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# TOXIC FUNGI

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## INTRODUCTION

Only in the last few years have the chemistry and pharmacology of the principal mushroom toxins been clarified. Some of these toxins have become important in biochemical research, e.g. α-amanitin, whereas others, e.g. muscimol, are of interest in neurophysiological investigations. Mushroom toxins are also significant to academic pharmacologists in that formal training in toxicology for medical students is conventionally part of their pharmacology course. In this regard, mushroom toxins have received scant interest because of the infrequency of actual poisonings in North America and Great Britain. English language textbooks have done little more than to perpetuate the myth that atropine is some kind of "universal antidote" for mushroom intoxications. The increased popularity of gathering uncultivated mushrooms for food as well as the search for hallucinogenic fungi has produced a marked increase in the number of such poisonings. For this reason, a major portion of this survey is devoted to the clinical aspects of mushroom intoxications. Both the pharmacology and clinical toxicology of mushroom toxins have been the subjects of two recent book length monographs (1, 2).

### *Classification of Toxic Mushrooms*

Since the taxonomic aid of a mycologist is rarely available following the ingestion of an unidentified mushroom by a child, and because certain types of mushroom intoxications are potentially very dangerous, the usual recommendation is to induce emesis followed by the instillation into the stomach of an aqueous slurry of activated charcoal. Following ingestions in which clinical poisoning has already become apparent, a classification based on symptoms may be a useful guide for prognosis and therapy. One such system (3, 4) divides all poisonous mushrooms into two groups, those



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producing signs of toxicity within two hours of ingestion, or immediately following the ingestion of alcohol, and those producing signs of toxicity six or more hours after ingestion.

The rapid onset group may be described as rarely of serious consequence, requiring only conservative, symptomatic management. This group can be subdivided according to the predominating symptoms: simple gastroenteric irritation (many species); parasympathetic hyperactivity (*Inocybe* spp., *Clitocybe* spp.); delirium or hallucinations not associated with sleep (*Psilocybe, Panaeolus, Copelandia,* and *Gymnopilus* species); delirium, excitement, or hallucinations associated with sleep or coma (*Amanita muscaria, A. pantherina*); or a disulfiram-like response to alcohol (*Coprinus atramentarius*).

Mushroom ingestions with a delayed onset of symptoms are associated with serious intoxications with a potentially fatal outcome. These may be divided into those producing headache, nausea, and fatigue approximately 6–8 hr after ingestion (*Gyromitra esculenta*), severe emesis and diarrhea approximately twelve hours after ingestion (the *Amanita phalloides* group), and those producing polydipsia and polyuria three or more days after ingestion (*Cortinarius* spp.).



## MUSHROOM INTOXICATIONS WITH DELAYED ONSET

### *The Amanita phalloides Group*

In western Europe and in North America nearly all fatal mushroom ingestions are due to certain species of the genus *Amanita.* These include *A. phalloides,* which has been studied in greatest detail, *A. verna, A. virosa, A. bisporigera,* and *A. ocreata.* The *Amanita* toxins are also found in toxicologically significant concentration in *Galerina autumnalis, G. marginata,* and *G. venenata.* There is chromatographic evidence but no quantitative data for the presence of *Amanita* toxins in *Lepiota helveola, L. brunneoincarnata, L. subincarnata* (5), and in *Conocybe filaris* (6). Poisoning by these mushrooms is characterized by a latent period of about 12 hr between ingestion and the initial phase of the intoxication, which begins with nausea, vomiting, severe abdominal pain, and a profuse, watery diarrhea. These signs subside after a few hours and the patient enters a symptom-free period which may last up to three days. This is followed by a severe, sometimes fatal, hepatitis.

