CHAPTER 113

Mushrooms

Lewis R. Goldfrank

A 58-year-old woman presented to the emergency department (ED) with severe, crampy, abdominal pain and profuse diarrhea. She had spent the summer morning picking wild mushrooms in a local park, as she had done for many years. She found numerous edible species and ate quite a few while picking them. Her symptoms began within 1 hour of returning from the park.

She explained that she was an expert in selecting edible mushrooms, that she picked at the same place every year, and that she never previously had trouble. Prior to coming to the United States she had foraged in the woods of Poland for years without difficulty. She insisted that the mushrooms could not be at fault because they were found growing on dead wood and that slugs had mutilated several of the mushrooms.

The patient had no known allergies and did not drink alcohol. No other family members had been ill recently. Physical examination revealed a pale, diaphoretic, dyspneic, and anxious woman who was persistently gagging. Her vital signs were: blood pressure, 110/60 mm Hg; pulse, 120 beats/min supine; respiratory rate, 24 breaths/min; temperature 98.6°F (37°C).

The patient's head was atraumatic. Her pupils were 4 mm, equal, and reactive. Sclerae were anicteric; and conjunctivae were pink. Her mucosa was moist with no excessive lacrimation or salivation, and her throat was unremarkable. There were no cutaneous abnormalities. Lungs were clear, heart sounds were normal, and abdominal examination revealed diffuse tenderness with hyperactive bowel sounds. Liver and spleen were unremarkable. The extremities were normal.

The patient was vehemently resistant to the suggestion that she stay in the hospital. However, her dizziness upon standing convinced her to remain. Blood samples were drawn, and an IV was started with 0.9% sodium chloride solution at 300 mL/h. The patient was admitted for observation and volume repletion.

As the patient prepared herself for admission, she gave her belongings and clothing to her daughter. At that point the staff noticed a large bag filled with mushrooms. The patient was so convinced of the quality of these mushrooms that she wanted to give them to her daughter to take home, but eventually she was persuaded to leave the mushrooms in the ED for further examination.

Her hematocrit was 42%, white blood cell count (WBC) was 8300/mm^3 (72% polymorphonuclear leukocytes, 20% lymphocytes, 4% monocytes, 4% eosinophils), and prothrombin time was 13 seconds. Blood glucose was 220 mg/dL; blood urea nitrogen (BUN) was 21 mg/dL; sodium was 140 mEq/L; potassium was 3.7 mEq/L; chloride was 101 mEq/L; and bicarbonate was 30 mEq/L. The chest radiograph was normal, and abdominal radiographs showed a nonspecific ileus pattern.

Despite the patient's certainty that the mushrooms were edible, her presentation persuaded the staff to have the mushrooms investigated. Microscopic spore assessment methods to identify toxic mushrooms conducted by a mycologist confirmed that the patient had mistakenly picked the jack-o'-lantern (*Omphalotus illudens*), an orange, bioluminescent mushroom,[3] believing it was the edible species of chanterelle (*Cantharellus cibarius*). This error is frequently reported.[38,92]

EPIDEMIOLOGY

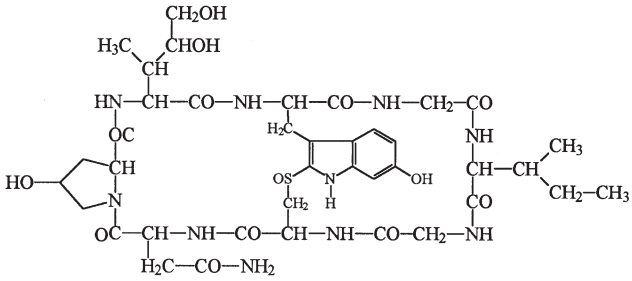
Unintentional exposures to mushrooms represent a small but relatively constant percentage of consultations requested from Poison Control Centers (see citations for American Association of Poison Control Centers [AAPCC] data in Chap. 130) A summary of the 19 years of AAPCC data reveals that mushrooms represent less than 0.5% of the reported exposures to poisons. Combined data accumulated by the AAPCC and the Mushroom Poisoning Registry of the North American Mycological Association indicates that approximately 5 patient exposures to toxic mushrooms per 100,000 population occur per year. Some variations result from geographic and climatic conditions and mycologic habitats.[90] Although the methods of analysis of patients with mushroom exposures have changed over the past 19 years, cumulative AAPCC Toxic Exposure Surveillance System (TESS) data consistently demonstrate the relative benignity

of the vast majority of exposures. The inability of most healthcare providers to correctly identify the ingested mushroom and the rarity of lethal ingestions are demonstrated by the accumulated data. In more than 95% of cases, the exact species was unidentified,[90] and only approximately 10% of the mushroom groups ingested were known. More than 50% of exposed individuals had no symptoms. Twenty-five percent of the patients were treated in healthcare facilities annually; of these 10–15% had minor toxicity, less than 5% had moderate toxicity, and approximately 0.3% had major toxicity. During the 19-year period covered by TESS, only 22 of the patients died of their ingestions. Of the mushrooms associated with a death, 14 probably were *Amanita* spp, 2 hallucinogens, 1 *Boletus* spp, 1 presumed gyromitrin-containing mushroom, and 4 unidentified. All reported deaths occurred in adults. Of the mushroom groups identified in intentional abuse and poisonings, hallucinogens and gastrointestinal (GI) toxins were the most common, yet accounted for less than 10% of ingestions. All other groups represented less than 2% of the total number of identified. Because 90% of mushrooms involved in exposures are never identified, a strategy for making significant decisions with incomplete data is needed.

CLASSIFICATION AND MANAGEMENT

Because mushroom species vary widely with regard to the toxins they contain and because identifying them with certainty is difficult, a clinical system of classification is more useful than a taxonomic system (Table 113–1). In many cases, management and prognosis can be determined with a high degree of confidence from the history and initial symptoms.[41,54,55] Ten groups of toxins are identifiable: cyclopeptides, gyromitrin, muscarine, coprine, ibotenic acid and muscimol, psilocybin, general GI irritants, orellinine, allenic norleucine, and myotoxins.[41,54]

Group I: Cyclopeptide-Containing Mushrooms



α-Amanitin

Most mushroom fatalities in North America and worldwide are associated with cyclopeptide-containing species.[4,24,102] These mushrooms include a number of *Amanita* species, including *A. verna, A. virosa*, and *A. phalloides*, *Galerina* spp, including *G. autumnalis, G. marginata,* and *Galerina venenata*, and *Lepiota* species, including *L. helveola, L. josserandi,* and *L. brunneoincarnata*. (See ILAMANITAPHALLOIDS and ILAMANITAVIROSA in the Image Library at goldfrankstoxicology.com)

Early differentiation of cyclopeptide poisonings from other types of mushroom poisoning is difficult. Patients poisoned with cyclopeptides may present to an ED with a seemingly innocuous picture of nausea, vomiting, abdominal pain, and diarrhea, which often is attributed to other causes. Such patients may be sent home, only to return moribund on a subsequent day. The delayed onset of more serious symptoms is typical of cyclopeptide poisoning and is a critical consideration in assessing any potential poisoning.

Amanita phalloides contains 15–20 cyclopeptides with an approximate weight of 900 daltons. The amatoxins (cyclic octapeptides), phallotoxins (cyclic heptapeptides), and virotoxins (cyclic heptapeptides) are the best studied.[27,51,97] Of these three chemically similar cyclopeptide molecules, phalloidin (the principal phallotoxin) appears to be a rapid-acting toxin, whereas amanitin tends to cause more delayed manifestations.[79] Phalloidin crosses the sinusoidal plasma membranes of hepatocytes by a carrier-mediated process. This process is shared by bile salts and can be prevented in the presence of extracellular bile salts, suggesting a competitive inhibition. A sodium-independent bile salt transporting system may be responsible for phalloidin hepatic uptake, elimination, and detoxification.[61] Phalloidin interrupts actin polymerization and impairs cell membrane function, but because of its limited oral absorption it appears to have minimal toxicity, restricted mostly to GI dysfunction. There is no evidence for the toxicity of virotoxins in humans.

The amatoxins appear to be the most toxic of the cyclopeptides, leading to hepatic, renal, and central nervous system (CNS) damage. These polypeptides are heat stable, insoluble in water, and lose activity over a period of years upon desication.[27] α-Amanitin is the principal amatoxin responsible for human toxicity following ingestion. Approximately 1.5–2.5 mg amanitin can be obtained from 1 g dry *A. phalloides,* and as much as 3.5 mg/g can be obtained from some *Lepiota* spp.[66,70,97] A 20-g mushroom contains well in excess of the 0.1 mg/kg amanitin considered lethal for humans.[25]

α-Amanitin absorption appears to be facilitated by a sodium-dependent bile acid transporter. Several studies demonstrate that the sodium taurocholate cotransporter polypeptide facilitates hepatocellular α-amanitin uptake.[40] In vitro studies show that α-amanitin is cytotoxic based on its interference with RNA polymerase II, preventing the transcription of DNA.[59,83] The LD_{50} of α-amanitin in mice is 0.1–0.75 mg/kg, and the LD_{50} of β-amanitin in mice is 0.2–0.4 mg/kg,[25] suggesting the two amanitins have comparable toxicity.

