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SPECIAL ARTICLE

MUSHROOM TOXINS — A BRIEF REVIEW OF THE LITERATURE

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DEATHS from mushroom poisoning are uncommon in this country chiefly because gathering wild mushrooms for the table is the hobby of only a few enthusiasts, but also because the great bulk of fungi are harmless. A few are deadly.

Of 24 fatal cases recorded in American literature since 1924 and in personal communications, 11 were due to the bulb agarics with white, amyloid-staining spores (*Amanita verna* and its subspecies and American phenotypes of *A. phalloides*),† 7 to the ascomycete *Gyromitra esculenta,* 1 to the panther mushroom *A. pantherina,* whose white spores do not take the amyloid stain, and 5 to undetermined or unrecorded species. Each of the identified varieties contains its own characteristic toxins. Serious but ordinarily nonfatal poisoning may follow ingestion of other species, most of which are known to mycologists and collectors.

These poisons may conveniently be considered in five groups: the highly lethal toxins contained in the bulb agarics (the "amanita toxins," with a fatality rate of perhaps 50 per cent); the less fatal but still serious poisons contained in *A. muscaria* and *A. pantherina* — muscarin and its concomitants; the *gyromitra* toxins; the hallucinogens; and a miscellaneous group. It may be that specific toxins are present in more than one group.

THE BULB AGARICS

The clinical picture after ingestion is well known: a latent period of six to twenty hours, then vomiting and diarrhea, which may result in death with cholera-like manifestations, or may be followed by a false remission and subsequent signs of liver and kidney damage. The blood sugar may rise initially, but then falls markedly. Terminally, there is central-nervous-system involvement, with excitation, convulsions and coma. The story of the isolation and identification of the amanita toxins has been comprehensively reviewed by Wieland and Wieland.[1] They are five in number, all cyclopeptides, and the amounts present in any given amanita may be determined by spectrophotometric assay after paper chromatographic separation and elution of the compounds. They are as follows:

Phalloidin. The chemical structure has been quite accurately determined. The toxin is quick acting, with a toxicity (LD_{50}) of 2 mg. per kilogram of body weight when tested by intraperitoneal injection in the albino mouse.

Phalloin. This is closely related to phalloidin. Its toxicity is about 1 mg. per kilogram.

Alpha amanitin, the γ-lactone of α-amino-β-methyl-γ-hydroxy-γ-hydroxymethyl-n-valeric acid. Its toxicity is 0.1 mg. per kilogram, twenty times that of phalloidin, but its action is twenty times as slow. This is probably the principal source of mischief in cases of human poisoning by *A. phalloides* or *A. verna.*

Beta amanitin. This component is neutral in reaction, and has a toxicity of 0.4 mg. per kilogram.

Gamma amanitin. Its toxicity is 0.8 mg. per kilogram.

THE MUSCARIA GROUP

There is no question that *A. muscaria* and *A. pan-*

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†The chief culprit in Europe is the greenish *A. phalloides,* which is not found in the eastern United States.

Amanita muscaria.
Courtesy J. W. Ballou.

Gyromitra esculenta.
Courtesy Mrs. John G. Curtis.

Coprinus atramentarius.
Copyright 1950,
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Amanita pantherina.
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Clitocybe illudens.
Courtesy J. W. Ballou.

Amanita verna.
R. W. Buck, M.D.

therina have caused fatal poisoning; however, *A. muscaria* (the fly agaric) is also known for two centuries to have been used as a pleasurable intoxicant by Kamchatka Eskimos, and there is little doubt that many people in many areas have eaten both species with impunity. The symptoms of intoxication are threefold, and depend upon which of three recognized toxic substances is predominantly present in the particular specimen eaten:

