minutes after ingestion. Bradycardia, hypotension and shock may also occur. Death is infrequent. Treatment is primarily supportive and symptomatic. Atropine is a specific antidote for muscarine intoxication. There appear to be species differences because only some have caused death.
	Isoxazole Derivatives: Muscimol Muscazone Ibotenic Acid Pantherin Tricholomic Acid	Amanita (Sp. muscaria, pantherina, cokeri, crenulata, solitaria)	Commonly found in wooded areas, especially conifer forests of western United States in spring and fall. These mushrooms are also known as "fly mushroom" or "fly agaric." These species have been associated with the toxin muscarine, but in fact contain toxicologically insignificant quantities of it. They produce symptoms resembling the central nervous system effects of excessive atropine and display anticholinergic and mild hallucinogenic properties. Symptoms occur within ¼-2 hours after ingestion and frequently resemble alcohol intoxication. Severity and duration of symptoms vary with individual. Muscle spasms can occur after ingestion of large quantities. Prognosis for recovery is good. Avoid use of sedatives; atropine is contraindicated in treatment. Death is rare.
	Psilocybin Psilocin	Psilocybe (Sp. cubensis, eaerulescens, silvatica) Panaeolus (Sp. foenisecii	Psychotropic "LSD-like" manifestations begin about 30 to 60 minutes after ingestion and may continue for several hours. Recovery is spontaneous and usually within a day. Treatment is symptomatic.

TABLE 2.—*Diagnosis of Mushroom Poisoning (Continued)*

Cause	*Toxic Constituents*[1,10]	*Genus and Species*	*Comments*
Gastrointestinal Irritants	Not Yet Identified	*Boletus (Sp. satanas, eastwoodii) Clitocybe (Sp. nuda, illudens) Chlorophyllum (Sp. molybdites) Russula (Sp. emetica) Tricholoma (Sp. venenatum, pardinum) Catharellus (Sp. floccosus) Hebeloma (Sp. crystuliniforme) Lactarius (Sp. torminosus, glaucescens) Naematoloma (Sp. fasciculare) Rhodophyllus (Sp. sinuatus)	Irritating constituents have not been identified. Probably many toxins are involved. Mild to severe nausea, vomiting, diarrhea, abdominal cramps, and other gastrointestinal symptoms occur ½ to 2 hours after ingestion and may persist for several hours. The incidence and severity of gastrointestinal symptoms are greater with raw mushrooms. Treatment is supportive, and symptoms usually terminate spontaneously within a short time. Rare fatalities have been reported.
Disulfiram-like Constituents	Monomethyl-hydrazine	Coprinus (Sp. atramentarius)	Disulfiram reaction-like symptoms of flushing, palpitation, hyperventilation and tachycardia occur only if alcohol is consumed in combination with these mushrooms. These effects may take place up to 48 hours between ingestion of mushroom and alcohol and last for a short time. Gastrointestinal symptoms of nausea, vomiting, and diarrhea have also occurred. The severity of symptoms is greatest after ingestion of raw mushrooms. Treatment is supportive and alcoholic beverages should be avoided.

*These species have been the most frequently associated with gastrointestinal irritants.

cyclic heptapeptides (phalloidins) and cyclic octapeptides (amanitins).[4] Phalloidin appears to disrupt hepatic cell membranes and to change the structure of the hepatic endoplasmic reticulum adversely. The role of phalloidin in the production of symptoms and pathologic changes in the liver of a poisoned patient is unclear because some species now known to contain this cyclopeptide and no amanitin have been consumed without causing the undue effects. The toxicity of amanitin has been compared *in vitro* with that of phalloidin and found to be 10 to 20 times greater. The amanitin is believed to be the major toxin responsible for the symptoms and pathology following the ingestion of Amanita phalloides-type mushrooms. This is best demonstrated by the toxicity of some species of the Galerina mushrooms that contain only amanitin. It has been shown that amanitin inhibits the enzyme ribonucleic acid polymerase II and interferes with the synthesis of messenger ribonucleic acid.[5,6] Histochemical examination of hepatic cells after exposure to amanitin shows the presence of abnormal concentrations of lipids and carbohydrates in the cell nuclei.[7,8] Amanitin is also a direct-acting nephrotoxin that produces necrosis of the distal and proximal convoluted tubules.[9]

Mushrooms containing phalloidin and amanitin belong to the genera Amanita and Galerina, although not all species of these genera contain these toxins (Table 2). In Europe, A. phalloides is the most frequent cause of mushroom poisoning; nearly 90 percent of all such deaths are attributed to A. phalloides, the "death cap."