In animals, cimetidine (a potent cytochrome P450 system inhibitor) may have a hepatoprotective effect against α-amanitin by inhibiting metabolism,[77] but it shows no protective effect against phalloidin toxicity.[79] Cimetidine is proposed as a therapeutic intervention,[78] but no available human data support its use. The amanitins are poorly but rapidly absorbed from the GI tract,[45] and α-amanitin may be enterohepatically recirculated. Target organs are those with the highest rate of cell turnover, including the GI tract epithelium, hepatocytes, and kidneys. Amatoxins do not appear to cross the placenta, as demonstrated by the absence of fetal toxicity in severely poisoned pregnant women.[6,11,88]

Amatoxins show limited protein binding and are present in the plasma at low concentrations for 24–48 hours.[45] In an intravenous radiolabeled amatoxin study in dogs, 85% of the amatoxin was recovered in the urine within the first 6 hours, whereas <1% was found in the blood at that time.[26] Amatoxins can be detected by high-performance liquid chromatography,[45] thin-layer chromatography, and radioimmunoassay in gastroduodenal fluid,

TABLE 113–1. Mushroom Toxicity

Genus/Species	Toxin	Time of Onset of Symptoms	Primary Site of Toxicity	Symptoms	Mortality	Specific Therapy[a]
I.						
Amanita phalloides, A. tenuifolia, A. virosa *Galerina autumnalis G. marginata, G. venenata* *Lepiota josserandi, L. helveola*	Cyclopeptides Amatoxins Phallotoxins	5–24 h	Hepatic	Phase I: GI toxicity-N V D Phase II: Quiescent, Phase III: Gastroenteritis, jaundice, ↑ AST, ↑ ALT	10–30%	Activated charcoal Hemoperfusion Penicillin G Silibinin
II.						
Gyromitra ambigua, G. esculenta, G. infula	Gyromitrin (metabolite: monomethylhydrazine)	5–10 h	CNS	Seizures, abdominal pain, N/V, weakness, hepatorenal failure	Rare	Benzodiazepines, Pyridoxine, 70 mg/kg IV
III.						
Clitocybe dealbata, Omphalotus olearius Most *Inocybe* spp	Muscarine	0.5–2 h	Autonomic nervous system	Muscarinic effects-salivation, bradycardia, lacrimation, urination, defecation, diaphoresis	Rare	Atropine: Adults: 1–2 mg Children: 0.02 mg/kg with a minimum of 0.1 mg
IV.						
Coprinus atramentarius	Coprine (metabolite: 1-aminocyclopropanol)	0.5–2 h	Aldehyde dehydrogenase	Disulfiramlike effect with ethanol, tachycardia, N/V	Rare	—
V.						
Amanita gemmata, A. muscaria, A. pantherina	Ibotenic acid, muscimol	0.5–2 h	CNS	GABAergic effects, rare delirium, hallucinations, dizziness, ataxia	Rare	Benzodiazepines during excitatory phase
VI.						
Psilocybe caerulipes, P. cubensis *Gymnopilus spectabilis* *Psathyrella foenisecii*	Psilocybin, psilocin	0.5–1 h	CNS	Ataxia, N/V, hyperkinesis, hallucinations	Rare	Benzodiazepines
VII.						
Clitocybe nebularis *Chlorophyllum molybdites, C. esculentum,* *Lactarius* spp *Paxillus involutus*	Various GI irritants	0.5–3 h	GI	Malaise, N/V/D	Rare	—
VIII.						
Cortinarius orellanus, C. speciosissimus, C. rainierensis	Orelline, orellanine	>24 h Days-weeks	Renal	Phase I: N/V Phase II: Oliguria, renal failure	Rare	Hemodialysis for renal failure
IX.						
Amanita smithiana	Allenic norleucine	0.5–12 h	Renal	Phase I: N/V Phase II: Oliguria, renal failure	None	Hemodialysis for renal failure
X.						
Tricholoma equestre	Unidentified myotoxin	24–72 h	Muscle (skeletal and cardiac)	Fatigue, nausea, muscle weakness, myalgias (↑CPK), facial erythema, diaphoresis, myocarditis	25%	—

D = diarrhea; N = nausea; V = vomiting.

[a]Supportive care (fluids, electrolyes, and antiemetics) as indicated.

Adapted, with permission, from Lincoff G, Mitchel DH: Toxic and Hallucinogenic Mushroom Poisoning: A Handbook for Physicians and Mushroom Hunters. New York, Van Nostrand Reinhold, 1977, pp. 246–247.

serum, urine, stool, and liver and kidney biopsies for several days following an ingestion.[25,27,50]

Some of the toxicokinetic analyses following unquantified ingestions demonstrate 12–23 μg amatoxin excretion in the urine over 24–66 hours, of which 60–80% occurred during the first 2 hours of collection. The extreme variabilities of the type and quantity of ingestant, the host, and the management make interpretations exceedingly difficult.[93] In another series, total maximal urinary α- and β-amanitin excreted over 6–72 hours were 3.19 and 5.21 mg, respectively. Two thirds of the patients had total amanitin toxin excretion >1.5 mg.[45] Urinary amanitin excretion concentrations differ by several orders of magnitude. Whether the variation results from exposure dose, time following ingestion, or laboratory technique is unclear. Several techniques for evaluating urinary amanitin presence qualitatively and quantitatively are under investigation. The sensitivity and specificity of these determinations are under investigation.[14,15,70,87] Most studies suggest that no circulating amatoxins are present by the time the need for transplantation is evident.[23]

Clinical. Phase I of cyclopeptide poisoning resembles severe gastroenteritis, with profuse watery diarrhea not occurring until 5–24 hours after ingestion. Supportive fluid and electrolyte replacement leads to transient improvement during phase II, which occurs between 12 and 36 hours after ingestion.[70,102] However, despite such supportive care, phase III, manifested by hepatic and renal toxicity and death, may ensue 2–6 days after ingestion.[4] Pancreatic toxicity may rarely occur.[32] The initial hepatotoxicity begins within the second phase, but clinical hepatotoxicity (Chap. 26) with elevated concentrations of bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), hypoglycemia, jaundice, and coma are not manifest until 2–3 days after ingestion. Pathologic manifestations include steatosis, central zonal necrosis, and centrilobular hemorrhage, with viable hepatocytes remaining at the rims of the larger triads. Lobular architecture remains intact.[4]

Cyclopeptide poisoning alters the hormones that regulate glucose, calcium, and thyroid homeostasis, resulting in widespread endocrine abnormalities.[48] Insulin and C-peptide concentrations are elevated at a stage of poisoning prior to hepatic and renal compromise.[22,48] These findings are suggestive of direct toxicity to pancreatic β cells, resulting in release of preformed hormone or induction of hormone synthesis. This insulin release necessitates vigilance for hypoglycemia prior to hepatocellular damage. Serum calcitonin concentrations may be elevated, and hypocalcemia may be present. Thyroxine concentrations may be depressed and triiodothyronine concentrations undetectable, whereas thyroid-stimulating hormone concentrations may not be elevated. These thyroid-related findings were reported in a single study and merit further investigation.[48]

In a series of 10 patients poisoned by diverse *Lepiota* spp, 50% developed a mixed sensory and motor polyneuropathy. Most of the patients spontaneously recovered within 1 year, although a single patient developed progressive clinical and electromyographic deterioration.[72] These neuropathic findings have not been recognized in other case reports.

Treatment. The search for treatments has been vigorously pursued in Europe because of the persistently large number of amatoxins victims each year.[31] Thioctic (α-lipoic) acid initially was reported to be beneficial in treating the amatoxin-induced liver toxicity in several different animal models, and a number of uncontrolled clinical trials in humans followed.[4] Because of its potential effects as a coenzyme in the tricarboxylic acid cycle or as a free radical scavenger, thioctic acid, was credited for the survival of 39 of 40 patients reportedly poisoned by *A. phalloides*.[52] Hypoglycemia is a common feature of thioctic acid therapy for *Amanita* poisoning, but whether hypoglycemia results from direct toxicity of the drug or is secondary to hepatic damage is not clear.

Despite the initial success, thioctic acid was not effective in various other studies.[33,34] Survival rates of patients poisoned by *A. phalloides* who received any of the following: supportive care, fluid and electrolyte repletion, high-dose penicillin G, dexamethasone, and thioctic acid are between 70% and 90%.[31,44,63,64,102]

Several laboratory investigations in mice and rats suggest that 1 g/kg penicillin G (1 g = 1,600,000 units) may have a time- and dose-dependent protective effect.[35,36] These results are limited because the amatoxins were administered intraperitoneally, resulting in the death of untreated animals 12–24 hours later. Additional investigations demonstrated that 1 g/kg penicillin G administered 5 hours after sublethal doses of α-amanitin decreased clinical and laboratory toxicity.[35] The mechanisms suggested include displacing α-amanitin from albumin, blocking its uptake from hepatocytes, binding circulating amatoxins, and preventing α-amanitin binding to RNA polymerase. None of these mechanisms is substantiated. Although the hepatoprotective effects of penicillin remain unclear,[24] a dose of 1,000,000 units of penicillin G/kg/d IV is recommended as safe and possibly efficacious.[49,50,81]

The active complex of milk thistle (*Silybum marianum*) is silymarin, which is a lipophilic extract composed of 3 isomeric flavonolignans: silibinin, silychristin, and silydianin. Silibinin represents approximately 50% of the extract, but is 70–80% of the marketed product.[43] Silibinin may modify or occupy cell membrane receptor sites, thereby inhibiting hepatocellular penetration by α-amanitin. Use of silibinin 50 mg/kg in dogs, 5 and 24 hours following exposure to α-amanitin, suppressed chemical evidence of hepatotoxicity and lethality. Although silibinin is routinely available in health food stores and appears to be safe and well tolerated in patients with chronic liver disease, no reduction in mortality, improvement in histology at liver biopsy, or biochemical marker has been identified in a systematic review and meta-analysis.[43] Silibinin 20–50 mg/kg/d is recommended for use in humans, even though this xenobiotic is not approved by the FDA for use in the United States.[50,96] Activated charcoal both adsorbs the amanitins and improves survival in laboratory animals.[25] Emesis, lavage, and catharsis are not necessary unless the patient is seen shortly after the ingestion, because the toxin usually induces emesis and catharsis. Activated charcoal is safe, logical, and a valuable therapeutic strategy. Although the clinical presentation often is delayed, 1 g/kg body weight of activated charcoal should be given orally every 2–4 hours (if the patient is not vomiting) or by continuous nasogastric infusion. Fluid and electrolyte repletion and treatment of hepatic compromise are essential. Intravenous 0.9% sodium chloride solution and electrolytes usually are necessary because of substantial fluid loss due to vomiting and diarrhea. Dextrose repletion may be necessary because of nutritional compromise, hepatic failure, or glycogen depletion. Because of its hepatoprotective effects, *N*-acetylcysteine is also suggested as an antidote, but no evidence for any specific benefit has been demonstrated.

