

Nutmeg Poisoning.

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IN most text-books on toxicology the oils of tansy, pennyroyal, and sage are mentioned as the members of the volatile oil group from which poisoning occurs, and I am not aware that any author has included nutmeg and its oils as a cause of symptoms. Yet a very considerable number of cases of poisoning with nutmeg are recorded in medical literature. Some years ago I suggested to Dr. G. B. Wallace, then my assistant, that he should collect these cases, and from a study of them he was induced to examine the pharmacological action in animals and to separate the poisonous constituent of the nutmeg. His results were published in 1903,¹ but as they are not very accessible I have thought it well to bring them before you.

Wallace found that cases of poisoning occurred exclusively from the use of the crude nutmeg or of mace, which, of course, is more readily accessible than most other poisons; in many instances it had been used as an abortifacient or emmenagogue, although in the cases of poisoning recorded it does not seem to have exercised any action on the uterus.

Curiously enough, the subject of nutmeg poisoning, which is ignored by present writers, was very early recognised by the older authorities on toxicology. Thus Lobelius, in 1576, relates a case in which a woman was rendered delirious by nutmegs, and Paullinus, in 1704, gives some experience in the matter. In recent years Wallace found twenty-five cases reported in the medical press, and there is every reason to believe that this represents only a small fraction of those occurring. Since Wallace's paper appeared, I have met two or three further instances of poisoning in the journals. The quantity of nutmeg used in these cases of poisoning varies, but a large number of patients stated that they had taken one or one and a half nutmegs grated or cut into fine pieces, so that this quantity appears to be sufficient to cause intoxication in many instances. One man is stated to have been poisoned by a teaspoonful of mace.

The symptoms generally come on in the course of one to six hours, and consist in drowsiness passing into stupor, from which the patient

¹ "Contributions to Medical Research," dedicated to V. C. Vaughan, Ann Arbor, Michigan, 1903.

sometimes can be aroused with difficulty, and then is unable to recognise his surroundings, sees double, and gives other evidences of cerebral depression, although sometimes he may be able to answer questions. Delirium is frequently present before the stage of stupor, or the patient, on being aroused, may be delirious for a time. In some patients spasmodic movements of the jaw are recorded, in others continual laughter or persistent disconnected talk. Sometimes the first symptom is burning pain in the stomach, præcordial anxiety, or giddiness. In one or two cases an alarming degree of collapse occurred, and in others the pulse is noted to be small and thready, the feet cold, and the face pale. The pupils are generally widely dilated, and dryness of the throat may be felt at first. The stupor lasts for four to thirty hours and then passes off, and the patient recovers. Only one death from nutmeg is recorded—in the case of a boy, aged 8, who ate two nutmegs and passed into a comatose condition, from which he could not be aroused, and which terminated in death after about twenty hours. These symptoms present a similarity to those of opium, and more especially to those of *cannabis indica*, in which there is often the same mixture of depression and stimulation. The stupor and delirium point to some such mixed action on the brain as is met with under *cannabis indica*, and, in fact, few of the symptoms indicate the involvement of any other organ than the higher parts of the central nervous system. The pain and burning in the stomach arise from the irritant local action of the oil, and the symptoms of collapse may suggest some action on the circulatory centres, but they were not observed in the majority of cases.

The nutmeg contains from 3 to 8 per cent. of volatile oil, and when this has been extracted from it the residue produces no effect whatever on animals, while small doses of the oil itself induce characteristic effects. The oil contains several terpenes and small quantities of higher boiling substances which can be separated by fractional distillation. The terpenes are devoid of action, except in enormous quantities, while the fraction boiling at 150° C. at 14 mm. pressure proved to be a powerful poison. The constituents of this highest fraction have been examined by several chemists, who have isolated bodies called myristicol (Wright) and myristicin (Semmler), and Wallace obtained a body which did not conform to the formulæ or properties of either of these, but which proved to be the active poisonous principle. He was inclined to consider his body closely related to myristicin (Semmler), and possibly derived from it, but the later investigations of Thoms and others indicate that Wallace's body was the true myristicin, while that described by

Semmler under this name was isomyristicin, formed from it by his manipulations and not occurring in the oil.

That nutmeg acts as a depressant on the central nervous system has long been recognised, and the older writers on *materia medica*—Murray,¹ Rumph, Pereira, Gmelin and others—describe its narcotic properties, and some of them even recommend it as a soporific. Experiments on animals have been performed by several investigators, who used the volatile oil, but did not isolate the active ingredient in it.