The orally active toxins of *A. phalloides* belong to two families of thermostable, cyclic peptides. The phallotoxins are cyclic heptapeptides, of which phalloidin is the most abundant member. The other peptides of this group are phalloin, phallisin, phallacidin, phallacin, and phallisacin. Phallin B, previously ascribed to this group, is now considered a mixture and should

be disregarded. An additional nontoxic heptapeptide, prophalloin, has recently been characterized that is presumed to be the probable precursor of the phallotoxins (6a). The amatoxins are cyclic octapeptides, of which there are five: α, β, γ, and ε-amanitin and amanin. A nontoxic octapeptide, amanullin, is also present. The concentrations of toxins in these mushrooms varies with geographic location, growing conditions, and the maturity of the specimen. Except in *A. phalloides,* some or all of the phallotoxins or amatoxins may be absent in a particular collection of one of the other species. The relative abundance of these toxins has been determined for European specimens of *A. phalloides, A. verna, A. virosa,* and *G. marginata* (7, 8) and for North American specimens of *A. phalloides, A. verna, A. virosa, A. bisporigera* (9), and *G. autumnalis* (10). *A. phalloides* and some related species also contain thermolabile hemolytic and cytotoxic glycoproteins which are toxic only on intravenous administration. The chemical structures of the *Amanita* toxins has been recently reviewed [11; with correction (12); 13], and the crystalline structure of β-amanitin has been determined (14).

A number of chromatographic procedures have been devised for the qualitative determination of the *Amanita* toxins (15). Palyza (16), for example, described a rapid procedure using miniature thin-layer chromatography on precoated plates which permits the detection of 0.025 μg of α-amanitin, which is equivalent to the content of about 0.5 mg of fresh mushroom. An extremely sensitive method for the quantitative determination of α-amanitin at concentrations down to 0.05 ng based on the inhibition of RNA polymerase has been published (17). Attempts have been made to develop a radioimmunoassay for amanitins (18, 19). This approach has recently been shown useful for the determination of amanitin levels in the serum of patients poisoned by *A. phalloides* (20).

The phallotoxins are membrane specific and act only on hepatocytes and, except in the rat, on the proximal convoluted tubules in the kidney. These toxins bind to protein microfilaments of the plasma liver cell. The phallotoxins promote the irreversible polymerization of G-actin to filamentous actin. F-actin is stabilized (21, 22). The modified filaments that bind the phallotoxins have been designated as Ph-actin by Wieland & Govindan (23) and Wieland (24, 25). The formation of Ph-actin is induced only by the toxic derivatives of phalloidin (26). The relationship between the conformation of the phallotoxins and their toxicity has been examined (25, 27, 28).

Deformation of the surface of isolated hepatocytes exposed to phallotoxins begins in 5 to 10 min (29–31). There is a rapid swelling of the liver cell with a marked loss of potassium and lysosomal enzymes (32). The lysosomal involvement precedes severe liver injury (33, 34). The movement of potassium ions has been extensively investigated (30, 35–38) and appears to be the result of the formation of potassium channels rather than inhibi-

tion of the cation pump. The uptake of extracellular fluids into the phalloidin-poisoned hepatocyte occurs by way of the endoplasmic reticulum (31, 39–41). Other biochemical changes are secondary to the loss of the integrity of the membrane.

Because of their low mammalian toxicity, the phallotoxins are considered to be of no clinical significance (42). The comparative $LD_{50}$ for parenterally administered *Amanita* toxins is given in Table 1. The lethal dose of the amatoxins in man is probably below 0.1 mg/kg. It can then be calculated that the toxin concentration of one fresh mushroom weighing about 50 g, equivalent to 7 mg of amatoxins, would be fatal for an adult (11). The toxicity of these mushrooms is not affected by cooking or drying.