In the United States, Amanita verna (the "destroying angel"), Amanita virosa and A. phalloides are the common causes of mushroom poisoning and death (90 percent). Recent deaths in California have been attributed to A. phalloides. Cases of severe mushroom poisoning by Galerina marginata, autumnalis and venenata have occurred in this country but are infrequent.[2] Poisoning by the very toxic Amanita and Galerina species will be referred to as A. phalloides-type poisoning in this article.

There appears to be considerable variability in individual susceptibility to the toxins of poisonous mushrooms.[2] For instance, several members of the family of one of our patients (Case 1) ate the meal containing the offending mushrooms, but only one other family member experienced any ill effects. Whether or not there is a quantity-consumed association to development of symptoms is unclear. Severity of symptoms has been thought to depend on the season and the state of maturation of the mushrooms when picked and eaten, the location where they were picked, and the amount ingested.[2] There is no evidence to vali-

date this impression. Approximately 75 percent of the cases in California occurred in the fall, probably coincident to the season when these poisonous mushrooms are most abundant and easily harvested.

During the past three years, we have managed five patients; two are reported here. We consulted in three other cases of severe A. phalloides-type mushroom poisoning. The results of our experience in identifying and treating A. phalloides-type mushroom poisoning are presented.

Diagnosis of Mushroom Poisoning

The time between ingestion and onset of symptoms and the type of systemic involvement (for example, neurologic versus gastrointestinal) can be helpful indexes for characterizing the type of mushroom poisoning. Mushroom poisoning can be divided into cases in which symptoms appear within several minutes to six hours after ingestion and those in which symptoms develop much later (Table 2).

TABLE 3.—*Cases of Mushroom Poisonings Treated with Thioctic Acid (TA) in the United States*

Case No. Age (year) Sex	*Year*	*State*	*Dose of TA and Duration of Treatment*	*Mushroom*	*Method of Identification* (Result)*	*Hospital Course†*
1 . . 32 ♂	1973	California	300 mg × 6 days	Amanita phalloides	TLC (+) mycologist	Refer to Case No. 1 described in text
2 . . 87 ♂	1974	California	100 mg × 1 day then 300 mg × 6 days	A. phalloides	TLC (+) mycologist	Refer to Case No. 2 described in text
3 . . 33 ♂	1974	California	100 mg × 1 day then 300 mg × 6 days	A. phalloides	TLC (+) mycologist	Admitted 12/30. Nausea, diarrhea, and vomiting beginning 12 to 16 hours after ingestion. Severe dehydration on admission. SGOT 728 and 850 and SGPT 1,018 and 2,320 units per ml. Treated with TA, glucose, and supportive measures. SGOT and SGPT returned to normal levels during treatment. Discharged 1/17.
4 . . 23 ♂	1974	California	100 mg × 1 day then 300 mg × 1 day	Chlorophyllum molybdites	TLC (−) mycologist	Admitted 8/26. Abdominal pain, nausea, diarrhea, vomiting, and fever 2 hours after ingestion. SGOT 25, SGPT 20, LDH 210, CPK 70 units per ml, bilirubin (total) 1.0 mg per 100 ml. Treated with TA, glucose, and supportive measures. Discharged 8/29.
5 . . 40 ♀	1974	New York	100 mg × 1 day then 300 mg × 4 days	Galerina autumnalis	TLC (+) mycologist	Admitted 10/30. Severe nausea, vomiting, diarrhea, and abdominal cramps 10 hours after ingestion. BUN 23, serum creatinine 1.2, bilirubin (total) 2.4 mg per 100 ml, SGOT 100, LDH 224 units per ml, urine glucose +1, acetone +1. Treated with TA, glucose, and supportive measures on day 2 of treatment. Course otherwise uncomplicated. Discharged 11/8.
6 . . 50 ♂	1974	New York	100 mg × 1 day then 300 mg × 2 days	G. autumnalis	TLC (+) mycologist	Admitted 10/30. Nausea, vomiting, diarrhea, and abdominal cramps 12 hours after ingestion. BUN 45, serum creatinine 1.8, bilirubin (total) 1.2 mg per 100 ml, SGOT 33, SGPT 36. Treated with TA, glucose and supportive measures. Course uncomplicated. Discharged 11/4.

