whose chemistry is now fully understood. The pharmacological investigations have shown, in fact, that muscarine itself is not the prime cause of the previously mentioned central activity of *A. muscaria*. The low plant content (2–3 mg./kg. undried fungus), in conjunction with its relatively weak activity on oral consumption, leads to the conclusion that muscarine can only be considered as a minor active component of *A. muscaria*.

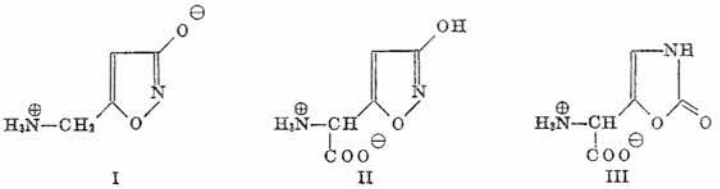
During the last few years it has been proposed that one or another of the bases bufotenine, atropine, hyoscyamine and scopolamine, could be responsible for the main central activity of *A. muscaria*. With regard to these suggestions the following comments can be made. The amounts of these compounds reported to have been isolated (0.1–0.2 mg. atropine; 0.4–0.7 mg. scopolamine per kg. undried carpophores), although not rigorously confirmed, in relation to their known activity, exclude them as possible causes of *A. muscaria* poisoning. Moreover, other authors have demonstrated that Belladonna alkaloids (atropine, hyoscyamine, scopolamine) do not occur in *A. muscaria*. In addition, in our hands investigation of both Swiss and South German varieties of *A. muscaria* has led to the isolation of several indolic substances the structures of which have not yet been elucidated. Bufotenin, however, was found not to be present.

Recently, the highly active muscimole and ibotenic acid have been isolated from *A. muscaria*.

The pharmacological tests (narcosis-potentiation) which were used as an aid in the isolation of these substances lead us to the conclusion that the materials are in fact active on the central nervous system. Their structures have been elucidated and several syntheses published.

Muscimole, $C_4H_6N_2O_2$, m.p. 155–156° (from water), 174–175° (from methanol-water), is a very polar and extremely water-soluble substance. It is the enol-betaine of 5-aminomethyl-3-hydroxy-isoxazole (formula I), i.e., it is an unsaturated cyclic hydroxamic acid. Muscimol is easily formed by decarboxylation and loss of water from ibotenic acid, $C_5H_8N_2O_5$, m.p. 145° (dec.). The latter is the zwitterion of α-amino-α-3-hydroxy-isoxazolyl-(5)-acetic acid monohydrate (formula II). It is to be considered a principal active constituent of *A. muscaria*, being present to the extent of 0.3–1 g. per kg. of undried carpophores.

The pharmacologically less active muscazone, $C_5H_6N_2O_4$, m.p. 190° (dec.), co-occurs in varying proportions with muscimole and ibotenic acid in *A. muscaria*. It is also an amino acid, namely, α-amino-α 2(3H)-oxazolonyl-(5)-acetic acid (formula III), and can be produced in the laboratory by UV-irradiation of ibotenic acid. It is probable that, in the plant also, ibotenic acid acts as a precursor for muscazone. We therefore assume that the widely known variation in toxicity of *A. muscaria* results from fluctuations in the ibotenic acid—muscazone ratio.



I II III

Our latest investigations have shown that *A. muscaria* produces still further physiologically active substances the structures of which are not yet known.

The Pharmacology of *Amanita muscaria*

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Because of its extraordinary pharmacological activity, muscarine, the best-known alkaloid of *Amanita muscaria*, has been investigated for more than 100 years by chemists and pharmacologists. It was the first drug with selective action on the autonomous nervous system. After its isolation in a pure and crystalline form (Eugster and Waser, 1954), its chemical structure and synthesis were established (review by C. H. Eugster, S. Wilkinson). During the isolation process different screen-

ing methods were used. They are based on the strong parasympathomimetic activity of muscarine (review by P. G. Waser, 1961). Until today nobody was able to show a direct psychotropic action of muscarine on animal or man, probably owing to its difficulty in passing the blood-brain barrier. In contrast, muscarine applied directly into the brain was shown to have an excitant action.

The active principles responsible for hallucinogenic or sedative symptoms described by different authors are only partly identified. Belladonna-like alkaloids, Serotonin and Bufotenin have not been extracted from the mushroom with certainty, but possibly there are other hydroxy-indoles present.

Lately Eugster, Theobald, and colleagues (1965) discovered muscimol, ibotenic acid, and muscazon in different varieties of amanita muscaria. These aminoacids and amines have pronounced sedative and hypnotic actions in mice, but little is known of their hallucinogenic activity. Their pharmacology on small animals was investigated with different methods. The temperature of reserpinized mice (2 mg./kg. i.p.) is increased with orally administered 4 mg./kg. muscimol as with LSD, psilocybin, amphetamine, or cocaine but not changed with 10 mg./kg. ibotenic acid.

The diameter of mouse pupil is enlarged by intraperitoneal injection and oral ingestion of muscimol (4–8 mg./kg.) and ibotenic acid (16 mg./kg.). Both compounds showed a marked anorexogenic effect on mice (2–3 mg./kg. oral) with sedation, hypnosis, muscle twitchings, and catalepsy.

Most important is the psychotomimetic action on man. Muscimol (10–15 mg. oral dose) makes a toxic psychosis with confusions, dysarthria, disturbance of visional perception and hearing, illusions of colour vision, muscle twitching and myocloni, disorientation in situation and time, weariness, fatigue, and sleep with dreams. Small doses (5 mg.) improve performance in concentration tests, but large doses diminish psychic performances and learning. Ibotenic acid and muscazon have less central action. Muscimol is excreated in the urine.

With different screening methods we are looking now for other psychoactive principles in amanita muscaria.

Ethnopharmacological Investigation of Some Psychoactive Drugs of Siberian and Far-Eastern Minor Nationalities

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With minor nationalities of Siberia and the Far East there have been in use various narcotics and stimulants either in popular medicine or as intoxicating liquors.

Fly agaric (*Amanita muscaria*) has been used chiefly by the paleoasiatic peoples of Kamchatka and Chukotka (Itelmeni, Koryaki, Chukchi, Yukaguiri). It has been used for merrymaking, overcoming certain difficulties, instilling one's nerve at the time of intertribal clashes and wars, or during a performance of rituals.

There have been known two uses of fly agaric: in its natural state and in the way of infusion. More drastic was an infusion of fly agaric in willow-weed wash. It was prepared from willow-weed (*Epilobium angustifolium L*) boiled down to a sweet and thick wash. In days of old, fly agaric was used in Siberia and Kamchatka for homebrewed or added-to underproof vodka, which led to intense excitement frequently ending in murder or suicide and now and again in death as a result of poisoning. To minor nationalities of the northeast of Asia there has been known a twofold use of fly agaric and its infusion—the so-called "moderate" and "immoderate." Itelmeni themselves considered the use of fly agaric up to four mushrooms at a time as moderate, which contributed to an increase of the organism resistance to fatigue, took off weariness, acted tonically. When immoderately used, from 5 to 10 mushrooms at a time, there came a second stage of fly-agaric effect which was accompanied by intoxication and hallucinations. The effect of fly agaric continued until the products were evacuated from the system of a man. Even the urine of a man would have an inebriating effect. "With sedentary Koryaki fly agaric is in so high esteem," wrote S. P. Krasheninnikov, "that a drunken man is not allowed