The phallotoxins act rapidly and, if given to experimental animals in quantities greater than the $LD_{100}$, produce death in 1 to 2 hr; death from the amatoxins, on the other hand, is always preceded by a prolonged latent period regardless of dosage. It has been shown experimentally that the target organ of the amatoxins is dose dependent (43). In the mouse the administration of the minimum lethal dose results in renal but not hepatic necrosis. Kidney damage never appears earlier than three days after the administration of an amatoxin, even with concentrations three times the minimal lethal dose. Hepatic damage can be produced only with the administration of amounts in excess of the minimum lethal dose, but generally appears within two days. Thus, if the animals receive substantially higher quantities than the minimum lethal dose, death may occur from hepatic failure before renal damage becomes apparent. An analogous clinical picture may be seen in patients who have ingested only small amounts of an *A. phalloides*-type mushroom who demonstrate only renal tubular necrosis (44).

The damage to the kidney in experimental animals involves only the cells of the proximal convoluted tubules, which has been ascribed to an elevated concentration in these cells due to reabsorption (43). The rat, however, does not exhibit renal toxicity since it has been shown that this species does not possess the capability for reabsorption of the toxin (43, 45). Administration of albumin-bound amanitin, which cannot be excreted by the glomerulus except in minute quantities, results in death of the animal without renal

Table 1 *Amanita phalloides* toxins: parenteral $LD_{50}$ in mice, mg/kg (182, 183)

| Phallotoxins | | Amatoxins | |
|---|---|---|---|
| Phallacidin | 1.5 | α-Amanitin | 0.3 |
| Phallisacin | 4.5 | β-Amanitin | 0.4 |
| Phallacin | 1.5 | γ-Amanitin | 0.15 |
| Phalloin | 1.8 | ε-Amanitin | 0.5 |
| Phallosin | 2.5 | Amanin | 0.5 |

injury. The complex will, however, produce hepatic injury indistinguishable from that produced by the free toxin (46–48).

The microscopic examination of kidney and liver tissue of both experimental animals exposed to pure amatoxins and humans intoxicated with *A. phalloides* shows vesicular-like damage to the cell nuclei within 1 to 2 hr of exposure (49). The finding that the DNA content of the nucleus was unaltered whereas the RNA content diminished rapidly (50, 51) stimulated considerable interest in the action of amatoxins on RNA synthesis [see references in (52, 53)] The primary effect was shown to be an inhibition of nucleoplasmic RNA polymerase II by preventing the elongation step of transcription (54). Subunit SB 3 was shown to be the amatoxin receptor protein of RNA polymerase II by affinity labeling experiments (55). Comparison of the association and dissociation rate constants for α-amanitin and RNA polymerase II inhibition suggests that it is the latter that governs the in vivo toxicity (56, 57). The in vitro inhibition of RNA polymerase II by the various amatoxins is related directly to their in vivo toxicity (58). The relationship of the toxicity of the amatoxins to their chemical configuration has also been established (59).

RNA polymerase III can also be inhibited by the amatoxins, but only at concentrations of about a thousandfold greater (60). Ribosomal RNA polymerase I is not affected at any concentration in vitro but it is depressed in vivo, presumably because of depletion of some precursor protein of short half-life as the result of RNA polymerase II inhibition. Quantitatively similar results have been demonstrated with the RNA polymerases of higher plants (61). The action of amatoxins on cellular polymerases II and III on the synthesis of viral RNA of infected cells has also been studied extensively [62; see also review in (63)]. The amatoxins apparently have no effect on bacterial growth (64).

The phallolysins, which are toxic only on parenteral administration, are found in both poisonous and nonpoisonous species of *Amanita* (65). Their chemistry has been studied by Seeger et al (66–68) and by Faulstich & Weckauf-Bloching (69). These substances are acid and thermolabile glycoproteins. Small intravenous doses produce death by intravascular hemolysis which may be associated with secondary renal failure. Higher doses produce cardiac arrest due to elevation of serum potassium following massive hemolysis (70). Their intravenous toxicity (70, 71) in the mouse is 0.04–0.2 mg/kg, in the rat 0.02–0.1 mg/kg, and in the rabbit 0.04 mg/kg. The phallolysins bind to N-acetylglucosamine on the erythrocyte surface in a manner analogous to other plant lectins (72). Their cytolytic activity on erythrocytes and other mammalian cells is in the concentration range of $10^{-8}$ M (reviewed in 71).