Muscarin. Schmiedeberg and Koppe,[2] in 1868, isolated an alkaloid from *A. muscaria* that, when given subcutaneously to cats, was found to cause within a very few minutes salivation, retching, vomiting, diarrhea and tenesmus, miosis, bradycardia, rapid breathing, dyspnea and finally cessation of respiration. In "winter frogs" *(R. esculenta)* it produced cardiac standstill in diastole. These symptoms were not unfamiliar to medical observers who had cared for victims of mushroom poisoning. The chemistry of muscarin has been reviewed by Bowden and Mogey.[3] They agree, with some reservations, that it is probably the quaternary trimethylammonium salt of 2-methyl-3-oxy-5-(aminomethyl)-tetrahydrofuran. Physiologically, it stimulates the effector organs innervated by postganglionic cholinergic fibers, slows the heart rate, increases muscle tone and motility of the stomach and intestines and causes miosis, sweating and salivation. Its effects are completely counteracted by atropine. *Inocybe patouillardi,* a European ochre spored mushroom that has caused fatal poisoning, contains one hundred and twenty to three hundred and eighty times as much of this toxin as *A. muscaria,*[4] a finding that had been anticipated by Loup's studies in 1938 of inocybe in Switzerland.[5] Muscarin has been found in numerous other mushrooms, including the common *Russula emetica.*[6]

Pilzatropin (mushroom atropine). Soon after the identification of muscarin as the active poisonous principle of *A. muscaria* and some other mushrooms, it was found that when an incompletely purified preparation was injected into frogs in larger doses than were needed to produce cardiac arrest, the heart was accelerated. The observation was confirmed by Schmiedeberg, and the impurity was named "pilzatropin" by Kobert[7] in 1891. Kobert also found it in *A. pantherina, Russula emetica* and *Boletus luridus.* Harmsen,[8] in 1903, restudied the relation of muscarin to *A. muscaria* poisoning, and although himself unable to find pilzatropin in specimens collected in the Bavarian alps, thought its existence could hardly be doubted. He recalled that as early as 1832 Krombholz had noted dilatation of initially contracted pupils and other symptoms that could not be attributed to muscarin alone. He believed that the clinical picture of *A. muscaria* poisoning varied in accordance with the amounts of each toxin present, and that this in turn depended upon environmental and climatic influences. In 1955 Lewis,[9] in South Africa, extracted *A. muscaria* and *A. pantherina* and obtained, in addition to muscarin, material that by its melting point, Vitali's test, bioassay and paper chromatography seemed identical with L-hyoscyamine. He therefore suggested that pilzatropin is in fact L-hyoscyamine. The racemic (DL) form of L-hyoscyamine is, of course, atropine. He consequently urged caution in the use of atropine as an antidote in cases of poisoning due to *A. muscaria* and *A. pantherina,* in which it had for many years been regarded as almost a specific. Brady and Tyler,[10] four years later, found no hyoscyamine in specimens of *A. pantherina* gathered in western Washington.

Pilztoxin. As suggested above, Harmsen, after experimentation not only with muscarin but with whole extracts, concluded that the poisonous effects of the fly agaric were not identical with those of muscarin. After neutralization of the muscarin effect with atropine, both in man and in laboratory animals central effects persisted: a narcotic intoxication, convulsions and occasional deaths that had occurred in spite of adequate administration of atropine. He postulated a pilztoxin in addition to the pilzatropin that he had been unable to find himself.

Bufotenine. Kobert had found what he thought might be pilzatropin in *A. mappa,* a congener of *A. phalloides,* distinguishable by the yellow color of its flesh and its odor of potato germ or onions. But when Wieland et al.[11] investigated *A. mappa,* they recovered bufotenine, the indole derivative 5-hydroxy-N-dimethyltryptamine. They also found it in *A. muscaria* and *A. pantherina.*

Bufotenine was originally isolated from the secretion of the parotid gland of the European toad *Bufo vulgaris* (Laur). It has also been found in a tropical shrub, *Piptadenia peregrina.* Fabing and Hawkins[12] reported that when it was injected in 8-mg. doses intravenously into human subjects, it caused lightheadedness, purple flushing, nausea, air hunger, dilated pupils, nystagmus, visual hallucinations and sweating. The symptoms disappeared in seven to forty minutes. Brady and Tyler[10] found no bufotenine in *A. pantherina* collected near Olympia Washington, but they noted that persons who had eaten the fungi experienced the typical color hallucinations attributed to the toxin by Fabing and Hawkins. Whether bufotenine is either pilzatropin or pilztoxin or both remains to be proved.

