Concerning the Pharmacology of Nutmeg

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(Our beatniks are providing us with some interesting data on human toxicology from a wide variety of deliriants these zany days. Airplane glue sniffing, marihuana smoking, Asthmador ingestion, and now nutmeg have been employed by the "beat" to increase their mental disorganization. Payne in the July 4, 1963 issue of the New England Journal of Medicine reports on the serious intoxication of two college students who had taken a large amount of nutmeg. The following article is published to provide the physician with background material about a common household product which might be used deliberately or accidentally as a poison.—Ed.)

Nutmeg is the name given to the dried ripe seed of the tree *Myristica fragrans* and which has been used in various forms for centuries as a condiment. The medical literature has concerned itself with the whole seed, the ground or powdered seed (which is subject, upon standing, to losses of the essential oils), the steam-distilled volatile oil fraction (5 to 15% of the original nutmeg), and the distillation cut of that volatile oil fraction, known as myristicin, that distills at 171 to 173°/40 mm or 109 to 112°/1 mm, which represents at least 6% of the volatile oils, and thus as much as 1% of the total nutmeg.

Animal Pharmacology

In the cat, nutmeg exhibits 2 entirely separate modes of activity. It has been shown[7] that there is an exceptionally acute sensitivity and that any level which will produce noticeable effects, will in time be fatal. The administration of 5 to 10 g. of the nutmeg, or of 1 ml myristicin, is without immediately apparent symptoms (except for salivation). However, in 2 or 3 days, there is a jaundiced appearance followed by coma, and, in turn, by death. Autopsy has shown death to be due to a severe fatty degeneration of the liver. (One human intoxication, severe but not fatal, showed no liver infiltration upon biopsy.[12] Dosages in the cat sufficiently large to evoke immediate effects (1.5 ml to 5 ml myristicin) led within half an hour to excitement, pulpillary dilation, tremors, and an unsteady gait, followed by a return to normal within several hours. Nonetheless, after a day or two, the above fatal symptoms became evident. Following premedication with morphine,[26] myristicin was found to aggravate the expected ataxia and sham rage. After a few hours, there was a catatonia, followed by death.

The dog is much less sensitive to nutmeg and to myristicin, than the cat.[20] Large quantities fed daily led, however, to fatty deposits in the liver.[5] A single injection of myristicin I.V. showed a slight drop in blood pressure without other disturbances.[26]

In the rat, toxicities of total nutmeg, the nonvolatile fraction thereof, and the myristicin fraction, have been determined.[26] For nutmeg there was established an LD_{50} of about 0.6 g/Kg. The residue following removal of the volatile con-

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stituents by steam distillation was much less toxic (an LD_{50} of 1.7 g/Kg). The myristicin fraction was found to possess an $LD_{50} > 1$ g/Kg. Large doses elicited hyperexcitability followed by a CNS depression. There was no liver or kidney damage. The post-mortem examination of rats maintained on a 10 mg/Kg diet daily for 600 mg total consumption, showed no morbid developments.

Monkeys[26] receiving myristicin at 50 to 75 mg/Kg displayed ataxia and disorientation for several hours. A dose of 100 mg/Kg caused respiratory arrest. Treatment with 5 g of nutmeg in acacia produced no effect whatsoever.

Human Pharmacology

Due to the fortuitous circumstance that nutmeg is both an easily available condiment, and that it is enveloped in a folklore maintaining its claim to emmenagogic and ecbolic potency, much more is known about the human toxicology of nutmeg than about the animal pharmacology.

Ingestion of about 5 g of the whole seed (approximately one large nutmeg) leads to the following general syndrome: after a period of a few hours, there is a more or less severe physical collapse, characterized by a weak pulse, hypothermia, clamminess of the extremities, giddiness, vertigo, nausea, and a feeling of congestion and pressure either in the region of the chest or the lower abdomen. Some 6 to 12 hours later an extended period of alternating delirium and stupor persists, usually resolved by a heavy sleep. After a recuperative period of several days, marred only by headaches and perhaps spells of dizziness, the subject returns to normal.

Variations from this idealized portrait are numerous. In some reports of toxic effects, the cyanosis of lips and nails, coupled with face flushing and initial hyperthermia,[11, 13, 16] strongly suggests an allergic response in some people. The initial tachycardia,[2, 4, 11, 30] often followed by stuporous confusion,[1, 3, 18, 25, 29] may be responsible for the apprehensive fear of death or the sense of impending doom[17] often expressed. The complaint of oppressive chest pressure[14, 21, 24] often accompanies the clamminess of arms and legs. There is, invariably, an extreme thirst.

