Note on Nutmeg-Poisoning.

By H. H. Dale, B.C.

About a year ago Professor Cushny\(^1\) made a communication to this Section of the Royal Society of Medicine on Nutmeg-Poisoning, basing his observations, in so far as they dealt with experimental results, chiefly on a paper by his former assistant, Dr. G. B. Wallace. I had, at that time, for some months been making experiments on the action of nutmeg, in connexion with a very exhaustive chemical investigation carried out by Power and Solway.\(^2\) Until Professor Cushny's communication was published I had not had access to the details of Wallace's results, though I had gathered, in conversation with Professor Cushny, that they were in many respects similar to those which I had obtained. There are some points of difference, however, which seem sufficiently important to mention.

My experiments with the numerous preparations placed at my disposal by Dr. Power had led me to the conclusion, identical with that of Wallace, that the whole activity resides in the volatile oil, and in particular in the substance of high boiling-point which, since Wallace's paper was published, has been chemically characterized and named "myristicin." I agree with Wallace, again, in finding the cat the most sensitive to nutmeg of the animals usually available for experiment. But whereas Cushny concludes, from Wallace's experiments, that "animals correspond very closely to man in their reaction to nutmeg-poison," the effects which I obtained, in my earlier experiments on the cat, appeared to me remarkably inconsistent with the numerous published accounts of nutmeg-poisoning in man. The characteristic result in man of ingesting the substance of one or more nutmegs—that is to say, 5 grm. or more of the drug—would appear from the recorded cases to be narcosis, varied by excitement and delirium, commencing a few hours after ingestion, and usually followed by recovery after twenty-four hours or more. It is stated that death has occurred, but Cushny points out that only one clear case is on record, the case being that of a

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child who took a large dose of the drug. The general impression given by most of the clinical records is of a temporary intoxication, which usually passes off without leaving any obvious bad result. One observer even recommends small doses of nutmeg as a mild and safe hypnotic for children. On the other hand, I found, early in the course of my experiments, that the smallest dose of nutmeg, which would produce in a cat any recognizable effect, invariably produced death; further, that the type of poisoning produced was widely different from what I had been led to expect by the clinical records. The following notes on experiments illustrate the nature of my results. It will be noticed that the doses are relatively large, 5 grm. being sufficient to produce marked symptoms in a human being, weighing on an average about twenty times as much as a cat. Smaller doses, however, did not affect the cat perceptibly.

A cat, weighing 2,640 grm., was given 5 grm. of grated nutmeg by the mouth. A small amount was vomited during the night, but no other effect was observed on the day of administration or the day following. On the third day, however, the animal was observed to be jaundiced and very drowsy. It passed into gradually deepening coma, and died about forty-eight hours after ingesting the nutmeg. In a second case, a dose of 10 grm. produced, in a cat of 3 kgm., no effect, except salivation and disinclination for food, upon the day of administration or the two following days. During the next night, however, it passed into very deep coma, and was found in this condition on the third morning after ingestion. The pupils were maximal, the eyeballs quite cold to the touch, there was no trace of corneal reflex. The only signs of life were a feeble, slow heart-beat, infrequent, long-drawn respirations, and the reflex movements which were readily elicited by tickling the pads of the hind feet. The rectal temperature was 26° C. (79° F.). The animal died during the morning—about seventy-two hours from the time of administration. In another case in which 5 grm. were given, nothing was noticed till the fourth day after administration, when fatal coma again appeared.

In all these cases the post-mortem examination revealed the same condition. There was advanced fatty degeneration of the liver, which, in sections appropriately stained, could be seen to affect practically every cell, extending to the middle of the lobules. Local necrotic changes were also obvious. Macroscopically other organs were little affected, but complete microscopical details are not yet available. There was marked jaundice of all the tissues, and the urine drawn off from the bladder
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was dark coloured with bile pigment, and gave a cloud of albuminous coagulum on boiling.

The contrast, then, seemed obvious enough. In the cat, a uniformly fatal coma appearing after a few days, always associated with, and probably secondary to degenerative liver changes, not at all unlike those seen in phosphorus poisoning: in man, on the other hand, as the result of relatively much smaller doses, a temporary condition of excitement, followed by narcosis, appearing a few hours after ingestion, and generally passing off without leaving any serious after-effects.

With chemically pure myristicin, the active constituent of the volatile oil, the results obtained were very similar, with the exception that the dose given must be proportionately larger. The difference may with great probability be attributed to the readiness of absorption of myristicin when it is associated with the fats and other constituents of the whole drug. Given pure it is probably lost to a considerable extent in the faces, or, if given hypodermically, very slowly absorbed. However, with 1 c.c. of myristicin given by the mouth, I obtained effects closely similar to those which I observed with 5 to 10 grn. of nutmeg. Again no symptoms were observed, except the salivation and defect of appetite, until two or more days after the myristicin had been given. Then the characteristic jaundice appeared, followed by coma, and the post-mortem findings were as before.