The Gyromitra Toxins

Gyromitra esculenta belongs to the tribe that includes both truffles and the morel *(Morchella esculenta),* both highly prized by epicures, and is eaten by country people in eastern Germany and Poland,

where most reported fatalities have occurred. At least 2 fatal cases have been reported in this country.[13,14] *Gyromitra* (formerly called *Helvella*) *esculenta* was exhaustively studied in 1882 by Bostroem[15] in a series of experiments that included feeding extracts and residues to dogs together with analysis of 151 cases of human poisoning, 59 of which (40 per cent) had resulted fatally. His results were so conclusive and have been confirmed by so many clinical observations that no one has been impelled to repeat them.

Helvellic acid. In 1885 Boehm and Külz[16] extracted from *Helvella esculenta* a yellow, transparent syrup, which they named helvellic acid and to which they ascribed a molecular formula $C_{12}H_{20}O_7$. They also found choline to be present in considerable amounts. Helvellic acid caused hemolytic poisoning when administered to dogs by mouth. Boiling resulted in almost complete destruction of the toxin (Bostroem had found that by boiling the mushroom for several minutes and discarding the water, he could remove the toxin). Friese,[17] in 1950, confirmed the removal of the poison content by scalding with boiling water twice, each time for five minutes, and stated that the pH values of the mushroom's juices vary between 5.78 and 6.4. No other chemical or experimental data concerning this toxin have been reported. In 1933 Aye[18] reported the presence in the fungus of a volatile, apparently O-free alkaloid, characterized by an unpleasant odor, similar to that of mouse urine, which yielded precipitates with tannin, picric acid, iodized potassium and other reagents. The amount present in the dried mushroom was minute, and nothing is reported of its toxic qualities.

The toxin is not uniformly present in *Gyromitra esculenta,* but seems to vary with climatic or other undetermined factors. The mushroom has caused poisoning in persons who had eaten it for years without ill-effect, and small, localized groups of cases have occurred more frequently in some years than others. Although helvellic acid is heat labile, experience has shown that simple parboiling before preparation for the table cannot be relied upon. Drying the mushroom reduces or perhaps destroys the toxic effect. Salting was found effective by Bostroem in removing the poison, possibly by its hygroscopic effect, but in the fatal case reported by Dearness, the mushrooms had been soaked overnight in salt water. Whether the water was discarded and whether the mushrooms were adequately cooked and drained is not reported. Helvellic acid is a hemolytic toxin and causes malaise, vomiting, diarrhea, jaundice and (in animals only) hemoglobinuria. Cases have also been reported that show such neurotoxic effects as giddiness, delirium and convulsions. It is of some interest that Apicius Caelius,[19] the celebrated Roman epicure, in describing the preparation of this fungus, advised that it be boiled, stirred and allowed to cook again, then drained, seasoned and served.

The Hallucinogens

In 1957 Heim,[20] who had accompanied V. P. and R. G. Wasson on an expedition to Mexico in 1956 in search of mushrooms, reputedly used by the Indians for divination, reported the discovery of five new species of psilocybe that caused narcotic intoxication of a type that has greatly interested psychiatrists, characterized among other effects by strange hallucinations. Heim, with Hofmann et al.,[21] was able to isolate from these fungi a compound possessing indole characteristics and containing phosphorus, which they named psilocybin.

Psilocybin. This compound, O-phosphoryl-4-hydroxy-N-dimethyltryptamine, has also been recovered from a species of stropharia and one of conocybe. Stein[22] reported, after eating 5 mg. of *Psilocybe cubensis,* visual hallucinations within fifteen minutes, memory impairment after twenty-five minutes and inability to concentrate after half an hour. There were smothering sensations and dryness of the mouth after one and a half hours. Recovery was complete after eight to ten hours. There were no pleasant effects such as were described by earlier reporters.