TABLE 3.—*Cases of Mushroom Poisonings Treated with Thioctic Acid (TA) in the United States (Continued)*

Case No. Age (year) Sex	*Year*	*State*	*Dose of TA and Duration of Treatment*	*Mushroom*	*Method of Identification* (Result)*	*Hospital Course†*
7 . . 71 ♀	1974	Washington	100 mg × 1 day then 300 mg × 5 days	G. autumnalis	TLC (+) mycologist	Admitted 11/21. Nausea, vomiting, profuse diarrhea, tachycardia, and slight abdominal pain 12 to 16 hours after ingestion. Treated with TA, glucose, and supportive measures. Course uncomplicated and laboratory indexes were within normal limits. Discharged 12/1.
8 . . 58 ♂	1972	Ohio	300 mg × 13 days	Amanita virosa	mycologist	Admitted 10/2. Severe hypotension, vomiting, and diarrhea 6 hours after ingestion. BUN 51, serum creatinine 4.5 mg per 100 ml, SGOT 900, SGPT 1,750, LDH 1,920 units per ml, Hct 58%. Complicated course requiring hemodialysis; biopsy revealed acute tubular necrosis, liver function tests returned to normal values at completion of a 13 day course of TA, glucose, and supportive measures. Maculopapular rash and erythema multiforme of unknown etiology developed at completion of TA treatment. Discharged 10/21.
9 . . 24 ♀	1972	Ohio	300 mg × 5 days	A. virosa	mycologist	Admitted 10/3. Nausea, vomiting, and diarrhea of 1½ day duration beginning about 6 hours after ingestion. Treated with TA, glucose, and supportive measures. Course uncomplicated. Discharged 10/12.
10 14 mo ♂	1972	Ohio	300 mg × 1 day	A. phalloides	mycologist	Admitted 10/3. No symptoms. Hepatic and renal functions normal throughout. Treated with TA, glucose, and supportive measures. Course uneventful. Discharged 10/8.
11 . . 52 ♀	1972	California	300 mg × 1 day	A. phalloides	mycologist	Admitted 11/5. Nausea, vomiting, diarrhea, and abdominal cramps developed 12 hours after ingestion. "Improved" on fourth day but then became progressively disoriented and obtundated. TA begun on day 7 after ingestion at "time of cerebral death." Died on 11/14.
12 . . 35 ♂	1970	Pennsylvania	300 mg × 6 days	A. verna	mycologist	Admitted 11/15. Severe abdominal pain, nausea, vomiting, and diarrhea developed 9 hours after ingestion. Treated for 5 days with glucose and supportive measures. Liver function decreased: SGOT 2,000+ units per ml and bilirubin (total) 7.6 mg per 100 ml. Condition complicated by hepatomegaly, ascites, and intermittent coma. TA started on day 8 after ingestion. Liver function tests returned to normal values by sixth day of TA. Liver biopsy showed necrosis with repair. Discharged 12/2.

*TLC = thin layer chromatography.
†SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase; LDH = lactic dehydrogenase; CPK = creatine phosphokinase; BUN = blood urea nitrogen, and Hct = hematocrit.

Most nonlethal poisonous mushrooms produce symptoms soon after ingestion, whereas A. phalloides-type mushrooms produce life-threatening reactions 6 to 24 hours after ingestion. However, since a mixture of wild mushrooms is often ingested, early onset of symptoms does not exclude the possibility of more serious poisoning. Poisoning with immediate onset of symptoms is further distinguishable by the type of symptoms; that is, gastrointestinal disturbance, parasympathetic stimulation and hallucinations. Such poisoning is rarely serious, and recovery usually occurs within 24 hours (Table 2).