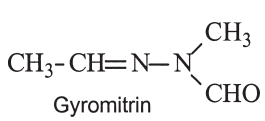
Forced diuresis, hemodialysis, plasmapheresis,[46,47] hemofiltration, and hemoperfusion[29] may be effective shortly after ingestion, but most studies neither offer clinical evidence of benefit nor supportive

pharmacokinetic data for any of these therapies.[50,69,70,93,95] Plasmapheresis, which is dependent on effective clearance, high plasma protein binding, and a low volume of distribution, does not remove more than 10 μg amatoxin. Because of the absence of prospective controlled studies of exposure to amatoxins in addition to the extreme variability of success with many regimens, multiple-dose activated charcoal and supportive care remain the standard therapy. Early recognition of exposure to amanitin is an indication for hemoperfusion, but most patients likely will not have the potential for benefit at the time they develop clinical manifestations of toxicity.[47] Future therapeutic interventions may be dependent on improved understanding of the hepatocellular bile acid transporter system.[40,53]

Extracorporal albumin dialysis[28] and molecular absorbent regenerating system[19] are variant detoxification techniques used in patients with fulminant hepatic failure to remove water soluble and albumin bound toxins while providing renal support. These two techniques permit time for hepatic regeneration or sufficient bridging time to orthotopic liver transplantation. The criteria and timing for liver transplantation in this setting are far less established than for fulminant viral hepatitis, where grade III or IV hepatic encephalopathy, marked hyperbilirubinemia, and azotemia are the well-established criteria for transplantation[68] (Chap. 26). When fulminant hepatic failure is present, *N*-acetylcysteine should be administered until the patient recovers from the encephalopathy because of its presumptive benefits under these circumstances (Antidotes in Depth: *N*-Acetylcysteine). Successful transplantations were performed in individuals whose resected livers showed 0–30% hepatocyte viability. In these cases, the authors did not wait for progression past grade II encephalopathy or for development of azotemia or marked hyperbilirubinemia.[68] Criteria for patient selection are essential to avoid unnecessary risk while offering the potential for survival to appropriate candidates who have no functional liver. The grim prognosis associated with hepatic coma secondary to *Amanita* poisoning has led several transplant groups to consider hepatic transplantation for encephalopathic patients with prolonged INRs, persistent hypoglycemia, metabolic acidosis, increased concentrations of serum ammonia and AST, and hypofibrinogenemia.[39,49,68] There are now case reports of successful liver transplantation for fulminant hepatic failure from presumed *Amanita ocreata,*[49,101] *A. phalloides*[45,68] *Amanita vivosa,* [13] *Lepiota helveola,*[62] and *Lepiota brunneoincarnata* poisoning.[72]

To enhance the likelihood of success, several authors suggest that individuals who manifest symptoms suggestive of hepatotoxic *Amanita, Galerina,* or *Lepiota* spp exposure should be told of the potential need for transplantation and, with their consent, rapidly transferred to a regional liver transplantation center.

Group II: Gyromitrin-Containing Mushrooms



Gyromitrin

Members of the gyromitrin group include *G. esculenta, G. californica, G. brunnea*, and *G. infula. Gyromitra esculenta* is a good example of a mushroom with a "Jekyll and Hyde" personality, enjoying a reputation of being edible in the western United States but of being poisonous in other areas. These mushrooms are found commonly in the spring under conifers and are easily recognized by their brainlike appearance. Poisonings with these mushrooms are exceptionally uncommon in the United States, representing <1% of all recognized events, whereas these poisonings are considered more common in Europe. Certain cooking methods may eliminate the toxin, but inhalation of the fumes while cooking may cause poisoning. Because of the potential for toxicity, all members of this mushroom family should be avoided. The most common error occurs in the spring, when an individual seeking the nongilled brainlike *Morchella esculenta* (morel) finds the similar *Gyromitra esculenta* (false morel). (See ILGYROMETRA in the Image Library.)

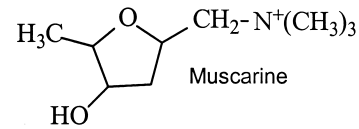
Gyromitra mushrooms contain gyromitrin (*N*-methyl-*N*-formyl hydrazone), which on hydrolysis splits into acetaldehyde and *N*-methyl-*N*-formyl hydrazine. Gyromitrin is unstable and therefore unlikely to exist in its free form. Subsequent hydrolysis, yields monomethylhydrazine (CH_3NHNH_2). The hydrazine moiety reacts with pyridoxine, resulting in inhibition of pyridoxal phosphate-related enzymatic reactions. This interference with pyridoxal phosphate disrupts the function of the inhibitory neurotransmitter γ-aminobutyric acid (GABA).[54] The implications of this decrease in GABA, which is thought to contribute to intractable seizures associated with isoniazid or gyromitrin toxicity in a fashion identical to isoniazid toxicity, is discussed in Antidotes in Depth: Pyridoxine.

The initial signs of toxicity for these mushrooms occur 5–10 hours after ingestion and include nausea, vomiting, diarrhea, and abdominal pain. Patients manifest headaches, weakness, and diffuse muscle cramping. Most patients improve dramatically and return to normal function within several days. Rarely, early in the clinical course patients develop delirium, stupor, convulsions, and coma. Infrequently, patients develop a hepatorenal syndrome and require extensive in-hospital care.

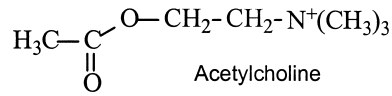
Activated charcoal 1 g/kg body weight should be given. Benzodiazepines such as diazepam or lorazepam are appropriate for initial management of seizures. Under most circumstances, supportive care is adequate treatment. Pyridoxine in doses of 70 mg/kg IV may be useful in limiting seizures (Antidotes in Depth: Pyridoxine).

There are no rapid diagnostic strategies in the laboratory, although thin-layer chromatography, gas-liquid chromatography, and mass spectrometry can be used for subsequent (delayed) identification of the various hydrazine and hydrazone metabolites.

Group III: Muscarine-Containing Mushrooms



Muscarine



Acetylcholine

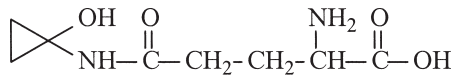
Mushrooms that contain muscarine include numerous members of the *Clitocybe* genus, such as *C. dealbata* (the sweater) and *C. illudens* (*Omphalotus olearius*), and the *Inocybe* genus, that in turn include *I. iacera* and *I. geophylla. Amanita muscaria* and *Amanita pantherina* contain limited quantities of muscarine. (See ILCLITOCYBEDEALBATA and ILOMPHALOTUSOLEARIUS in the Image Library.)

Muscarine and acetylcholine are similar structurally and have comparable clinical effects at the muscarinic receptors. Peripheral manifestations typically include bradycardia, miosis, salivation, lacrimation, vomiting, diarrhea, bronchospasm, bronchorrhea, and micturition. Central muscarinic manifestations do not occur because muscarine, a quaternary ammonium compound, does not cross the blood–brain barrier (Chap. 14). No nicotinic manifestations occur.

The effects of muscarine often last longer than those of acetylcholine. Because muscarine lacks an ester bond, it is not susceptible to acetylcholinesterase hydrolysis. Clinical manifestations, which typically are mild, usually develop within 0.5–2 hours and last several additional hours. Significant toxicity is uncommon, limiting the need for more than supportive care. Rarely, atropine (1–2 mg given IV slowly for adults or 0.02 mg/kg with a minimum of 0.1 mg IV for children) can be titrated and repeated as frequently as indicated to reverse symptomatology.

No current, clinically available, analytic techniques can identify muscarine, although high-performance liquid chromatography would be appropriate for investigative purposes.