So far my results with cats had no point in common with those recorded for man. They resembled the effects obtained by Jürss, who, by injecting relatively very large doses of myristicin into rabbits and guinea-pigs, produced degenerative changes in the liver which he compared to those of phosphorus poisoning, and in some cases recorded a condition of narcosis or coma. I was even in doubt whether the effects in man could be attributed to myristicin until Professor Cushny made his communication, and it became clear that Wallace had produced the primary effects on the nervous system in cats by using even larger doses than those which I had employed. I proceeded, therefore, to try larger doses, and obtained the expected results; 1·5 c.c. of myristicin given by the mouth to a cat of 3 kgm. caused, after an hour, a condition of excitement, with dilated pupils, tremors, unsteady gait and imperfect avoidance of obstacles. The condition was reminiscent of that produced by a small dose of cannabis indica, and passed off in a few hours without having deepened into actual narcosis. On the following day the cat

1 Schimmel's Bericht, Leipz., 1904, p. 159.
seemed rather apathetic, but otherwise normal; late in the day, however, the sclerotics showed signs of slight jaundice. On the third morning the jaundice was marked, and fatal coma followed during the day. In another cat 5 c.c. of myristicin produced excitement and inco-ordination in about half an hour. Complete narcosis followed, lasted for about three hours, and then passed off, leaving the animal practically normal. Again, after an interval of a day, the second stage of jaundice and coma followed. In both cases the post-mortem examination revealed the usual fatty degeneration of the liver.

The meaning of these results seems clear. The primary effects on the nervous system, when produced in the cat, are, indeed, closely similar to those observed in man. But, whereas man is so sensitive to this primary action of myristicin that he can be temporarily narcotised by doses of nutmeg too small to leave any permanent bad effects, the nervous system of the cat is relatively so little responsive that doses considerably in excess of that which will certainly kill the cat are necessary if the primary effects, as seen in man, are to be reproduced. The death of the cat is, in any case, due to secondary coma. This was also mentioned by Professor Cushny, who suggested that it might be attributable to irritation of the stomach and kidneys. My chief point of dissent from his conclusions is that I regard the coma as due to the pronounced degenerative changes in the liver which Wallace seems to have looked for without observing them. The secondary coma I regard as an entirely different phenomenon from the primary action on the nervous system, the two being as distinct, in fact, as primary chloroform anesthesia and coma due to delayed chloroform-poisoning.

The other point which seems to me to need further emphasis is the very great difference in dosage between man and the lower animals. Whereas one nutmeg, weighing on an average about 5 grm., is said to have produced a pronounced effect in man, the smallest dose with which I elicited the primary effects on the brain of the cat was 1·5 c.c. of myristicin, representing at least 75 grm. of nutmeg. Even if we allow, as apparently we must, that some of the myristicin is not absorbed, we are yet left with a dose which is enormously large in comparison with that which causes very definite effects in man. The fact that man is thus readily affected by doses too small to produce remote toxic effects on the liver seems to me to make the therapeutic application of nutmeg at least worth consideration. The results in the cat, which is unaffected by doses not ultimately fatal, do not afford any strong argument against the recommendation of those who have found in
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nutmeg a substitute for chloral, though a more likely use would seem to be as an alternative to cannabis indica.

At the same time the production of secondary coma in the cat must be regarded as an index of a possible danger in the use of the drug except in very moderate doses, a danger which one might, perhaps, on the analogy of secondary anaesthetic poisoning, regard as particularly important in the case of children.

DISCUSSION.

Professor CUSHNY said he thought that Dr. Dale's paper really closed the question of nutmeg-poisoning. When his own paper was read some time ago, Dr. Power suggested that nutmeg might contain some other poisonous principle besides myristicin, but he thought that idea had been disproved by Dr. Dale's paper. His co-worker, Dr. Wallace, did not try to find out whether more nutmeg was needed to poison the cat than man, because it was generally recognized that the nerve poisons acted more readily and in smaller doses in man than even in the cat. In regard to the fatty changes in the liver, he did not know how he had missed them. He would not suggest that the American cat differed in its reactions from the English variety. Their attention was specially drawn to the liver, because, just previously, Lindemann had written about the fat-producing effects of pulegon. The fat was very evident in the liver now exhibited by Dr. Dale, and he did not know how it was missed in his cats; it must have been an error of observation. The fatty degeneration explained the late deaths which Wallace had observed.

Dr. J. GRAY DUNCANSON regretted that—from his standpoint—the most practical feature had not been referred to by Dr. Dale. People in this country did not take nutmeg to cause death, but to produce abortion; and he would like to hear whether Dr. Dale had experimented with it on the lower animals when they were pregnant. Nutmeg was somewhat frequently taken by women, especially in the neighbourhood of London, to bring on a miscarriage, but as it was done surreptitiously it was very difficult for the medical man to ascertain in what form and what quantity it was taken. Those cases which he had seen had been marked by gastro-intestinal disturbance, and it was difficult to know whether to attribute that to the nutmeg entirely, or in part to the gin with which it was most frequently administered. In one case which he saw some years ago there were certainly cerebral symptoms—hallucinations and delusions. It would be very interesting if it could be known, on experimental data, whether nutmeg or its essential principle (myristicin) were emmenagogues.

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Dr. Dale, in reply, said he had not experimented with the view of ascertaining whether nutmeg was an emmenagogue, though the point was mentioned by Professor Cushny in his paper some time ago. The purpose of the present communication was to correct the idea about fatty degeneration of the liver. Professor Cushny had just mentioned to him that it seemed to be the fact that several of the drugs causing fatty degeneration of the liver, such as nutmeg, pulegon, and even phosphorus, also had a reputation of being emmenagogues and abortifacients. None of the animals on which he experimented were pregnant.