Symptoms of the more toxic A. phalloides-type mushrooms characteristically occur in three stages. (1) The first stage occurs abruptly, 6 to 24 hours after ingestion: abdominal pain, nausea, vomiting, diarrhea (occasionally bloody) and hematuria. These are frequently accompanied by fever, tachycardia, hyperglycemia, hypotension, dehydration and electrolyte imbalance. (2) During the next 24 to 48 hours (two to three days after ingestion), there appears to be remission of symptoms in the face of progressive deterioration of hepatic and renal function. (3) During the subsequent 24 to 48 hours (three to four days after ingestion), hepatocellular damage and renal impairment progressively worsen, and jaundice, hypoglycemia, oliguria, delirium and confusion develop. Myocardiopathy and coagulopathy may be present, and convulsions, coma and death may occur. The mortality rate varies from 40 to 90 percent.[1,11] Death from A. phalloides-type poisoning is usually the result of hepatic or renal failure or both.[11-13]

Because of the delayed onset of symptoms in A. phalloides-type poisoning, patients frequently fail to associate their symptoms with the ingestion of wild mushrooms. Therefore, a careful history of the patient's activities before onset of symptoms is imperative. Failure to suspect mushroom poisoning, to identify the more toxic A. phalloides-type mushrooms and to implement early treatment contribute to the high morbidity and mortality associated with the ingestion of A. phalloides-type mushrooms.

Morphologic and Toxicologic Identification of Mushrooms

In a suspected case of mushroom poisoning, identification of the species by morphologic characteristics is a formidable task because the appearance of the mushroom may be distorted by handling and cooking. Attempts to identify them retrospectively by collecting mushrooms from the area where the ingested ones were harvested is unreliable because poisonous species frequently grow in immediate proximity to nontoxic ones. Examination of fungus spores in the gastric contents may also be inconclusive. If poisoning by A. phalloides-type mushrooms is suspected, gastric contents, mushroom samples, and stool specimens, if available, should be assayed to verify the presence of the amanitin and phalloidin toxins.

To confirm the diagnosis of mushroom poisoning, we modified a thin-layer chromatographic assay that can rapidly detect the presence of amanitin and phalloidin. (This assay is done in the Toxicology Laboratory at San Francisco General Hospital.) Vomitus, intestinal aspirate, stool or uneaten specimens are dehydrated in a rotovacuum evaporator. Fat is removed by refluxing with benzene in a Soxhlet apparatus. The defatted material is then extracted with methanol. This extract, containing the toxic cyclopeptides, is taken to dryness *in vacuo* and the residue is dissolved in 2 ml of anhydrous methanol. Aliquots of this extract are then spotted on commercially available 0.25 mm silica G-60 thin-layer chromatography plates.

For comparison, extracts prepared from A. phalloides mushroom and 5, 10 and 20 μl of alpha-amanitin and phalloidin (both as 0.1 percent solutions in methanol) are spotted as comparison standards. The thin-layer chromatographic solvent system consists of a mixture of 100 ml of glycol monobutylether, 85 ml concentrated aqueous ammonia and 0.5 ml transcinnamaldehyde. The average time for the solvent front to ascend 12 cm is approximately three hours. The plate while still moist is sprayed with 0.1 percent fluorescamine in methanol. Fluorescamine reacts with the primary amino group of alpha-amanitin to form derivatives that fluoresce as bluish-white spots under ultraviolet light.

These are compared with the standards. The same chromatogram is then sprayed with 0.5 percent transcinnamaldehyde in methanol. The solvent is allowed to evaporate and the chromatogram is exposed for 15 minutes to hydrogen chloride gas. The amanitin and phalloidin appear as bluish- to purplish-colored spots. The chromatogram should be evaluated immediately because the color of the toxins fades rapidly. The solvent system gives average relative distance (rf) values of 0.35 for alpha-amanitin, 0.31 for beta-

amanitin, 0.50 for gamma-amanitin and 0.25 for phalloidin. Alpha-amanitin and phalloidin when applied as pure substances have a minimum detection limit of 50 μg and 80 to 100 μg respectively.

Treatment

Early Modes

No specific treatment of A. phalloides-type poisoning has been available in the past. The only treatment available has been supportive, including correction of fluid, metabolic and coagulation disturbances. Induction of emesis is not beneficial, unless it is done soon after ingestion, because of the long interval between ingestion and the appearance of symptoms. Cathartics and activated charcoal have been recommended,[14] although there is no proof of their usefulness in the treatment of A. phalloides-type poisoning. If used, they should be administered soon after ingestion. Numerous forms of therapy such as exchange transfusion[13] and administration of large doses of corticosteroids[15] or antiphalloidin antisera[16] have been used, but none has been shown to be more effective than supportive care. Hemodialysis has been used successfully to treat renal failure,[12,16-18] but its effectiveness is not attributed simply to the removal of amanitin and phalloidin. These toxins appear to be poorly dialyzable when studied *in vitro;* hemodialysis would not remove them effectively in the poisoning circumstance.