Group IV: Coprine-Containing Mushrooms

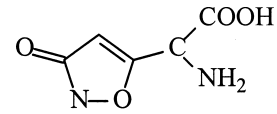


Coprine

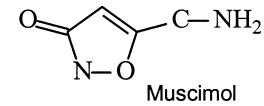
1-Aminocyclopropanol

Coprinus mushrooms, particularly *C. atramentarius,* contain the toxin coprine. (See ILCOPRINUSATRAMENTARIUS in the Image Library.) These mushrooms grow abundantly in temperate climates in grassy or woodland fields. They are known as "inky caps" because the gills that contain a peptidase autodigest into an inky liquid shortly after picking. The edible member of this group, *Coprinus comatus* (shaggy mane) is nontoxic, and probably its misidentification results in collectors' errors. Coprine, an amino acid, its primary metabolite, 1-aminocyclopropanol,[17,60,89] or, more likely, a secondary in vivo hydrolytic metabolite, cyclopropanone hydrate, has a disulfiramlike effect.[100] Although both of these metabolites appear to inhibit aldehyde dehydrogenase, the most stable in vivo inhibitory effect is present in cyclopropane hydrate.[100] Inhibition of acetaldehyde dehydrogenase results in buildup of acetaldehyde and its accompanying adverse effects, which occur if the patient ingests alcohol concomitantly or for as long as 48–72 hours after the mushroom ingestion. Within 0.5–2 hours of ethanol ingestion, an acute disulfiram effect is noted, with tachycardia, flushing, nausea, and vomiting. Interestingly, alcohol ingested simultaneously does not result in clinical manifestations because inhibition of aldehyde dehydrogenase is slightly delayed during coprine metabolism. Treatment is symptomatic with fluid repletion and antiemetics such as metoclopramide, although clinical manifestations usually are mild and resolve within several hours. Prophylactic use of fomepizole immediately following ingestion of ethanol and coprine-containing mushrooms has a theoretical basis, but no case reports or studies are published. This group of mushrooms rarely causes fatalities (disulfiram is discussed further in Chap. 77).

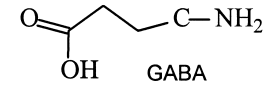
Group V: Ibotenic Acid- and Muscimol-Containing Mushrooms



Ibotenic acid



Muscimol



GABA

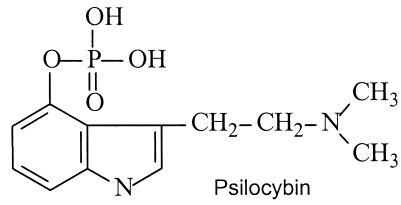
Most of the mushrooms in this class are primarily in the *Amanita* genus, which includes *A. muscaria,* (fly agaric) *A. pantherina,* and *A. gemmata*. (See ILAMANITAMUSCARIA1, ILAMANITAMUSCARIA2 and ILAMANITAMUSCARIA3 in the Image Library.) They exist singly and are scattered throughout the US woodlands. The brilliant red or tan cap (pileus) is that of the mushroom commonly depicted in children's books and is easily recognized in the fields during summer and fall.

Small quantities of the isoxazole derivatives ibotenic acid and muscimol are found in these mushrooms, which have been used in religious customs throughout history. Ibotenic acid is structurally similar to the stimulatory neurotransmitter glutamic acid. The stereochemistry of muscimol is very similar to that of the neurotransmitter GABA and may act as a GABA agonist.

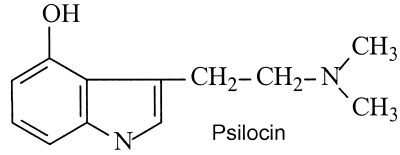
Most patients who develop symptoms intentionally ingested large quantities of these mushrooms while seeking an hallucinatory experience. Within 0.5–2 hours of ingestion, these compounds produce the GABAergic manifestations of somnolence, dizziness, hallucinations, dysphoria, and delirium in adults, whereas the excitatory glutamatergic manifestations of myoclonic movements, seizures, and other neurologic findings predominate in children.[7]

Treatment is invariably supportive. Most symptoms respond solely to supportive care, although a benzodiazepine such as diazepam or lorazepam is appropriate for excitatory CNS manifestations.

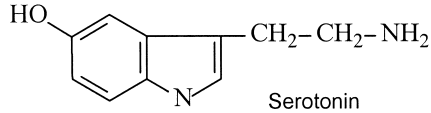
Group VI: Psilocybin-Containing Mushrooms



Psilocybin



Psilocin



Serotonin

Psilocybin-containing mushrooms include *Psilocybe caerulescens, Psilocybe cubensis*, *Conocybe cyanopus*, *Panaeolus foenisecii*, *Gymnopilus spectabilis,* and *Psathyrella foenisecii.* (See ILPSILOCYBECYANESCENS, ILPSILOCYBECAERULIPES, and ILGYMNOPILUSSPECTABILIS in the Image Library.) These mushrooms have been used for native North and South American religious experiences for thousands of years. They grow abundantly in warm, moist areas of the United States. Drug culture magazines and Internet sources advertise mail-order kits containing *P. cubensis* spores to grow "magic mushrooms" domestically.

Toxicity from this group is common because of the popularity of hallucinogens.[9] The quality, quantity, and variety of mushroom ingested may or may not be related to the hallucinogenic effects. Psilocybin is rapidly and completely hydrolyzed to psilocin in vivo. Serotonin, psilocin, and psilocybin are very similar structurally and presumably act at a similar 5-HT_2 receptor site. The effects of psilocybin as a serotonin agonist and antagonist are discussed in Chaps. 14 and 80.

The psilocybin and psilocin indoles, like those of lysergic acid diethylamide (LSD), rapidly (within 1 hour of ingestion) produce CNS effects, including ataxia, hyperkinesis, visual hallucinations, and illusions.[42] Rare cases of renal failure,[37,71] seizures, and cardiopulmonary arrest[9] are associated with psilocybin-containing species. However, such associations should always be questioned when reported in a substance-using population potentially simultaneously exposed to other toxins.

Some patients manifest tachycardia, anxiety, hallucinations, tremor, agitation, and mydriasis. Anxiety and light-headedness may develop quite rapidly (<1 hour), and most manifestations are recognized within 4 hours of ingestions with a return to normalcy within 6–12 hours. A single patient who intravenously administered an extract of *Psilocybe* mushrooms experienced chills, weakness, dyspnea, headache, severe myalgias, vomiting associated with hyperthermia, hypoxemia, and mild methemoglobinemia.[20]

Treatment for hallucinations usually is supportive, although a benzodiazepine such as diazepam or lorazepam may be necessary when reassurance proves inadequate.

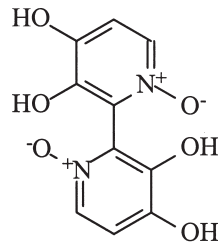
Group VII: Gastrointestinal Toxin-Containing Mushrooms

By far the largest group of mushrooms is a diverse group that contains a variety of ill-defined GI toxins. Many of the hundreds of mushrooms in this group fall into the "little brown mushroom" category. Some *Boletus*, *Lactarius* spp, *Omphalotus olearius*, *Rhodophyllus* spp, *Tricholoma* spp, *Chlorophyllum molybdites*, and *Chlorophyllum esculentum* are mistaken for edible or hallucinogenic species. (See ILRUSSULAEMETICA and ILCHLOROPHYLLUMMOLYBDITES in the Image Library.) The toxins associated with this group are not identified. The malabsorption of proteins and sugars such as trehalose and the ingestion of a mushroom infected or partially digested by microorganisms or allergy may be responsible for symptoms. GI toxicity occurs 0.5–3 hours after ingestion when epigastric distress, malaise, nausea, vomiting, and diarrhea are evident. Treatment with regard to fluid resuscitation, vomiting, and diarrhea is supportive. The clinical course is brief and the prognosis excellent.

Others have described a *Paxillus* syndrome, which may be associated with involutin, one of the constituents of *Paxillus.*[50] A small number of patients with ingestions of *Paxillus involutus*, and possibly *Clitocybe claviceps* and *Boletus luridus,* develop a mild GI syndrome followed by an immune-mediated hemolytic anemia, hemoglobinuria, oliguria, and renal failure. IgG antibodies to a *Paxillus* extract were detected by a hemagglutination test in these patients.[98,99]

Rarely, clinical presentations are life threatening, with hypovolemic shock necessitating fluids and vasopressors.[84] Resolution of symptoms usually occurs within 6–24 hours. The clinical courses associated with specific mushroom ingestions are variable.[7] Death is rare.

Group VIII: Orellanine-and Orellinine-Containing Mushrooms



Orellanine

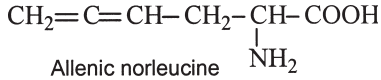
Cortinarius mushrooms, such as *Cortinarius speciosissimus.* (See ILCORTINARIUSSPELIOSISSIMUS in the Image Library.) and *Cortinarius orellanus,* are commonly found throughout Europe. *Cortinarius rainierensis* is a common North American species.[16,80] The *C. orellanus* toxin orellanine is reduced by photochemical degradation to orellinine, another bipyridyl agent that is further reduced to the nontoxic orelline.[2,65,74] The toxic compound orellanine is a hydroxylated bipyridine compound activated by its metabolism through the P450 system. Toxicologically, these molecules are similar to paraquat and diquat and may have comparable mechanisms of action, although precise knowledge is limited (Chap. 111). Other nephrotoxins, such as cortinarines, are isolated from certain *Cortinarius* species[87] and result in tubular damage, interstitial nephritis, and fibrosis.