Wallace, using the pure principle, found that frogs placed in a dilute watery solution of it at first showed some symptoms of restlessness (probably from the irritant action on the skin), but soon became depressed and finally completely paralysed, with abolition of the reflexes. The animal may recover from this if removed from the dish, but otherwise dies. The same effect is obtained when the drug is injected into the lymph sacs. The action is confined to the nervous system, the peripheral nerves and muscles being unaffected and the heart beating quite normally even when bathed in the oil. The rabbit reacts in a very similar way, showing symptoms of depression and finally of paralysis of the central nervous system, without any significant change in the circulation, even when the oil is injected intravenously. The animal passes into a condition of depressed reflexes, lessened movement and incoördination, which deepens into complete stupor; sometimes tremor occurred or sudden twitches at intervals of some minutes. The cause of death is failure of respiration, the heart continuing to beat for some time afterwards. The cat is much more susceptible to the action than the rabbit, as is very generally the case with drugs acting on the central nervous system. About 0·4 G per kilo of the highest distillate given *per os* causes restlessness with weak spasmodic movements and tremor resembling that seen in carbolic acid poisoning, and profuse salivation. The restlessness passes into quiet with persistence of the tremor, incoördination of the movements, weak reflexes and partial anæsthesia. The pupils are dilated. Soon a stage of stupor, gradually deepening, sets in, the respiration is laboured and feeble and finally ceases some eight to twelve hours after the ingestion of the poison. In many cases, however, after some hours of stupor, a gradual improvement begins, and in fifteen hours from the taking of the poison the animal appears fairly normal save for unusual quietness and

¹ This old Göttingen pharmacologist is perhaps one of the last believers in the tradition regarding the bird of paradise—"Avi quoque paradisiacæ in deliciis (nux myristica) est quæ vero inde inebriatur et mortua decedit, quibus factis formicæ adrepunt et pedes consumunt" (*Appar. Medicam*, 1792, vi., p. 138).

disinclination to move about. This improvement is only temporary, however, the cat again becoming weaker and more depressed, eating nothing and paying no attention to its surroundings, until coma returns followed by death in thirty-six to seventy-two hours from the time the oil was taken. Vomiting and purging are often seen. The blood-pressure remains unaffected even when large quantities of the oil are injected intravenously. When the oil is administered hypodermically the same symptoms follow, except that there is no salivation. If death is delayed symptoms of local irritation develop at the point of injection. The symptoms in the dog resemble those described in the cat.

The symptoms in mammalia are thus, as in the frog, to be attributed to action on the central nervous system, which is depressed for the most part, but exhibits some indications of stimulation in the form of restlessness, slight convulsive movements, and tremor. Animals, therefore, correspond very closely to man in their reactions to nutmeg poison.

In addition, the oil exercises a marked local irritant action, whether given by the mouth or hypodermically. The wall of the stomach is found to be red and injected when it is given *per os*, and even more obvious signs of local reaction may often be met with in extravasations of blood and small areas of necrosis. The urine very often contains albumin along with some glycuronate. These effects in the stomach and kidney perhaps explain the secondary coma and death which follow apparent recovery in the cat. Many volatile oils induce fatty degeneration of the liver and other organs, but nutmeg poison has little or no action in this direction.

Wallace's results do not indicate any useful purpose which nutmeg might serve in therapeutics, but are of interest in drawing attention to the possibility of serious poisoning from one of our common domestic flavouring agents.

DISCUSSION.

Dr. F. B. POWER said he had been particularly pleased to hear Professor Cushny's paper on "Nutmeg Poisoning," and he was also pleased to have an opportunity of saying a few words on the subject. For several years past the subject had been one of considerable interest to him, not from the medical, but from the chemical standpoint; that was to determine, if possible, what were the constituents of nutmeg. He had observed in the journals numerous accounts of nutmeg poisoning from time to time, but nothing definite seemed to have been known respecting the cause of the poisoning. He was not aware whether Professor Cushny's work had been published. Some considerable time ago he (the speaker) decided to make a thorough investigation of the subject, and be