Studies with dogs given up to 0.044 mg of ^{14}C-methyl alpha-amanitin per kg of body weight by intravenous injection showed that after five hours, the concentration in serum fell below detection limit, which is <0.3 percent of the toxin dose administered. After six hours, 85 percent of the radioactivity associated with the toxin could be accounted for in the urine.[19]

Cytochrome C has protected mice given lethal doses of amanitin from symptoms of poisoning.[20] Penicillin, phenylbutazone, chloramphenicol and sulfamethoxazole administered to animals poisoned with amanitin resulted in improved survival rates.[21] It has been suggested that these compounds displace amanitin from plasma albumin binding sites, thus enhancing renal excretion of the cyclopeptide toxin.

Thioctic Acid

During the past ten years, the use of thioctic acid (alpha lipoic acid) in the successful treatment of A. phalloides-type mushroom poisoning has been reported enthusiastically in the European literature.[15,18,22,23] Finestone and co-workers reported the first successful treatment of A. phalloides-type mushroom poisoning with thioctic acid in the United States in 1968.[24,25] In their patient, eight days after ingestion of A. verna, 300 mg of thioctic acid was infused intravenously over 24 hours for three days. After 72 hours, the dosage was tapered over six days and discontinued when the serum transaminase levels returned to normal.

Since 1968, thioctic acid has been used experimentally in the United States in 11 other patients with A. phalloides-type poisoning. A review of these cases shows that in nearly all there was chemical and clinical evidence of hepatocellular damage; ten of the patients recovered without major sequelae (Table 3).

The only side effect of thioctic acid to date has been hypoglycemia. Whether the hypoglycemia was a direct effect of the drug[26,27] or a result of severe hepatic damage[2] secondary to mushroom poisoning remains unclear. To date, the only patient in the United States who did not respond favorably to thioctic acid as far as we know received the drug late in the course,[28] since the patients in all other reports survived when given the drug two to three days after ingestion (except that of Finestone and co-workers[25]). This indicates that early administration may be necessary for the drug to produce its effect.

Results of studies of thioctic acid use in animals in which toxic effects were induced with amanitin are varied. In two studies, administration of thioctic acid failed to reverse the toxic effects[20,26] and in one[26] hypoglycemia occurred. The significance of the hypoglycemia observed in man and animals and the reported lack of effectiveness of thioctic acid in animals need to be studied further.

The investigational drug protocol approved by the Food and Drug Administration for the use of thioctic acid states that it should be used only in known or strongly suspected cases of ingestion of A. phalloides, A. virosa or A. verna mushrooms.[29] Although they are not included in the protocol, G. autumnalis, marginata and venenata contain amanitin, and thioctic acid is appropriate treatment (Table 3) in poisonings by these mushrooms as well.

Initially, 25 mg of thioctic acid in a solution of glucose and water may be infused intravenously four times a day. On the second day, depending on clinical status, the dose may be increased to 75 mg four times a day. This may be continued

for 14 days using findings on daily liver enzyme function tests as a guide. Measurement of serum glutamic oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), lactic dehydrogenase (LDH), creatinine, blood urea nitrogen and glucose levels and urinalysis should be carried out at least once a day and more frequently if necessary. Because thioctic acid is sensitive to light and heat, bottles and infusion lines containing the solution must be covered.

The mechanism of action of thioctic acid in patients with A. phalloides-type poisoning is unclear. Lipoic acid is a component of coenzymes necessary to oxidize ketoacids such as pyruvate. It has been suggested that (1) thioctic acid may produce its protective effect at the level of the enzymes of the Krebs cycle[29] or (2) that the disulfide constituents of thioctic acid form a complex with the cyclopeptides to modify their toxicity.[20,29]

Because of the high morbidity and mortality of A. phalloides-type poisoning, it would seem impossible to conduct a random double-blind clinical study of thioctic acid. While the cases represented here and the three in which we consulted cannot offer unequivocal evidence that thioctic acid was useful, they do show that the agent is safe to administer and apparently contributed to the recovery of these patients despite clinical and chemical evidence of severe liver impairment before it was given (Table 3). However, the contribution of intense supportive care is difficult to assess.