Initial symptoms occur 24–36 hours after ingestion and include headache, chills, polydipsia, anorexia, nausea, vomiting, and flank and abdominal pain. The largest case review demonstrated that numerous patients repetitively ingested the *Cortinarius* spp prior to diagnosis.[21] Oliguric renal failure may develop several days to weeks after initial symptoms.[10] The only initial laboratory abnormalities may be hematuria, leukocyturia, and proteinuria. Nephrotoxicity is characterized by interstitial nephritis with tubular damage and early fibrosis of injured tubules with relative glomerular sparing.[16,80] Hepatotoxicity is rarely reported.[10] Hemoperfusion, hemodialysis, and renal transplantation are used for treatment.[10,21] No evidence suggests that secondary detoxification by plasmapheresis or hemoperfusion is of any benefit in preventing chronic renal failure even when initiated in the first 48 hours.[21,50,73] The data are inadequate to define management or prognosis precisely, as many patients improve rapidly, while some require acute hemodialysis and others require chronic therapy for renal failure.[10] No laboratory or clinical parameters to assist in predicting the individual reactions to the toxins are available. Although case reports in the literature commonly lack definitive proof of ingestion or confirmation of toxin presence, the more

rapid the onset of GI and renal manifestations, the greater the risk of both acute and chronic renal failure appear to be.[21]

Orellanine is rapidly removed from the plasma within 48–72 hours and concentrated in the urine in a soluble form. It can be detected in the plasma at the time of clinical symptoms by some investigators[73] but not by other investigators.[75] Thin-layer chromatography on renal biopsy material can detect orellanine long after clinical exposure.[73,75]

Group IX: Allenic Norleucine-Containing Mushrooms



This relatively new diagnostic group is associated with ingestion of *Amanita smithiana*. (See ILAMANITASMITHIANA in the Image Library.) The 13 cases of *A. Smithiana* poisoning reported have all occurred in the Pacific Northwest.[56,91,94] Because the mature specimen often lacks any evidence of a partial or universal veil, these mushrooms are not recognized as *Amanita* species. It appears that all of the poisoned individuals were seeking the edible pine mushroom matsutake (*Tricholoma magnivelare*), a highly desirable look-alike. (See ILTRICHOLOMAMAGNIVELARE in the Image Library.) The *A. smithiana* and *A. abrupta* possess 2 amino acid toxins: allenic norleucine (amino-hexadienoic acid) and possibly l-2-amino-4-pentynoic acid.[18,67,103] In vitro renal epithelial tissue cultured with allenic norleucine developed morphologic changes similar to those that occur following *A. smithiana* ingestion.[67] In mice the extract of *Amanita abrupta* was also hepatotoxic, which suggests that other toxic agents in addition to the two described amino acids were present.[103]

Initial symptoms were noted from 30 minutes to 12 hours following ingestion of either raw or cooked specimens. GI manifestations, including anorexia, nausea, vomiting, abdominal distress, and diarrhea, occurred frequently, accompanied by malaise, sweating, and dizziness. In some cases, vomiting and diarrhea persisted. The patients were oliguric or anuric upon presentation. Acute renal failure manifested 4–6 days following ingestion with marked elevation of BUN and creatinine. ALT and lactate dehydrogenase concentrations frequently were elevated, whereas amylase, AST, alkaline phosphatase, and bilirubin were only infrequently abnormal.

Risk of toxicity was greatest in older patients and in patients with underlying renal insufficiency. Patients who required hemodialysis underwent the procedure 2–3 times per week for approximately one month. None of the patients in the three series died.

There is no known antidote for these nephrotoxins. Activated charcoal, although of no proven benefit, should be used in standard doses when a patient in the northwest United States presents with early GI manifestations after mushroom ingestions. The clinician will be forced to consider the circumstances of ingestion to assess the probability of *A. smithiana* ingestion as opposed to ingestion of mushrooms containing a GI toxin.

In view of the substantial morbidity associated with *A. smithiana* ingestions, historic, clinical, and/or temporal evidence of this ingestion should lead to activated charcoal hemoperfusion or hemodialysis as a strong consideration when the patient presents in the early phase of exposure. When a patient presents with renal compromise several days, as opposed to weeks, following mushroom ingestion and with a history of early, as opposed to delayed, GI manifestations, the clinician may be able to differentiate *A. smithiana* from *Cortinarius* spp exposure.

Group X: Rhabdomyolysis-Associated Mushrooms

Twelve patients who ingested *Tricholoma equestre* (*T. flavovirens*) mushrooms for three consecutive days developed severe rhabdomyolysis that was lethal in three cases.[5] All patients developed fatigue, muscle weakness, and myalgias 24–72 hours following the last mushroom meal. The individuals also developed facial erythema, nausea without vomiting, and profuse sweating. The mean maximal creatine phosphokinase (CPK) was 226,067 units/L in women and 34,786 units/L in men, with some values >500,000 units/L. Electromyography revealed muscle injury with myotoxic activity. The biopsies showed myofibrillar injury and edema consistent with an acute myopathy.

Dyspnea, muscle weakness, pulmonary congestion, acute myocarditis, dysrhythmias, cardiac failure, and death ensued in three patients. Autopsy demonstrated myocardial lesions identical to those found in the peripheral muscles. Although muscle toxicity was reproduced using *T. equestre* extracts in a mouse model, the etiology of the toxicity is not defined.[5] All the triterpenoids, sterols, indoles, and acetylenic compounds extracted from these mushrooms previously were assumed to be without toxicity. Currently all the clinical experience originates from Europe; no cases are reported in the United States.

MANAGEMENT

Because ingestion of certain mushrooms may lead to toxicity with substantial mortality, patients with suspected mushroom ingestions require rigorous management. A serious effort at precise identification of the genus and species involved will make assessment, management, and followup easier and more logical. The basic regimen of adsorption should be initiated if potentially toxic mushrooms are ingested. If nausea and vomiting persist, an antiemetic can be used to ensure that the patient can retain activated charcoal 1 g/kg. Appropriate life support measures should be instituted as necessary. Fluid, electrolyte, and glucose repletion are essential.

There is a wide variability in quantity and type of toxin present in mushrooms according to geography, local conditions, and individual susceptibility. The clinical course for *A. smithiana* poisoning has led us to suggest an alteration in the initial approach to patients in the northwest United States who have early onset (0.5–3 hours) of GI distress following mushroom ingestion. Until recently, all patients who had early onset of nausea, vomiting, diarrhea, and abdominal cramps were presumed to be poisoned by a member of the groups containing either the GI toxins or muscarine. However, a better understanding of *A. smithiana* led us to limit the use of an algorithm we and others frequently used in the past (see Goldfrank's Toxicologic Emergencies, 6th edition, Figure 75–1). The routine use of specific antidotes should be avoided because they usually are unnecessary.

DISPOSITION

It is important to remember that many patients with mushroom ingestions present with signs and symptoms suggestive of mixed

poisonings. Whereas some ingestions produce "purer" symptom complexes than others, some ingestions, such as those of *A. muscaria,* produce GI and CNS effects, and still other ingestions, such as of *Cortinarius* spp, have acute GI and delayed renal manifestations. Treatment or partial treatment may further confound the assessment. In addition, it is essential to remember that any acute GI disorder actually may be the manifestation of mushroom toxicity. In the spring and fall, in areas with moderate weather and humidity, it is particularly important to consider intentional or unrecognized exposure to mushroom toxins, although a logical approach to management is impossible in the absence of a precise history.

Because the clinical course of mushroom poisoning can be deceptive, all patients who manifest early symptoms (<3 hours) and remain symptomatic despite supportive care (Tables 113–1 and 113–2) should be admitted to the hospital. In this group of patients inhabiting the Pacific Northwest, *A. smithiana* should be of particular concern. Patients whose delayed initial presentation (≥5 hours) is suggestive of amatoxin exposure should be hospitalized, as should any patient postingestion who cannot be followed safely or reliably as an outpatient. Tables 113–1 and 113–2 list the characteristic times of appearance and evolution of symptoms caused by mushroom toxins and groups. Confusion may result from atypical clinical manifestations or, commonly, ingestion of several different mushrooms species, some of which may produce early symptoms and others delayed toxicity. Patients with certain types of ingestions may appear to improve initially with only supportive care. This latency period, which is characteristic of *Amanita* spp, may not be appreciated when several different species are eaten simultaneously. However, because hepatotoxicity leading to death may not appear until 2–3 days after ingestion (amatoxins) and nephrotoxicity may not appear for 3–21 days (orellanine and allenic norleucine), all patients with symptoms require subsequent followup.

Visualizing and analyzing the gross, microscopic, or chemical characteristics of the ingested mushroom remain vital strategies that are infrequently used. When the whole mushroom or parts are unavailable, the diagnosis must be based on the clinical presentation. No rapidly available studies in emergency departments or clinical chemistry laboratories are available to assist with management. The development of a rapid clinical test for amatoxins,[14,15,50] gyromitrin, orellanine, and allenic norleucine would be useful and permit early use of hemoperfusion and greater vigilance with regard to use of hemodialysis. We have not yet achieved the ability to use thin-layer chromatography, high-performance liquid chromatography, gas chromatography, or gas chromatography-mass spectrometry for clinically relevant circumstances.

TABLE 113–2. Mushroom Toxicity: Correlation Between Symptomatology and Time of Onset of Symptoms

	Early <3 h	Middle 5–24 h	Late >24 h
Gastrointestinal	Muscarine Gastrointestinal toxins Allenic norleucine	Amatoxin Allenic norleucine Gyromitrin	Orelline and orellanine
Hepatic			Amatoxin Gyromitrin
Neuropsychiatric	Ibotenic acid and muscimol Psilocybin	Gyromitrin	
Renal			Orelline and orellanine Allenic norleucine

LYCOPERDONOSIS

Lycoperdonosis is not related to either the toxic or hallucinogenic characteristics of a mushroom. This syndrome occurs in patients following acute inhalation of spores as a folk medical therapy for epistaxis[85] and in adolescents for various experimental reasons.[86] Puffball mushrooms (*Lycoperdon perlatum*, *Lycoperdon pyriforme,* or *Lycoperdon. gemmatum*), which are edible in the fall and can (upon decay or drying) release large numbers of spores by compression or agitation. (See ILLYCOPERDONPYRIFORME and ILLYCOPERDONPERLATUM in the Image Library.) Massive inhalation, insufflation, and chewing of spores can lead to the development of nasopharyngitis, nausea, vomiting, and pneumonitis within hours. Over a period of several days, cough, shortness of breath, myalgias, fatigue, and fever develop. Rarely patients require intubation because of pulmonary compromise associated with diffuse reticulonodular infiltrates.[86] Lung biopsy demonstrates an inflammatory process with the presence of *Lycoperdon* spores.[85] Patients treated with prednisone and antifungal agents such as amphotericin B recovered within several weeks without sequelae.