Wieland et al (73) isolated a cyclic decapeptide from *A. phalloides* which if administered to a mouse prior to or with phalloidin or α-amanitin would

raise the threshold of sensitivity to these toxins. The mechanism of action of this substance, antamanide, has been examined only in respect to its antagonism of the phallotoxins. It was found to delay absorption of the toxin into the liver, probably because of its action on the cytoplasmic membrane (74). This proposed mechanism is supported by studies using isolated hepatocytes (75).

A comprehensive review of the chemistry and biochemistry of the various peptide constituents of *A. phalloides* by Wieland & Faulstich is in press (75a).

The prolonged latent period, averaging 12 hr, between ingestion and the onset of nausea, emesis, diarrhea, and abdominal pain is pathognomonic for an *A. phalloides*-type mushroom intoxication. The principal manifestation of the usual case is the rapid development of a severe hepatic insufficiency. An increase in serum transaminase levels is the most sensitive indicator of the extent of hepatocellular damage. The values for lactic dehydrogenase are also significantly increased with a marked elevation in LDH isoenzymes of fractions IV and V (76). Serum cobalt–activated acylase initially shows a rapid and intense increase, but the values decline over the subsequent five days regardless of the progress of the patient (77). After a transient increase in blood glucose, hypoglycemia becomes marked as stored glycogen is exhausted. Jaundice may appear and quickly intensify, but it is not a consistent finding, even with severe hepatic damage. All clotting factors of hepatic origin fall simultaneously. A return toward normal of fibrinogen and Factor V is the first sign of recovery in surviving patients and is considered of prognostic value (78). Appropriate early attention to fluid and electrolyte balance usually prevents serious renal involvement. In a survey of a large number of cases made by Cavalli et al (79), only 18% of the patients exhibited oligouria beyond the fourth day of therapy, and there was a low incidence of anuria (see also 80–82). Neurologic signs are presumed to reflect the degree of hepatic encephalopathy. Postmortem examination sometimes reveals necrosis of the pancreas (83). Extracts of *A. phalloides* were found to selectively involve the glucagon-secreting $\alpha$ cells in the rat (84–85a) and guinea pig (85a). In mice, on the other hand, $\alpha$-amanitin was found to affect only the insulin-containing $\beta$ cells (85b). Neither the histopathology nor significance of these findings has been evaluated in man. Hemorrhages and atrophic changes may also be seen in the adrenal cortex (86).

The initial therapy of *A. phalloides* poisoning is to correct the fluid and electrolyte imbalance and metabolic acidosis secondary to the persistent emesis and cholera-like diarrhea. Rehydration should be made with glucose in water with the appropriate electrolyte correction. Thereafter, an infusion of 20% mannitol may afford some protection against oliguria. If the patient can retain orally administered fluid, a slurry of activated charcoal in water

will serve to interrupt the enterohepatic cycling of the amatoxins (87, 88), which should reduce the extent and severity of the lesions in the duodenum. Laboratory determinations (SGOT, SGPT, LDH, BUN, bilirubin, creatinine, glucose), blood clotting factors, body weight, and mental status examinations (tests for constructional apraxia) should be made daily in order to monitor the severity of the intoxication and direct therapy. Further management is no different from that for acute viral hepatitis and fulminant hepatic coma.

Such a regimen of intensive care will reduce the overall mortality rate of 30% (90% if hepatic coma develops) to between 5 to 10%. Since this figure is still unacceptable, a great number of drugs and ancillary measures have been and are continuing to be introduced, particularly in Europe, into the overall management of these patients (52). The employment of hemoperfusion through polymer-coated charcoal for the extraction of metabolites and amino acids involved in the pathogenesis of hepatic encephalopathy has been used effectively in cases of *A. phalloides* intoxications (89, 90). The various drug therapies, however, are extremely controversial. Two of these, because of their current interest, have been selected for discussion here.