Since the chromatographic assay method now enables specific and definitive diagnosis of A. phalloides-type mushroom poisoning and since thioctic acid lacks significant toxicity, we believe that the use of thioctic acid concomitantly with vigorous supportive treatment in such cases is justified. Except for the occurrence of hypoglycemia, this agent appears to be safe when used properly. Despite the much larger initial dose given in Case 1 and the reported use of this drug for over 13 days in another (Table 3, Case No. 8), no ill effects have been observed. In Case 2, a seven day course of thioctic acid was administered according to the protocol, and the response was impressive.

Reports of Cases

Case 1. A 32-year-old man had been well until March 2, 1973 when nausea, vomiting, fever and severe diarrhea developed 12 hours after he had eaten four large wild mushrooms picked in Fresno County, California. The family physician administered atropine and prochlorperazine, but the nausea and vomiting persisted. The patient was admitted to a local hospital with severe dehydration and oliguria. Laboratory data included SGOT, 2,580; SGPT, 4,420 units per ml; total bilirubin, 1.9 (direct, 1.3 and indirect, 0.6); blood urea nitrogen, 41, and creatinine, 1.9 mg per 100 ml.

The patient was transferred to the University of California Moffitt Hospital in San Francisco, where symptoms of severe hepatic injury continued, although renal function returned toward normal values. Because of strong suspicion that the mushrooms ingested by the patient were A. phalloides-type (subsequently confirmed by chromatographic detection of alpha- and gamma-amanitins and phalloidin at the Toxicology Laboratory of San Francisco General Hospital) informed consent was obtained from the patient to administer thioctic acid.

A total of 300 mg per 24 hours in 10 percent glucose in H_2O were infused intravenously on day three after ingestion. The patient's condition improved and there was resolution of symptoms. By the sixth day of thioctic acid administration, the following values were noted: total bilirubin, 0.8 mg per 100 ml; direct bilirubin, 0.3 mg per 100 ml; SGOT, 40 units, and SGPT, 250 units per ml. Thioctic acid therapy was terminated and the patient was discharged.

Case 2. An 87-year-old man had been in good health until December 16, 1974 when severe nausea, vomiting, profuse diarrhea, and cramping pain of the arms, lower abdomen and legs developed suddenly; he was admitted to a local hospital. The patient 22 hours before had eaten approximately a half cup of mushrooms collected in Santa Clara County. There was no excessive salivation, lacrimation, photophobia or diplopia but the patient was confused and disoriented. He became progressively oliguric and was transferred to the University of California Moffitt Hospital in San Francisco.

On admission, the patient was alert and oriented, but anorectic, nauseated and vomiting occasionally. Prothrombin time was 15.4 seconds (control 11.4) and partial thromboplastin time was 43.7 seconds (control 28.6). The serum creatinine level was 4.4, glucose level was 208 and blood urea nitrogen value was 43 mg per 100 ml. Cooked and uncooked specimens of mush-

rooms collected by the patient were obtained for chromatographic analysis (also done at San Francisco General Hospital's Toxicology Laboratory) and found to contain amanitin and phalloidin.

Treatment with thioctic acid, 25 mg every six hours infused intravenously in 10 percent glucose in H_2O or saline solution, and neomycin, 1 gram per day given orally, was started on day three after ingestion. After 24 hours, the dosage of thioctic acid was increased to 75 mg every six hours. On day two of thioctic acid therapy, levels of blood urea nitrogen decreased to 39 and creatinine to 2.1 mg per 100 ml. The following clinical values were noted: SGOT, 2,160; SGPT, 1,350; LDH, 4,640; alkaline phosphatase, 65 units per ml, bilirubin, 2.3 mg per 100 ml, and prothrombin time, 18.4 seconds (control 11.3). On day seven of thioctic acid therapy, administration of the drug was discontinued because liver function tests had returned to normal values.

On December 23, blood urea nitrogen and serum creatinine levels were 73 and 14.8 mg per 100 ml, respectively; hemodialysis was begun. On December 30, findings on liver function tests had returned to within normal limits except for slight hypoalbuminemia and an elevated alkaline phosphatase level. Dialysis was carried out on three subsequent occasions (January 2, 6 and 10). On January 23, 1975, renal function was stable, with blood urea nitrogen levels varying between 100 and 110 and serum creatinine levels between 7 and 8 mg per 100 ml, and except for a persistently elevated alkaline phosphatase level, findings on liver function tests had returned to the normal range and gastrointestinal bleeding, atrial fibrillation, and pericardial and pleural effusions had successfully resolved; the patient was discharged.