IDENTIFICATION

General

Although mushroom identification is a difficult science, this section may be helpful to the clinician dealing with a suspected case of mushroom toxicity. However, it is generally best to rely on symptomatology, not mushroom appearances, to confirm a diagnosis. As a general rule, positive identification of the mushroom should be left to the mycologist or qualified toxicologist. Digital images sent over the Internet with verbal descriptions to a mycologist have enhanced diagnostic potential, although definitive identification could not be achieved in a limited study.[30]

The most important anatomic features of both edible and poisonous mushrooms are their pileus, stipe, lamellae or gills, and volva.

- *Pileus:* Broad, caplike structure from which hang the gills (lamellae), tubes, or teeth.
- *Stipe:* Long stalk or stem that supports the cap; the stipe is not present in some species.
- *Lamellae:* Platelike or gill-like structures on the undersurface of the pileus that radiate out like the spokes of a wheel. The spores are found on the lamellae. Some mushrooms have pores or toothlike structures on their pili, which contain the spores. The mode of attachment of the lamellae to the stipe is noteworthy in making an identification.
- *Volva:* Partial remnant of the veil found around the base of the stipe in some species.
- *Veil:* Membrane that may completely or partially cover the lamellae, depending on the stage of development. The "universal" veil covers the underside, the spore-bearing surface of the pileus.

- *Annulus:* Ringlike structure that may surround the stipe at some point below the junction, with the cap that is a remnant of the partial veil.
- *Spores:* Microscopic reproductive structures that are resistant to extremes in temperature and dryness, produced in the millions on the spore-bearing surface (see Lamellae). Of all the characteristics of a particular mushroom species, spores are the least variable, although many mushrooms have similar-appearing spores. A spore print is helpful in establishing an identification. (See ILSPOREPRINT 1 and ILSPOREPRINT 2 in the Image Gallery.) A spore print viewed microscopically is comparable to a bacterial Gram stain. Spore colors range from white to black and include shades of pink, salmon, buff, brown, and purple. Spore color in general is constant for a species.

The Unknown Mushroom

1. The most important determinant is whether the ingested mushroom is one of the deadly varieties, especially *Amanita.* Outside of the Pacific Northwest, the onset of GI symptoms within 3 hours of ingestion does not result from amatoxin poisoning. In the Pacific Northwest, symptoms may represent *A. Smithiana* (allenic norleucine) poisoning (Tables 113–1 and 113–2).
2. Attempt to obtain either the collected mushrooms or a detailed description of their features. Arrange for transport of the mushroom in a dry paper bag (not plastic). Ensure that the mushroom is neither moistened nor refrigerated, either of which will alter its structure. Remember that gastric contents may contain spores that can be crucial for analysis.
3. If the mushroom cap is available, make a spore print by placing the pileus spore-bearing surface side down on a piece of paper for at least 4–6 hours in a windless area. The spores that collect on the paper can be analyzed for color. White spore prints can be visualized more easily on white paper by tilting the paper and looking at it from an angle.
4. Concomitant with step 3, contact a mycologist and use the best resources available for identification. A botanical garden usually has expert mycologists on staff, or a local mycology club can locate a mycologist. Alternatively, the North American Mycological Association through its Internet site (*http://www.namyco.org/*) can furnish this information. A regional poison control center almost always can provide this expertise or locate an expert.
5. If none of the resources in step 4 is accessible, Melzer reagent can be useful in differentiating look-alike species and defining the presence of an amatoxin. A positive reaction is indicated by the development of a dark blue color upon contact with Melzer reagent.[58] Melzer reagent is a solution of 20 mL water, 1.5 g potassium iodide, 0.5 g iodine, and 20 g chloral hydrate. Staining a sample of the spores with 1 drop of reagent and then viewing the sample under a microscope helps to determine whether the mushroom is a deadly *Amanita,* with bluish-black "amyloid"-reacting round spores.
6. An additional test used by some is the Meixner reaction. Several drops of 10–12N hydrochloric acid are applied to an amatoxin-containing mushroom sample squeezed onto newspaper, resulting in a blue reaction.[50] The reliability of this test is doubtful, and most mycologists prefer to use Melzer reagent. Although the Meixner test is sensitive, false-negative and false-positive tests are of concern.[8]

POISONING PRINCIPLES: MYTHS AND SCIENCE

Differentiating myths from science is a difficult task in any field of medicine. This effort is even more complex when discussing mushrooms. The following principles are of great value in developing a logical approach to a potential ingestion.

1. Wild mushrooms should never be eaten unless an experienced mycologist can absolutely identify the mushroom. Even experts have trouble identifying some mushrooms, yet some foragers boldly indicate that distinguishing edible from toxic mushrooms is "as easy as telling brussels sprouts from broccoli." Remember the saying, "There are old mushroom hunters, and bold mushroom hunters; but there are no old, bold mushroom hunters."
2. The toxicology of any species can vary, depending on geographic location.
3. If poisoning is suspected, attempt to obtain samples of the mushrooms eaten and identify them. Every ED should have a readily available resource on mushrooms, such as one of the major mycology field guides.[1,12,57,58,76,82] In any case, identification is best made with the aid of the poison center's consultant mycologist.
4. Mushrooms often are implicated as the cause of an illness when, in fact, infections or other diseases are responsible. Other etiologies include the mode of preparation (the sauce or wine) or the cooking utensil.
5. There are no absolute generic approaches for evaluating the potential toxicity of a mushroom. Myths suggesting the safety or lack of safety by staining of silver, presence of insects or slugs, peeling off the mushroom cap, or the area of mushroom growth are unreliable or false. Neither odor nor taste is a good predictor of toxicity. Pure white mushrooms, little brown mushrooms, large brown mushrooms, and red- or pink-spored boletus (a mushroom without lamellae) should be considered potentially toxic.
6. Cooking may inactivate some toxins but not others. In general, no wild mushroom should be eaten raw or in large quantities. Examples of toxicity associated with lack of cooking include *Armillariella mellea* (honey mushroom), which usually is well tolerated when cooked but not raw, and *Verpa bohemica* (a morel-like mushroom), which is edible but causes illness if eaten in excess.
7. Associated phenomena may be responsible for or contribute to toxicity. Could insecticides have been sprayed on the mushrooms? Is it an alcohol-related response? Besides the well-known disulfiram reaction involving *C. atramentarius*, other good edibles, including the black morel *(Morchella angusticeps)* and the sulfur polypore (*Laetiporus sulfureus*), can cause adverse reactions if consumed with alcohol. The etiology of these adverse reactions is not understood.
8. "Edible" mushrooms that are allowed to deteriorate become toxic. Therefore, only young, recently matured specimens should be eaten when adequate mycologic support is available.
9. The finding that only some people who ate a mushroom species manifested characteristic toxicity should not exclude the diagnosis of mushroom poisoning. The degree of toxicity may be dose related or genetically determined, or a person may have a pathologic predisposition to toxicity.

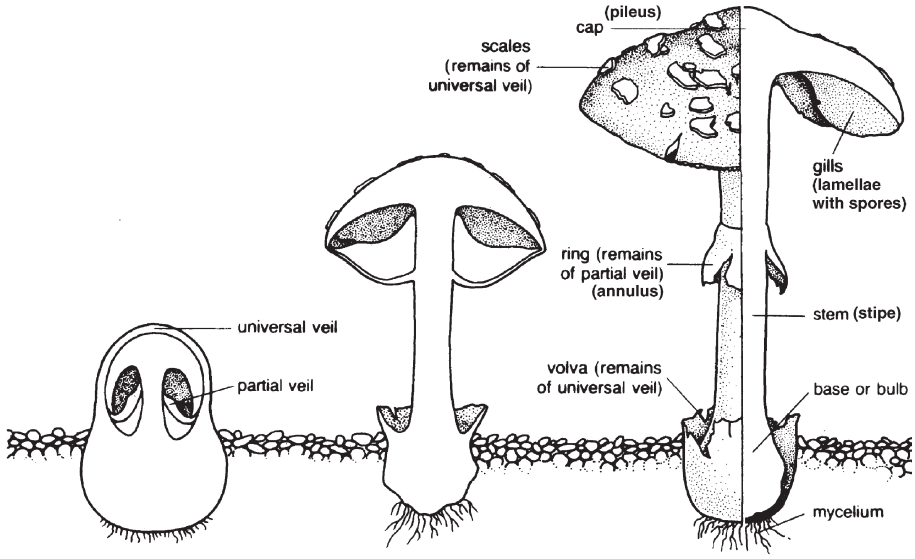


Figure 113–1. In the more highly specialized and evolved mushrooms, various protective tissues cover the fruit body and its constituent parts during its development. In the toadstool shown, an *Amanita* species, 2 veils of tissue are involved—one an outer enclosing bag, the universal veil, which ruptures as the fruit body expands to leave a volva at the base and fragments on the cap, the other an inner partial veil covering the developing gills, which is pulled away as the cap opens to leave a ring on the stem. (Reprinted, with permission, from Kibby G: Mushrooms and Toadstools, A Field Guide. Oxford, Oxford University Press, 1979, p. 14.)