Panaeolus campanulatus, var. *sphrinctrinus,* a black spored mushroom, was identified in 1938 by Schultes[23] as the sacred fungus *teonanacatl* of the Aztec Indians of Mexico. Stein et al.[24] reported in 1959 that *P. venenosus,* a related species, in 1.0-gm. doses by mouth produced dilated pupils, sweating, slight dizziness and tingling of the fingers after half an hour, disturbance of equilibrium and a bitter sensation at the tip of the tongue after another ten minutes and complete recovery at the end of about five hours. Paper chromatography showed no psilocybin, but a chromophore (a 4-oxygenated indole system) like that of psilocybin. Tyler[25] found serotonin in this mushroom. Serotonin had no physiologic effect in human beings in 20-mg. doses, but its dimethyl derivative, bufotenine, has been mentioned above as a constituent of *A. mappa, A. muscaria* and *A. pantherina.*

Miscellaneous Toxins

Coprinus atramentarius, a black spored mushroom, has the peculiar quality of causing nitritoid symptoms if alcoholic beverages are drunk before, during or after its ingestion. *Boletus luridus* is reputed to cause similar symptoms under the same circumstances. The fact that disulfiram (Antabuse), which is tetraethylthiuram disulfide, causes flushing, palpitation, dyspnea, hyperventilation, acceleration of the pulse, a fall in blood pressure, nausea, vomiting and collapse when a person who has taken it drinks alcoholic beverages suggested that this chemical substance might be found in the mushroom. Simandl and Franc[26] reported its isolation from coprinus in 1956. Wier and Tyler[27] found none in laboratory cultures of the fungus.

List and Reith,[28] in Würzburg, were unable to demonstrate any untoward effects after ingestion of raw *Coprinus atramentarius* and alcohol, but a glass of wine taken twenty-four hours after the cooked mushrooms were eaten resulted in the clinical picture of alcohol disulfiram (Antabuse) intoxication. They could not find any disulfiram in the specimens that they examined chemically.

Clitocybe dealbata has been reported by American observers to cause profuse sweating moments to several hours after ingestion. Atropine or belladonna relieves the symptom. Jelliffe[29] has described his own experience and summarized other reports.

Lepiota morgani, common in the Midwest, but rarely found in New England, when eaten raw has caused thirst, nausea, vomiting, giddiness, tingling and a sensation that light was unusually bright.[30]

Cortinarius (Dermocybe) orellanus has recently been found by a Polish investigator[31] to cause an acute intoxication of the kidneys, with a mortality rate of 14 per cent (19 deaths in 132 cases).

Clitocybe illudens (the jack-o'-lantern) and many other fungi have quite regularly caused gastrointestinal disturbances. Mushroom eaters know of dozens of other species that are traditionally supposed to be inedible or in varying degrees toxic, but little or nothing is known of their chemical constituents.

A good deal of time has been unprofitably spent in injecting decoctions of various fungi or their alcoholic extracts into guinea pigs, rabbits or mice. Such experiments indicate that the material is or is not toxic under the circumstances, but throw little light on the identity of the offending substance. Dupetit,[32] in 1882, was able to kill rabbits by injecting into them the juices of such harmless and edible mushrooms as *Boletus edulis, A. caesarea, A. rubescens* and even the common table mushroom *Agaricus campestris*. Much more can be learned by feeding of whole mushrooms, or an extract and the residue separately, through a stomach tube to cats or dogs.

When confronted with a case of suspected mushroom poisoning the physician should make every effort to recover and identify the fungus, even though only fragments from the stomach contents are available, to record the date and the place where it was gathered, a careful history of the symptoms in the exact chronologic order of their appearance, to treat the patient symptomatically rather than by rule, and to call in expert assistance if it is available.

From a list of more than 800 species of mushrooms gathered in New England and identified by members of the Boston Mycological Club since 1896, Dr. Emil F. Guba, professor of plant pathology, University of Massachusetts, has listed only 53 varieties that are considered to be poisonous.[33] In Table 1 these have been arranged alphabetically, and their probable toxins identified so far as possible in the light of present knowledge.

Suggested Principles of Treatment of Intoxication

Encourage early emesis and evacuation by any appropriate means. Vomiting is preferable to lavage, since portions of fungus may be too large to pass through a stomach tube.