had advanced considerably along the line. In the first place he obtained good Ceylon nutmegs, and having had all the volatile oils distilled from them, he subjected them to chemical investigation. He found that the essential oil of nutmeg was an exceedingly complex body, about which not much was known. One or two of the constituent oils were known, but what struck him as peculiar was, he noticed that, when oil of nutmeg was injected into the circulation of a dog it produced pronounced narcotic effects that seemed somewhat different from those produced by nutmeg taken internally. In considering the character of the essential oil he found it to consist to the extent of about 90 per cent. of terpenes or bodies of the same composition as hydro-carbons, which were not practically regarded as narcotic, being particularly stimulants. In the essential oil of nutmeg he found no less than four alcohols. The points he particularly wished to bring forward for consideration were these: nutmeg poisoning was generally stated to be produced by one or two nutmegs, usually not more than two. The weight of two average nutmegs was about 10 grm. If they made a liberal allowance for the essential oil as being 10 per cent., then in two nutmegs weighing 10 grm. there would be 1 grm. of essential oil, and the question which he thought ought to be settled was, whether 1 grm. of the essential oil of nutmeg, when taken internally, would produce these effects. So far as he knew that had not been done. The effect was due to the high boiling constituents of the oil, although there was only a very small amount in the normal oil of nutmeg—about 4 per cent.; in 1 grm. of essential oil there would, therefore, be 4 cg. (about 0.6 gr.), or a little more than $\frac{1}{2}$ gr. in two nutmegs. Now the point was, would that amount of myristicin, when taken internally, produce the soporific action? He thought that point ought to be decided. In the course of his work he had looked up a number of papers on the subject, and he found some work had been carried out in Kobert's laboratory about four years ago by one of his assistants, who especially investigated the action of myristicin. But those experiments were all conducted with small animals, such as rabbits and fowls, rabbits chiefly. The experimenter injected from 1 grm. to 2 grm. of pure myristicin into the circulation, and, of course, that produced death. That 1 grm. of myristicin would represent about twenty-five times as much as was contained in two nutmegs, and yet that was given to an animal weighing about 2 lb., therefore it would seem that the effect of the substance when administered in that way could hardly be compared with the effects produced when it was taken through the mouth. It was also evident that the action upon animals was very much less than in the case of man. At the present time he was engaged in investigating the other constituents of the nutmeg. They thought perhaps some other toxic principle might be found in the nutmeg itself. That idea seemed to be borne out by some reports published by an American physician, who some years ago stated that he had been called in to a great many cases of nutmeg poisoning. He said sometimes children ate them without knowing the effects, and the effects were very similar to those of an overdose of chloral. Much of the essential oil contained very little myristicin. The "*British Pharmacopœia*," unfortunately, prescribed certain

requirements for the oil of nutmeg with regard to specific gravity which really excluded some of the more important aromatic parts of the oil, including some myristicin. Such an oil might have been administered, and hence the difference in action. He could not yet say very much about the other constituents of the nutmeg. The fatty oil would naturally not be expected to contain this principle; it contained the glycerides and ordinary fatty acids. They, however, were examining very carefully the material from which the fatty oil of nutmeg was expressed. They had had large quantities of it, and, of course, that contained everything except the fatty and essential oils; it contained a number of principles of a resinous nature which had not yet been tested, and he did not know whether they would find anything active in it; but he thought it would be very interesting and very important that they should be able to definitely decide as to the cause of the poisoning, and that could best be accomplished by using the essential oils and administering them in such amounts as were actually contained in the nutmeg. And, if they found it required such a large amount to produce the effect, it could hardly be due, it seemed to him, to these bodies.

Dr. J. GRAY DUNCANSON said he thought they had all been pleased to hear so much about nutmeg. There were various varieties of nutmeg, and these were now grown both in Asia and America, the Penang being the best. Some people were very susceptible to nutmeg, and even a small quantity grated on the top of a pudding made them sick. He would like to direct Professor Cushny's attention to the fact that nutmeg poisoning had not been quite so much neglected in English medical literature as he had led them to believe. A week or two ago he (the speaker) had occasion to look up Taylor's "Medical Jurisprudence," and, knowing this paper was going to be given, he read the article on nutmeg poisoning and he found Taylor cited two or three cases; the symptoms in those cases seemed to be of two kinds, cerebral and gastro-intestinal hallucinations and stupor. He had only met with one case of nutmeg poisoning himself, and that was a pregnant woman who had taken the whole of a nutmeg grated up in gin. She certainly aborted, but whether this was entirely due to the nutmeg or to some other mixture she had been taking at the same time he did not know. She had severe symptoms of the character already described, and ultimately made a good recovery. In India the oils were obtained from the nutmeg by pressure and then used as a lotion for the hair, said to have stimulating and anti-parasitical properties.

Professor CUSHNY, in reply to Dr. Jackson, who asked whether it were possible that the narcotic and stimulating principles were one and the same, said he had no reason to suppose that they were different substances. He might also mention that they had considered the question of the large dose comparatively that was necessary to poison animals, and they found it required a much larger dose to narcotise a dog with other bodies, such as cannabis indica, than was necessary to induce symptoms in man.