10. Mushroom allergy can manifest as anaphylaxis.
11. Most poisonous mushrooms resemble edible mushrooms at some phase of their growth. For this reason, even careful examination of the ring, cap, consistency, form, and color may not reliably identify the edible species. Also, characteristic features of specific toxic mushrooms may not be present under certain conditions. Although the deadly *A. phalloides* and *A. virosa* usually have remnant patches of tissue from the universal veil that envelops the mushroom in its "button" stage, rain may wash these remnants away. Similarly, a subterranean basal cup may not be noticed if the mushroom is cut at the ground level by a novice forager (Figure 113–1).
12. Even the new in-vogue "wild mushrooms" in the fanciest markets may not be entirely safe.

Acknowledgments

Alan G. Kulberg, MD, Kenneth E. Lampe, PhD (deceased), and Eddy A. Bresnitz, MD, contributed to this chapter in a previous edition.

REFERENCES

1. Ammirati JF, Traquair JA, Horgen PA: Poisonous Mushrooms of the Northern United States and Canada. Minneapolis, University of Minnesota Press, 1985.
2. Antkowiak WZ, Gessner WP: Photodecomposition of orellanine and orellinine, the fungal toxins of Cortinarius orellanus fries and Cortinarius speciosissimus. Experentia 1985;41:769–771.
3. Ayer WA, Browne LM: Terpenoid metabolites of mushrooms and basidiomycetes. Tetrahedron 1981;37:2199–2248.
4. Becker CE, Tong TG, Boerner U: Diagnosis and treatment of *Amanita phalloides*-type mushroom poisoning: Use of thioctic acid. West J Med 1976;125:100–109.
5. Bedry R, Baudrimont I, Deffieux G, et al: Wild mushroom intoxication as a cause of rhabdomyolysis. N Engl J Med 2001;345: 798–802.
6. Belliardo F, Massano G, Accomo S: Amatoxins do not cross the placental barrier. Lancet 1983;1:1381.
7. Benjamin DR: Mushroom poisoning in infants and children: The *Amanita pantherina/muscaria* group. J Toxicol Clin Toxicol 1992;30: 13–22.
8. Beuhler M, Lee DC, Gerkin R: The Meixner test in the detection of α-amanitin and false-positive reactions caused by psilocin and 5-substituted tryptamines. Ann Emerg Med 2004;44:114–120.
9. Borowiak KS, Ciechanowski K, Walosczyk P: Psilocybin mushroom *(Psilocybe semilanceata)* intoxication with myocardial infarction. J Toxicol Clin Toxicol 1998;36:47–49.
10. Bouget J, Bousser J, Pats B, et al: Acute renal failure following collective intoxication by *Cortinarius orellanus*. Intensive Care Med 1990;16:506–510.
11. Boyer JC, Hernandez F, Estorc J, et al: Management of maternal *Amanita phalloides* poisoning during the first trimester of pregnancy: A case report and review of the literature. Clin Chem 2001; 47:971–974.
12. Bresinsky A, Besl H: A Colour Atlas of Poisonous Fungi. Wurzburg, Germany, Wolfe, 1990.
13. Broussard CN, Aggarwal A, Lacey SR, et al: Mushroom poisoning—From diarrhea to liver transplantation. Am J Gastroenterol 2001;96: 3195–3198.
14. Butera R, Coccini T, Randine G, et al: Validation of the ELISA test for urinary alpha-amanitin analysis in human Amanita phalloides poisoning. J Toxicol Clin Toxicol 2004;42:535. (Abstract.)
15. Butera R, Lonati F, Georgatos J, et al: Diagnostic value of urinary amanitin analysis in mushroom poisoning: A prospective study. J Toxicol Clin Toxicol 2004;42:463. (Abstract.)
16. Carder CA, Wojciechlowski NJ, Skoutakis VA: Management of mushroom poisoning. Clin Toxicol Consult 1983;5:103–118.
17. Carlson A, Henning P, Lindberg P, et al: On the disulfiram-like effect of coprine, the pharmacologically active principle of *Coprinus atramentarius*. Acta Pharmacol Toxicol 1978;42:292–297.
18. Chilton WS, Tsou G, Kirk L, Benedict RG: A naturally-occurring allenic amino acid. Tetrahedron Lett 1968;60:6283–6284.
19. Covic A, Goldsmith DJA, Gusbeth-Tatomir P, et al: Successful use of molecular absorbent regenerating system (MARS) dialysis for the treatment of fulminant hepatic failure in children accidentally poisoned by toxic mushroom ingestion. Liver Int 2003;23(Suppl 3):21–27.
20. Curry SC, Rose MC: Intravenous mushroom poisoning. Ann Emerg Med 1985;14:900–902.
21. Danel VC, Saviuc PF, Garon D: Main features of *Cortinarius spp*. poisoning: A literature review. Toxicon 2001;39:1053–1060.

22. De Carlo E, Milanesi A, Martini C, et al: Effects of *Amanita phalloides* toxins on insulin release: In vivo and in vitro studies. Arch Toxicol 2003;77:441–445.
23. Detry O, Arkadopoulos N, Ting P, et al: Clinical use of a bioartificial liver in the treatment of acetaminophen-induced fulminant hepatic failure. Am Surg 1999;65:934–938.
24. Enjalbert F, Rapior S, Nouguier-Soulé J, et al: Treatment of amatoxin poisoning: 20-year retrospective analysis. J Toxicol Clin Toxicol 2002;40:715–757.
25. Faulstich H: New aspects of *Amanita* poisoning. Klin Wochenschr 1979;57:1143–1152.
26. Faulstich H, Talas A, Wellhoener HH: Toxicokinetics of labeled amatoxins in the dog. Arch Toxicol 1985;56:190–194.
27. Faulstich H: Structure of poisonous components of *Amanita phalloides*. Curr Probl Clin Biochem 1977;7:2–10.
28. Faybik P, Hetz H, Baker A, et al: Extracorporeal albumin dialysis in patients with *Amanita phalloides* poisoning. Liver Int 2003;23(Suppl 3):28–33.
29. Feinfeld DA, Mofenson HC, Caraccio T, Kee M: Poisoning by amatoxin-containing mushrooms in suburban New York—Report of four cases. J Toxicol Clin Toxicol 1994;32:715–721.
30. Fischbein CV, Mueller GM, Leacock PR, et al: Digital imaging: A promising tool for mushroom identification. Acad Emerg Med 2003; 10:808–811.
31. Floersheim GL: Treatment of human amatoxin mushroom poisoning: Myths and advances in therapy. Med Toxicol 1987;2:1–9.
32. Floersheim GL: Treatment of mushroom poisoning. JAMA 1984; 252:3130–3132.
33. Floersheim GL: Antagonistic effects against single lethal doses of *Amanita phalloides*. Naunyn Schmiedebergs Arch Pharmacol 1976; 293:171–174.
34. Floersheim GL: Rifampicin and cysteamine protect against the mushroom toxin phalloidin. Experientia 1974;30:1310–1311.
35. Floersheim GL, Eberhard M, Tschumi P, Buchert F: Effects of penicillin on liver enzymes and blood clotting factors in dogs given a boiled preparation of *Amanita phalloides*. Toxicol Appl Pharmacol 1978;46:455–462.
36. Floersheim GL, Schneeberger J, Bucher K: Curative potencies of penicillin in experimental *Amanita phalloides* poisoning. Agents Actions 1971;2:138–141.
37. Franz M, Regele H, Kirchmair M, et al: Magic mushrooms: Hope for a "cheap high" resulting in end-stage renal failure. Nephrol Dial Transplant 1996;11:2324–2327.
38. French AL, Garrettson LK: Poisoning with the North American jack-o'-lantern mushroom: *Omphalotus illudens*. J Toxicol Clin Toxicol 1988;26:81–88.
39. Galler GW, Weisenberg E, Brasitus TA: Mushroom poisoning: The role of orthotopic liver transplantation. J Clin Gastroenterol 1992;15: 229–232.
40. Gundala S, Wells LD, Milliano MT, et al: The hepatocellular bile acid transporter Ntcp facilitates uptake of the lethal mushroom toxin α-amanitin. Arch Toxicol 2004;78:68–73.
41. Hanrahan JP, Gordon MA: Mushroom poisoning: Case reports and a review of therapy. JAMA 1984;251:1057–1061.
42. Hatfield GM, Brady LR: Toxins of higher fungi. Lloydia 1975;38: 36–55.
43. Jacobs BP, Dennehy C, Ramirez G, et al: Milk thistle for the treatment of liver disease: A systematic review and meta-analysis. Am J Med 2002;113:506–515.
44. Jacobs J, Von Behren J, Kreutzer R: Serious mushroom poisonings in California requiring hospital admission 1990–1994. West J Med 1996; 165:283–288.
45. Jaeger A, Jehl F, Flesch F, et al: Kinetics of amatoxins in human poisoning: Therapeutic implications. J Toxicol Clin Toxicol 1993;31:63–80.
46. Jander S, Bischoff J: Treatment of Amanita phalloides poisoning: I. Retrospective evaluation of plasmapheresis in 21 patients. Ther Apher 2000;4:303–307.
47. Jander S, Bischoff J, Woodcock BG: Plasmapheresis in the treatment of amanita phalloides poisoning: II. A review and recommendations. Ther Apher 2000;4:308–312.
48. Kelner MJ, Alexander NM: Endocrine hormone abnormalities in *Amanita* poisoning. J Toxicol Clin Toxicol 1987;25:21–37.
49. Klein AS, Hart J, Brems JJ, et al: *Amanita* poisoning: Treatment and the role of liver transplantation. Am J Med 1989;86:187–193.
50. Koppel C: Clinical symptomatology and management of mushroom poisoning. Toxicon 1993;31:1513–1540.
51. Kostansek EC, Lipscomb WN, Yocum RR, et al: The crystal structure of the mushroom toxin β-amanitin. J Am Chem Soc 1977;99: 1273–1274.
52. Kubicka J: Neue Moglichkeiten in der behandlung von vergiftung mit dem grunen Knollenblatterpilz—*Amanita phalloides*. Mykol Mitteil 1963;7:92–94.
53. Kullak-Ublick GA, Stieger B, Meier PJ: Enterohepatic bile salt transporters in normal physiology and liver disease. Gastroenterology 2004;126:322–341.
54. Lampe KF: Toxic fungi. Annu Rev Pharmacol Toxicol 1979;19:85–104.
55. Lampe KF, McCann MA: Differential diagnosis of poisoning by North American mushrooms with particular emphasis on *Amanita phalloides*-like intoxication. Ann Emerg Med 1987;16:956–962.
56. Leathem AM, Purssell RA, Chan VR, Kroeger PD: Renal failure caused by mushroom poisoning. J Toxicol Clin Toxicol 1997;35:67–75.
57. Lincoff GH: The Audubon Society Field Guide to North American Mushrooms. New York, Knopf, 1981.
58. Lincoff G, Mitchel DH: Toxic and Hallucinogenic Mushroom Poisoning: A Handbook for Physicians and Mushroom Hunters. New York, Van Nostrand Reinhold, 1977.
59. Lindell TJ, Weinberg F, Morris PW, et al: Specific Inhibition of nuclear RNA polymerase II by alpha-amanitin. Science 1970;170:447–449.
60. Marchner H, Tottmar O: A comparative study on the effects of disulfiram, cyanamide, and L-aminocyclopropanol on the acetaldehyde metabolism in rats. Acta Pharmacol Toxicol 1978;43:219–232.
61. Meier-Abt F, Faulstich H, Hagenbuch B: Identification of phalloidin uptake systems of rat and human liver. Biochim Biophys Acta 2004; 1664:64–69.
62. Meunier BC, Camus CM, Houssin DP, et al: Liver transplantation after severe poisoning due to amatoxin containing *Lepiota*—Report of three cases. J Toxicol Clin Toxicol 1995;33:165–171.
63. Moroni F, Fantozzi R, Masini E, Mannaioni PF: A trend in the therapy of *Amanita phalloides* poisoning. Arch Toxicol 1976;36:111–115.
64. Olson KR, Pond SM, Seward J, et al: *Amanita phalloides*-type mushroom poisoning. West J Med 1982;137:282–289.
65. Oubrahim H, Richard JM, Cantin-Esnault D: Perioxidase mediated oxidation, a possible pathway for activation of the fungal nephrotoxin orellanine and related compounds. Free Radic Res 1998;28:497–505.
66. Paydas S, Kocak R, Erturk F, et al: Poisoning due to amatoxin containing *Lepiota* species. Br J Clin Pract 1990;44:450–453.
67. Pelizzri V, Feifel E, Rohrmoser MM, Gstraunthaler G, Moser M: Partial purification and characterization of a toxic component of *Amanita smithiana.* Mycologia 1994;86:555–560.
68. Pinson CW, Daya MR, Benner KG, et al: Liver transplantation for severe *Amanita phalloides* mushroom poisoning. Am J Surg 1990;159: 493–499.
69. Piqueras J, Duran-Suarez JR, Massuet L, Hernandez-Sanchez JM: Mushroom poisoning: Therapeutic apheresis or forced diuresis. Transfusion 1987;27:116–117.
70. Pond SM, Olson KR, Woo OF, et al: Amatoxin poisoning in northern California, 1982–1983. West J Med 1986;145:204–209.
71. Raff E, Halloran PF, Kjellstrand CM: Renal failure after eating "magic" mushrooms. Can Med Assoc J 1992;147:1339–1341.
72. Ramirez P, Parrilla P, Sanchez-Bueno F, et al: Fulminant hepatic failure after *Lepiota* mushroom poisoning. J Hepatol 1993;19:51–54.
73. Rapior S, Delpech N, Andary C, Huchard G: Intoxication by *Cortinarius orellanus*: Detection and assay of orellanine in biological fluids and renal biopsies. Mycopathologia 1989;108:155–161.