In 1963, Kubička credited thioctic acid (α-lipoic acid) with having a beneficial response in some 40 *A. phalloides*–intoxicated patients (91). Since the late 1950s, there had been some interest in this coenzyme for the treatment of a variety of liver diseases including hepatic necrosis due to exogenous toxins. Kubička outlined his management as follows (92). The patient is lavaged and given an enema. Fluid and electrolytes are replaced. The SGOT and SGPT and serum bilirubin are determined twice daily and used as an index for thioctic acid therapy. From the beginning of the intoxication, the patient is given 75 mg/day of thioctic acid as a continuous infusion. If the transaminases show an increase, the dosage is immediately elevated to 300 mg/day and continued at that level until the SGOT and SGPT start to decrease. If coma intervenes, the dosage is further elevated to 500 mg/day. During this period, the patient also receives glucose, thiamine, and ascorbic acid.

There were a number of favorable reports, particularly from Italy, in support of this agent (52). Some doubts were cast on its value in *A. phalloides* intoxications (93–95), and its use for this purpose has declined in France, Switzerland, and Poland. Nevertheless, the first case in which thioctic acid was used in North America (96) received considerable publicity (97–99). Subsequently, three additional reports on its use in mushroom poisoning in the United States have appeared (76, 95, 100).

Remarkably little animal experimentation has been done to evaluate thioctic acid. Confirmations of its value were reported by Obauer & Schön, who unfortunately studied its efficacy only against phalloidin and not against a whole mushroom extract or one of the amatoxins (101). Floer-

sheim found no protective action afforded by thioctic acid alone (102) or in conjunction with glucose (103) in the mouse. Alleva et al (104) and Alleva (105) demonstrated a lack of protective action in the mouse and dog, but this work has been criticized on the basis that inadequate amounts of glucose were given to counteract the hypoglycemic action of the thioctic acid (105). Since this drug is currently recommended in the United States (1), this matter may be resolved in the near future. It is noteworthy that Kubička and his co-workers, while still advocating the use of thioctic acid, point out in their most recent publications that the agent is not an amanitin antidote but rather a vitamin-like compound that makes it possible for the hepatocyte to survive, by catalysis of the Krebs cycle and the respiratory enzymes within the hepatocyte, for the critical period of 5 to 10 days until regeneration of the mitochondria can take place (106, 107).

Various compounds, including penicillin G, were discovered to reduce mortality in *A. phalloides*-poisoned animals (108–111). It was presumed that such drugs acted by displacing the amatoxins from binding sites on serum albumin thus permitting their renal excretion. A number of clinical reports supported the application of high dose therapy with penicillin G (250 mg/kg per day by continuous infusion for 3 to 10 days) as an adjunct in the management of *A. phalloides* poisoning (112–114), and its use in Europe for this purpose is increasing. It has been recently shown, however, that the amanitins do not bind to serum albumin (115), so its beneficial action, if any, cannot be ascribed to enhanced renal excretion.

## *The Cortinarius Group*

A few species of the genus *Cortinarius* induce an acute renal failure which becomes evident only three or more days after ingestion (116). These intoxications were first described for *C. orellanus* in Poland (117) and more recently from that species in Germany (118) and France (119). It has also been found with *C. speciosissimus* (120–122) and *C. gentilis* (123) in Finland. Although *C. gentilis* is found in North America, intoxications have not as yet been reported there. The toxic activity has been ascribed to polypeptides (124), not chromatographically similar to those of *Amanita phalloides* (125, 126), but as yet otherwise uncharacterized. The toxicity of these mushrooms is unaffected by cooking or drying.