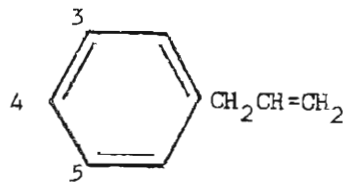
In several instances of experimental[26, 28] and inadvertent[12] intoxication, the active material was in the physical form of ground or powdered nutmeg. Unfortunately, the residual volatile oil content of the ground spice is extremely dependent upon history, origin, and age of the sample.[8] Nonetheless, cases involving the ingestion of 12 to 20 g of powdered nutmeg seem to parallel the general syndrome. There was pupillary contraction and a general narcotic state exhibited as described above.

The sole report on the human pharmacology of myristicin[26] describes the effects of a total dose of 400 mg. Two or three hours following ingestion, there were suggestions of elation or of anxiety in several of the experimental subjects. The same report describes the sole evaluation of nutmeg deprived of its volatile oil content. There were some side effects (flushing and abdominal discomfort) but no narcotic or psychotropic effects following a 10 g dose. Preliminary trials employing total whole nutmeg in treatment of mental disorders have been mentioned.[27]

Oil of nutmeg has been recommended as a carminative and as a local stimulant to the gastrointestinal tract, at dosages of 0.03 to 0.2 ml,[8] but no reports of its effectiveness or of the consequences of excess are available in the literature.

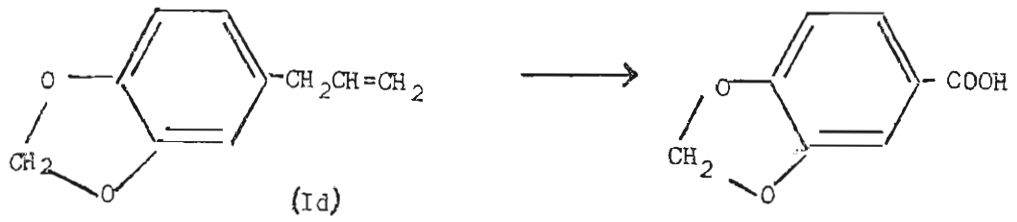
Active Components

The component classically credited as being the toxic principle of oil of nutmeg is myristicin (Ia), which has been recently shown to contain a sizable percentage of elemicin (Ib) as isolated by distillation.[22] This fraction is strongly suspect of



(I)

	3	4	5
a	OCH_3	$O—CH_2—O$	
b	OCH_3	OCH_3	OCH_3
c	OCH_3	OH	H
d	$O—CH_2—$	O	H



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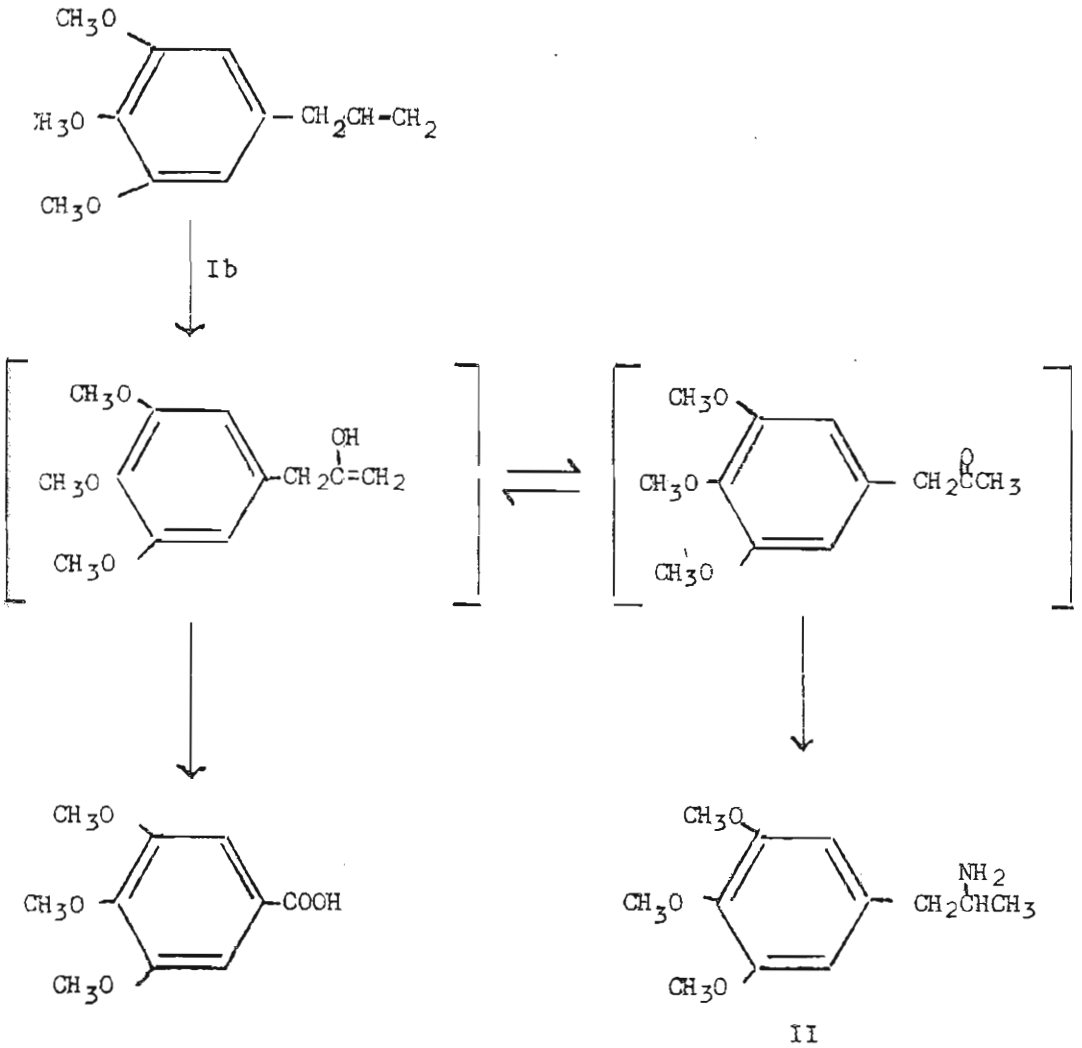