REFERENCES

1. Buck RW: Mushroom toxins—A brief review of the literature. N Engl J Med 265:681-686, Oct 1961

2. Buck RW: Poisoning by wild mushrooms. Clin Med 71:1353-1363, Aug 1964

3. Litten W: The most poisonous mushrooms. Sci Am 232:90-101, Mar 1975

4. Wieland T: Poisonous principles of mushrooms of the genus *Amanita*. Science 159:946-952, Mar 1968

5. Derenzini M, Fiume L, Marinozzi V, et al: Pathogenesis of liver necrosis produced by amanitin-albumin conjugates. Lab Invest 29:150-158, Aug 1973

6. Marinozzi V, Fiume L: Effects of alpha amanitin on mouse and rat liver cell nuclei. Exp Cell Res 67:311-322, Aug 1971

7. Panner BJ, Hanss RJ: Hepatic injury in mushroom poisoning. Electron microscopic observations in two non-fatal cases. Arch Path 87:35-45, Jan 1969

8. Kisilevsky R: Hepatic nuclear and nucleolar changes in *Amanita* poisoning. Arch Path 97:253-258, Apr 1974

9. Myler RK, Lee JC, Hopper J Jr: Renal tubular necrosis caused by mushroom poisoning. Arch Intern Med 114:196-204, Aug 1964

10. Hatfield GM, Brady LR: Toxins of higher fungi. Lloydia 38:36-54, Jan-Feb 1975

11. Abul-Haj SK, Ewald RA, Kazyak L: Fatal mushroom poisoning. Report of a case confirmed by toxicologic analysis of tissue. N Engl J Med 269:223-227, Aug 1963

12. Harrison DC, Coggins CH, Welland FH, et al: Mushroom poisoning in five patients. Am J Med 38:787-792, May 1965

13. Lough J, Kinnear DG: Mushroom poisoning in Canada: Report of a fatal case. Can Med Assoc J 102:858-860, Apr 1970

14. Lampe KF: Current concepts of therapy in mushroom intoxication. Clin Toxicol 7:115-121, 1974

15. Grossman CM, Malbin B: Mushroom poisoning: A review of the literature and report of two cases caused by a previously undescribed species. Ann Intern Med 40:249-259, Feb 1954

16. Elliott W, Hall M, Kerr DNS, et al: Mushroom poisoning. Lancet 2:630-635, Sep 1961

17. Skrabal F, Dittrich P: Death-cap poisoning. Lancet 1:767, Apr 1973

18. Steyn DG: The treatment of cases of *Amanita phalloides* and *Amanita capensis* poisoning. S Afr Med J 40:405-406, May 1966

19. Faulstich H, Fauser U: Untersuchungen Zur Frage der Hämodialyse bei der Knollenblätterpilzvergiftung—Serumspiegel und Ausscheidung von Amanitin. Dtsch Med Wochenschr 98:2258-2259, 1973

20. Floersheim GL: Curative potencies against α-amanitin poisoning by cytochrome c. Science 177:808-809, Sep 1972

21. Floersheim GL: Antidotes to experimental alpha-amanitin poisoning. Nature [New Biol] 236:115-117, Mar 1972

22. Kublicka J, Adler AE: Uber eine neuer Behandlungsmethode der Vergiftung durch den Knollenblätterpilz. Praxis 38:1304-1306, Nov 1968

23. Zulik R, Bakó F, Budavári J: Death-cap poisoning. Lancet 2:228, Jul 1972

24. Culliton BJ: The destroying angel: A story of a search for an antidote. Science 185:600-601, Aug 1974

25. Finestone AJ, Berman R, Widmer B, et al: Thioctic acid treatment of acute mushroom poisoning. Pa Med 75:49-51, Jul 1972

26. Alleva FR: Thioctic acid and mushroom poisoning. (Letters). Science 187:216, Jan 1975

27. Bartter FC: Thioctic acid and mushroom poisoning. (Letters). Science 187:216, Jan 1975

28. Passo B, Harrison DC: A new look at an old problem: Mushroom poisoning—Clinical presentations and new therapeutic approaches. Am J Med 58:505-509, Apr 1975

29. Bartter F: Fact Sheet on Thioctic Acid. (IND # 9957) National Heart and Lung Institute, Jul 1974, p 1