The remarkable feature of *Cortinarius* mushroom poisoning is the prolonged latent period between the ingestion and the onset of symptoms, between three and seventeen days. In those cases reported by Grzymala (117), the first effect is a marked polydipsia during which the patient may drink several liters of fluid a day. This is followed by nausea, emesis, constipation, headaches, muscular pains, and chills. In severe poisoning there is an initial polyuria succeeded by oliguria or anuria which is ultimately responsible for the death of the patient.

Postmortem examination shows renal tubular necrosis, fatty degeneration of the liver, severe inflammation of the intestine, and pulmonary and cerebral edema. Nonfatal poisonings are characterized by a prolonged hospitalization averaging seven to nine weeks followed by a convalescence of several months. Treatment is entirely symptomatic.

## *Gyromitra esculenta*

*Gyromitra esculenta* (*Helvella esculenta*) is only rarely involved in poisonings in either North America or western Europe, but such intoxications are seen frequently in eastern Europe. In Poland, for example, 23% of mushroom fatalities each year have been attributed to this species (127). This mushroom contains a number of hydrazones, the first of which was characterized by List & Luft (128, 129). This prototoxin, named gyromitrin, is the N-methyl-N-formyl hydrazone of acetaldehyde. Additional homologues, in which the acetaldehyde is replaced by pentanal, 3-methylbutanal, or hexanal, were later identified by Pyysalo (130, 131). All of these compounds hydrolyze easily in vivo to form the toxin monomethylhydrazine.

A chromatographic method for separation coupled with spectral analysis of the eluent provides a rapid method for the detection of gyromitrin in mushroom fragments (132). Gyromitrin and its higher homologues and monomethylhydrazine are readily extracted from the mushroom by boiling water. This treatment removes 99.5% of the toxins from the mushroom within 10 min (133) but a significant amount of the hydrazine may be retained in the cooking water if this is to be consumed as a soup or stew. None of the toxins are present in clinically significant concentration in the canned or air dried mushrooms of *G. esculenta* of commerce; their content of gyromitrin for example, is about 3 mg/kg (134) compared to 1.2 to 1.6 g/kg in fresh specimens (133, 135). Residues of the higher homologues remaining after drying or boiling have also been determined (136).

In 1883, Bostroem published a review of 151 cases of poisoning including 59 fatalities caused by *G. esculenta* which had been reported in the European literature (137). This review updated to 1965 by Franke et al (138). The intoxications are characterized by a sudden onset of symptoms commonly appearing about 6 to 8 hr after ingestion. The initial effects are fatigue, dizziness, severe headache, and a feeling of fullness or abdominal pain. This is often accompanied by emesis that may persist intermittently for several hours. Generally, poisoning will be no more severe than this, the patient recovering completely in two to six days. In more serious cases an acute hepatitis may appear which may result in death.

The early gastroenteric phase of the intoxication may require fluid and electrolyte replacement, particularly in children. Since hydrazines interfere with the action of pyridoxine, the daily intravenous administration of pyridoxine should be initiated. The clinical features and management do not

differ from that for an acute overdose of isoniazid (139). A rare complication is hemolysis with secondary renal involvement which may require dialysis until kidney function returns.

## MUSHROOM INTOXICATIONS WITH RAPID ONSET

### *Mushrooms Inducing Parasympathetic Hyperactivity*

A number of species of *Inocybe* and *Clitocybe* mushrooms contain clinically significant concentrations of muscarine. There was some suspicion that other muscarine isomers might be present in a few of these, e.g. *I. napipes,* since their muscarine content was not sufficient to account for the parasympathetic response attainable in a bioassay (140, 141). This was shown to be the case; all four diastereoisomers of muscarine may occur in *Inocybe* (141a) and in varying distribution in other genera (141b).