74. Richard JM, Louis J, Cantin D: Nephrotoxicity of orellanine, a toxin from the mushroom Cortinarius orellanus. Arch Toxicol 1988;62: 242–245.
75. Rohrmoser M, Kirchmair M, Feifet E, et al: Orellanine poisonings: Rapid detection of the fungal toxin in renal biopsy material. J Toxicol Clin Toxicol 1997;35:63–66.
76. Rumack BH, Salzman E, eds: Mushroom Poisoning: Diagnosis and Treatment. Boca Raton, FL, CRC Press, 1978.
77. Schneider SM, Borochovitz D, Krenzelok EP: Cimetidine protection against alpha-amanitin hepatotoxicity in mice: A potential model for the treatment of *Amanita phalloides* poisoning. Ann Emerg Med 1987;16:1136–1140.
78. Schneider SM, Cochran KW, Knenzelok EP: Mushroom poisoning: Recognition and emergency management. Emerg Med Rep 1991;12: 81–88.
79. Schneider SM, Vanscoy G, Michelson EA: Failure of cimetidine to affect phalloidin toxicity. Vet Hum Toxicol 1991;33:17–18.
80. Schumacher T, Hoiland K: Mushroom poisoning caused by species of the genus *Cortinarius Fries*. Arch Toxicol 1983;53:87–106.
81. Serné EH, Toorians AW, Geitema JA, et al: *Amanita phalloides*, a potentially lethal mushroom: Its clinical presentation and therapeutic options. Neth J Med 1996;49:19–23.
82. Smith AH: The Mushroom Hunter's Field Guide. Ann Arbor, University of Michigan Press, 1969.
83. Sperti S, Montanaro L, Fiume L, Mattioli A: Dissociation constants of the complexes between RNA polymerase II and amanitins. Experientia 1973;29:33–34.
84. Stenklyft PH, Augenstein WL: Chlorophyllum molybdites: Severe mushroom poisoning in a child. J Toxicol Clin Toxicol 1990;28: 159–168.
85. Strand RD, Neuhauser EBD, Sornberger CF: Lycoperdonosis. N Engl J Med 1967;277:89–90.
86. Taft TA, Cardillo RC, Letzer D, et al: Respiratory illness associated with inhalation of mushroom spores. Wisconsin, 1994. MMWR Morb Mortal Wkly Rep 1994;43:525–526.
87. Tebbett IR, Caddy B: Mushroom toxins of the genus *Cortinarius*. Experientia 1984;40:441–446.
88. Tímár L, Czeizel AE: Birth weight and congential anomalies following poisonous mushroom intoxication during pregnancy. Reprod Toxicol 1997;11:861–866.
89. Tottmar O, Lindberg P: Effect on rat liver acetaldehyde dehydrogenases *in vitro* and *in vivo* by coprine, the disulfiram-like constituent of *Coprinus atramentarius*. Acta Pharmacol Toxicol 1977; 40:476–481.
90. Trestrail III JH: Mushroom poisoning in the United States: An analysis of 1989 United States Poison Center Data. J Toxicol Clin Toxicol 1991;29:459–465.
91. Tulloss RE, Lindgren JE: *Amanita smithiana*—Taxonomy, distribution, and poisonings. Mycotaxon 1992;45:373–387.
92. Vander Hoek TL, Erickson T, Hryhorczuk D, et al: Jack-o'-lantern mushroom poisoning. Ann Emerg Med 1991;20:559–561.
93. Vesconi S, Langer M, Iapichino G, et al: Therapy of cytotoxic mushroom intoxication. Crit Care Med 1985;13:402–406.
94. Warden CR, Benjamin DR Acute renal failure associated with suspected *Amanita smithiana* mushroom ingestions: A case series. Acad Emerg Med 1998;5:808–812.
95. Wauters JP, Rossel C, Farquet JJ: *Amanita phalloides* poisoning treated by early charcoal hemoperfusion. Br Med J 1978;2:1465.
96. Wellington K, Jarvis B: Silymarin: A review of its clinical properties in the management of hepatic disorders. BioDrugs 2001;15:465–489.
97. Wieland TH, Faulstich H: Amatoxins, phallotoxins, phallolysin, and antamanide: The biologically active components of poisonous *Amanita* mushrooms. CRC Crit Rev Biochem 1978;5:185–260.
98. Winkelmann M, Borchard F, Stangel W, Grabensee B: Todlich verlaufene immunhamolytische anamie nach genub des kahlen kremplings (*Paxillus involutus*). Dtsch Med Wschr 1982;107:1190–1194.
99. Winkelmann M, Stangel W, Schedel I, Grabensee B: Severe hemolysis caused by antibodies against the mushroom *Paxillus involutus* and its therapy by plasma exchange. Klin Wochenschr 1986;64:935–938.
100. Wiseman JS, Abeles RH: Mechanism of inhibition of aldehyde dehydrogenase by cyclopropanone hydrate and the mushroom toxin coprine. Biochemistry 1979;18:427–435.
101. Woodle ES, Moody RR, Cox KL, et al: Orthotopic liver transplantation in a patient with *Amanita* poisoning. JAMA 1985;253:69–70.
102. Yamada EG, Mohle-Boetani J, Olson KR, Werner SB: Mushroom poisoning due to amatoxin. Northern California, winter 1996–1997. West J Med 1998;169:380–384.
103. Yamaura Y, Fukuhara M, Takabatake E, Ito N, Hashimoto T: Hepatotoxic action of a poisonous mushroom, *Amanita abrupta,* in mice and its toxic component. Toxicol 1986;38:161–173.