Ib

II

representing the effective toxic factor for cats (v.s.) wherein an application of small dosage of myristicin imitated, completely, corresponding dosages of total nutmeg. Quite to the contrary, this same fraction appeared ineffective in duplicating the psychological effects of total nutmeg in man.[26] The non-volatile components of nutmeg need not be considered in light of their decreased toxicity to rats and their loss of effectiveness in man. The minor aromatic ethers, eugenol (Ic) and safrol (Id), have been suggested as possible active components,[26, 28] This seems unlikely, as the amounts ingested from a 5 g nutmeg (0.001 g and 0.003 g resp.)[19] are much below the usual therapeutic levels of these substances (3.0 ml and 0.5 ml, resp.).[9] The only component, aside from the myristicin fraction, of the volatile oils from nutmeg that deserves serious consideration as an active agent, is the pinene-dipentene fraction. Many descriptions of the toxic syndromes of representative terpene medicines parallel the common toxic manifestations of nutmeg (i.e., nausea, cyanosis, stupor, cold extremities, often delirium). Actual toxic dosages of oils that are of make-up similar to the hydrocarbon fraction of nutmeg (as oil of turpentine) are as a rule 20 to 60 times higher than that which would be encountered in nutmeg intoxication.[10] Thus, as yet, no known pharmacology of any known component of oil of nutmeg can explain the syndrome of the whole nutmeg.

Mode of Action

The inability to assign to a single component of nutmeg the role of being the toxic factor makes a discussion of the mode of action, by definition, totally theoretical.

If one concedes that the myristicin fraction of nutmeg is responsible for the reported effects, then several speculative extensions may be made. The *in vivo* metabolism and biochemistry of the various aromatic ethers found in essential oils, are virtually unknown. The conversion of safrol to piperonylic acid shows the presence of a detoxication mechanism capable of oxidizing an olefinic side-chain,[15] and both myristicin and total nutmeg have shown activity as an MAO inhibitor.[27] If the above metabolic degradative processes are applicable to myristicin (Ia), or especially to elemicin (Ib), a theoretical intermediate, a vinyl alcohol, could undergo transamination producing the known psychotomimetic drug, 3, 4, 5-trimethoxyamphetamine (II).

The reported effective dosage of dl-trimethoxyamphetamine,[28] 280 mg, is too high to be generated from the elemicin content of a toxic amount of nutmeg, even if one allows all activity to be concentrated in one optical isomer, and that that isomer be synthesized exclusively. Further, the ingestion of 400 mg myristicin[26] presumably containing 120 mg elemicin evoked only marginal mental effects in human subjects. Nonetheless, some combination of factors in total nutmeg is capable of producing a psychotropic response; the structure of elemicin wanting only an ammonia molecule to become a recognized mental agent must be accepted as at least an intriguing coincidence.

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