The toxic response to these mushrooms is not affected by cooking. Symptoms are usually evident within 15 to 30 min, rarely beginning after one hour. An analysis of published case reports (52) shows a dose-response relationship in the occurrence of symptoms, the most sensitive indicator being profuse sweating. More severe intoxications produce nausea, emesis, and abdominal pain. Occasionally reported effects are blurred vision, salivation, rhinorrhea, lacrimation, and diarrhea. Rare symptoms include tremors, dizziness, and bradycardia.

This is the only type of mushroom poisoning for which atropine is indicated. It may be given until symptoms are abolished or until dryness of the mouth is produced. The symptoms will normally abate, even without therapy, within 2 hr.

### *Mushrooms Inducing Delirium Or Hallucinations*

PSILOCYBIN-CONTAINING MUSHROOMS Certain species of *Psilocybe, Copelandia, Panaeolus,* and *Gymnopilus* mushrooms contain psychoactive concentrations of psilocybin and psilocin. The presence of these toxins in the latter genus depends upon its geographic source (142). Although psilocin is sensitive to oxidation, psilocybin is relatively resistant, so considerable activity is retained in dried mushrooms. Psilocybin may be extracted into boiling water.

The clinical response to these mushrooms does not differ from that using the pure drug. The psychological response is determined by the dose, setting, sophistication with similar psychoactive substances, mood, and personality of the subject. The temporal sequence of onset of the clinical effects (143, 144) and the frequency of different physical and psychological responses at identical dosage in experimental subjects (145) have been determined. The usual duration of action is 2 to 4 hr.

Intoxication with psilocybin-containing mushrooms is usually deliberate. The hallucinatory oral dose of psilocybin in a nontolerant adult is 6 to 12 mg, which will require a fairly large number of mushrooms depending upon the species and its growth conditions. The accidental poisoning of small children is therefore unlikely unless the mushrooms have been inappropriately gathered and cooked for food. There have been a few reports (146, 147) of mydriasis, hyperthermia, loss of conciousness, tonic-clonic convulsions, and death in small children. No systematic study seems to have been conducted on the pharmacology of psilocybin at extremely high dosage. Because of the brevity of the response at the usual hallucinatory dosage range, therapeutic intervention is rarely sought or required. The effects may be terminated, however, by the administration of diazepam or a phenothiazine.

THE AMANITA MUSCARIA GROUP Although there are a number of reports, particularly in the European literature, of poisonings by members of the *A. muscaria* group when prepared as food, intoxications are now more generally associated with the deliberate ingestion of the mushroom for its psychoactive response. Despite its species name, *A. muscaria* usually contains only traces of muscarine, but an occasional strain may induce sweating and salivation. Its principal toxins were elucidated independently by Bowden et al (148, 149), Takemoto et al (150, 151), and by Müller & Eugster (152). These are an isoxazole amino acid named ibotenic acid and its decarboxylation product muscimol. These substances are also found in *A. pantherina, A. cothurnata,* and, in low concentrations, in *A. gemmata* (153). Both compounds have been examined singly as pure substances in man (154–156). Cooking does not markedly affect activity, but the dry mushroom gradually loses activity with time.

Both ibotenic acid and muscimol may be detected in human urine within 1 hr of ingestion. It is presumed that most of the muscimol is metabolized (157), but the metabolic products have not been identified. Although their action is similar, it is thought that muscimol because of its potency and concentration is more likely to be responsible for the observed CNS effects. Both compounds are GABA receptor agonists (158–162).

Symptoms normally appear within 20 to 90 min after ingestion. There may be an initial gastroenteritis, but this is often minimal or absent. After about 1 hr there is drowsiness and dizziness which may be associated with sleep. This may be followed by elation, increased motor activity, tremors, illusions, e.g. echo pictures, micropsia, confused identities, or even manic excitement. This phase may alternate with periods of drowsiness or sleep. The delirium is both subjectively and electroencephalographically different from psilocybin hallucinations and more nearly approaches that produced by the belladonna alkaloids although it is not affected by physostigmine

(163). A complex neurological pattern may be seen in children suffering severe intoxications from ingestion of these mushrooms. Such poisonings may progress to tonic-clonic convulsions and coma. Despite the apparent severity of such intoxications in children, they usually resolve within 6–9 hr without therapy, although airway management and anticonvulsant medication may be required in some circumstances. Poisoning in adults is rarely severe, but may require protective care in cases with severe manic excitement.