If ingestion of a mushroom of the bulb agaric group (*A. verna* and so forth) is suspected, emptying the stomach and bowels within the first six

Table 1. *Poisonous Varieties of Mushrooms.*

Mushroom	Toxin
Amanita brunnescens	? Amanita toxins
A. mappa	Bufotenine[11]; pilzatropin.[7]
A. muscaria	Muscarin[2,9]; pilztoxin[8]; levohyoscyamine[9]; bufotenine.[11]
A. pantherina (cothurnata)	Muscarin; pilzatropin[7]; levohyoscyamine[9]; bufotenine.[11]
A. spreta	? Amanita toxins
A. verna	Amanita toxins[1,33]
A. virosa	Amanita toxins[1]
Amanitopsis volvata (agglutinata)	Undetermined
Boletus luridus	Pilzatropin[7]; ? disulfiram.[26]
	Unidentified gastrointestinal irritant
Boletus miniato-olivaceus	Unidentified gastrointestinal irritant
Clitocybe dealbata (sudorifica)	? Muscarin[29]
Cl. illudens	Unidentified gastrointestinal irritant
Conocybe	Psilocybin[21]
Coprinus atramentarius	Disulfiram[26]
Cortinarius caerulescens	Undetermined
Entoloma grande	Unidentified violent gastrointestinal irritant
E. lividum	Unidentified
E. strictius	Unidentified
Gyromitra esculenta	Helvellic acid[16]
Hebeloma crustuliniforme	Undetermined
H. fastibile	Undetermined
H. infula	? Helvellic acid
Hypholoma capnoides	Undetermined
H. fasciculare	Undetermined
H. lachrymabundum	Undetermined
Inocybe infelix	? Muscarin[5]
I. infida	? Muscarin[5]
I. rimosa	? Muscarin[5]
Lactarius fumosus	Undetermined
L. rufus	Unidentified mild heat-labile toxin
L. torminosus	? Muscarin (undetermined)
L. uvidus	Undetermined
Lepiota morgani	? Muscarin[30]
Marasmius peronatus (urens)	Undetermined
Mycena splendidipes (viscosa)	Undetermined
Panaeolus campanulatus	? Serotonin[25]
P. papilionaceus	? Serotonin[25]
Pholiota autumnalis (marginata)	Undetermined
Psilocybe	? Psilocybin[21]
Russula adusta	Undetermined
R. emetica	Pilzatropin[6]; muscarin.[32]
R. fellea	Undetermined
R. foetans	Undetermined
R. fragilis	Undetermined
R. nigricans	Undetermined
R. rubra	Undetermined
R. sanguinea	Undetermined
Stropharia	? Psilocybin[21]
Tricholoma album	Undetermined
T. pardinum	Unidentified gastrointestinal irritant
T. saponaceum	Undetermined
T. sulphureum	Thermolabile hemolysin
T. venenata	? Muscarin

hours, even though no symptoms have occurred, may save a life. Serious symptoms occurring more than twelve hours after ingestion must be met with counteractive or supportive measures as suggested by the clinical findings. Liver damage may be combated by procedures similar to those followed in the treatment of carbon tetrachloride poisoning.

Sweating, constricted pupils and abdominal cramps call for the administration of adequate doses of atropine. If the pupils are dilated and the pulse is very rapid, caution is necessary in the use of this antidote.

Syndromes not attributable to the amanita toxins or to muscarin and pilzatropin (levohyoscyamine) are in general self-limited, and may be treated symptomatically.

Every possible effort should be made to identify the offending fungus and the toxin responsible for symptoms.

Summary

Four specific groups of toxins occur in a relatively small number of mushrooms: the amanita toxins, which are responsible for the great majority of deaths; muscarin, levohyoscyamine and probably bufotenine; helvellic acid; and the hallucinogens, typified by psilocybin. Other mushrooms contain gastrointestinal and other irritants that have not been satisfactorily isolated or identified. Principles of treatment of intoxication are suggested.

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MEDICAL PROGRESS

ACUTE GLOMERULONEPHRITIS*

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In the past decade significant contributions have been made to the understanding of acute glomerulonephritis by virtue of advances in many fields, including epidemiology, immunology, histopathology and cardiovascular physiology. In addition, a variety of careful clinical observations have clarified many aspects of the natural history of the disease. Accordingly, a critical summary of these new data and an analysis of their clinical implications seem both desirable and timely.

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Epidemiology

It has long been known that acute glomerulonephritis, like acute rheumatic fever, often follows infections with beta-hemolytic streptococci, but many