### *Mushrooms with a Disulfiram-Like Activity*

By far the most common mushroom capable of inducing a disulfiram-like sensitization to alcohol is the edible and desirable species *Coprinus atramentarius.* This mushroom contains the protoxin coprine, whose structure was determined independently by Lindberg et al (165) and by Hatfield & Schaumberg (166). This thermostable toxin, $N^5$-(1-hydroxycyclopropyl)-L-glutamine is inactive in vitro. It is converted in the body to 1-aminocyclopropanol (167), a potent aldehyde dehydrogenase inhibitor. The coprine content of fresh *C. atramentarius* is about 160 mg/kg.

Maximal sensitization to alcohol following consumption of the mushroom probably requires about 3–6 hr, but this has not been systematically evaluated in man. The duration of sensitization varies from 24 to 72 hr. The nausea, emesis, hypotension, sweating, headache, and other manifestations of acetaldehyde accumulation following alcohol ingestion in the sensitized individual persists for about 2–3 hr. Therapeutic intervention other than reassurance is usually not required but it has been reported that propranolol will moderate the untoward response (168).

### *Simple Gastroenteric Irritants*

Numerous compilations are available for both Europe and North America listing those mushrooms whose principal response is gastroenteritis (1, 52, 169–173). Little is known of their chemistry (52, 169) or toxicology. All produce varying degrees of abdominal discomfort within 3 hr of ingestion. Some may produce a persistent emesis and diarrhea which, particularly in children, may rapidly result in severe dehydration, electrolyte loss, and hypovolemic shock. From a therapeutic standpoint, the identification of the irritant mushroom is not really necessary. Beyond replacement of fluids and electrolytes, treatment is entirely symptomatic as for gastritis of any other etiology.

## UNCLASSIFIED TOXIC MUSHROOMS

Although the chemistry and pharmacology of the mushrooms most frequently involved in serious and fatal intoxications have now been deter-

mined, a large number of toxic species remain to be examined. Most of these have received only single or a limited number of case reports of poisonings, but from these it is possible to select a number of intriguing pharmacological properties of potential research interest, e.g. *Scleroderma aurantium,* tetany and paresthesias (174); *Stropharia coronilla,* "bone pain" (175), *Paxillus involutus,* an immunohemolytic action which may be complicated by secondary renal failure (176); *Verpa bohemica,* muscular incoordination (177); *Hypholoma* (*Naematoloma*) *fasciculare,* an *Amanita phalloides*-like hepatitis, but with a more rapid onset of symptoms (178, 179); *Volvariella volvacea,* an edible mushroom with a cardiotoxic protein (180); and *Omphalotus* (*Pleurotus, Clitocybe*) *olearius,* paresthesias, sensory disturbances, and a potent muscle relaxant (181).



## SUMMARY

Much progress in the areas of identification of active components and elucidation of the toxic mechanisms for the principal poisonous mushrooms has been made in the past decade. This affords a more rational approach to therapeutic management which has consequently resulted in a decrease in the morbidity and mortality associated with these species. However, the effectiveness of a large number of adjuvants for *Amanita phalloides* poisoning still needs critical laboratory evaluation. The current status of knowledge concerning the toxic potential and contituents of many mushroom species, including the gastroenteric irritants, is inadequate. The problem of geographic variation or genetic strain in the concentration of toxins of many species also requires further investigation.

The recent awareness and interest in the pharmacology and toxicology of uncultivated mushrooms in North America and Great Britain should encourage continued active research.

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