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On the Relative Toxicity of Nicotine and Nornicotine.

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In recent years, Markwood[1] has called attention to the fact that certain strains of *Nicotiana tabacum* may contain relatively large amounts of nornicotine (a substance that differs chemically from nicotine only in that the nitrogen atom in the pyrrolidine ring is not methylated). While such "high nornicotine" strains probably constitute only a small minority of those generally used by man, we have recently shown[2] that on an average, tobacco of cigarette quality contains 15 to 20% as much nornicotine as it does nicotine. More complete knowledge concerning the toxicity of nornicotine therefore seems pertinent.

An earlier publication by us[3] included the following data pertaining to the toxicity of nicotine and nornicotine:

Nicotine: intraperitoneal LD 50 for mice = 10.3 mg per kg, for rabbits = 14 mg per kg; intravenous LD 50 for rabbits = 6.25 mg per kg.

Nornicotine: intraperitoneal LD 50 for mice = 21.7 mg per kg, for rabbits >13.7 mg* per kg; intravenous LD 50 for rabbits = 3.0 mg per kg.

From the above data it would appear that nornicotine is less toxic than nicotine by intraperitoneal administration and more toxic than nicotine by intravenous administration. This reversal in toxicity we ascribed to the difference in the dissociation constants of the two substances, a difference which would result in slower absorption of nornicotine as compared to nicotine following intraperitoneal administration. In other words, from the above data alone, it would seem that nornicotine is inherently more toxic than nicotine when factors of absorption are minimized. Recently we have obtained the following additional toxicologic data showing that as a generalization this is not valid:

Nicotine: intravenous LD 50 for mice = 0.55 mg per kg.

Nornicotine:† intravenous LD 50 for mice = 3.4 mg per kg.

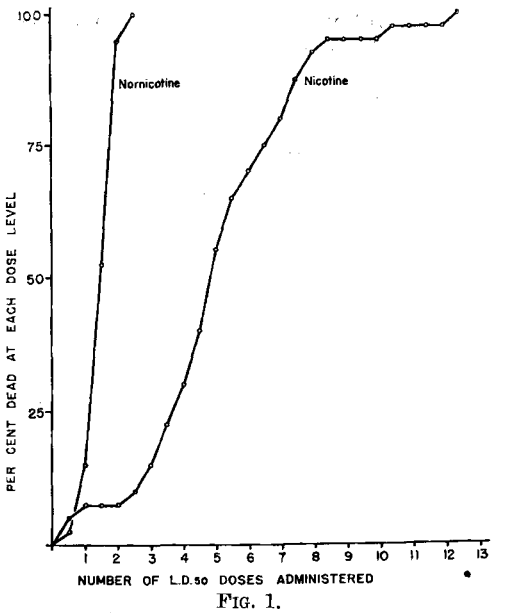

FIG. 1.

Toxicity curves for nicotine and nornicotine, administered intraperitoneally to mice in one-half LD_{50} doses at 15-min intervals.

Thus, whereas the intravenous LD 50 for nornicotine is about equal for both species, the intravenous LD 50 values for nicotine show it to be definitely more toxic than nornicotine to the mouse and less toxic than nornicotine to the rabbit.

In view of this, it seemed of interest to compare the ability of the two species to detoxify

1 Markwood, L. D., *Science*, 1940, **92**, 204.

2 Larson, P. S., and Haag, H. B., *Ind. and Eng. Chem. Analyt. Ed.*, 1944, **16**, 86.

3 Larson, P. S., and Haag, H. B., *J. Pharm. and Exp. Therap.*, 1943, **77**, 343.

* The L.D. 50 is definitely greater than this value, but lack of sufficient nornicotine prevented a more exact estimation.

† Kindly furnished to us by Dr. R. C. Roark, United States Department of Agriculture, Bureau of Entomology and Plant Quarantine.

4 Weatherby, J. H., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 593.

nicotine and nornicotine. Following the technique employed by Weatherby[4] and administering intravenously one-sixth LD 50 doses at 2 min intervals to the point of death, we have previously shown[3] that the rabbit disposes of nornicotine at a rate comparable to that found for nicotine.[4] Since repeated intravenous injections into the mouse offer some difficulty, the comparison in this species was carried out as follows:

Employing 2 groups of 40 mice each, each mouse in one group was given ½ the LD 50 dose of nicotine intraperitoneally every 15 min until death, and each mouse in the second group was similarly treated with ½ LD 50 doses of nornicotine. The results are expressed graphically in Fig. 1. From this it is seen that the mouse detoxifies nicotine much more rapidly than it does nornicotine. In this respect then, the mouse again differs from the rabbit.

Summary. Whereas, the mouse and the rabbit as regards acute toxicity are about equally sensitive to nornicotine, they differ markedly in their sensitivity to nicotine as well as in their ability to detoxify the two substances. In view of such species variation it would seem impractical to evaluate the relative toxicity of nicotine and nornicotine for man on the basis of animal data. Since nicotine and nornicotine are quite closely related structurally, these results again emphasize the hazard of transferring to man toxicity data on related compounds obtained on one species of animal.

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Acute Nature of Alloxan Damage.*

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Neutralization of an alloxan solution with NaOH completely abolishes its diabetogenic action.[1] Since alloxan, if injected intravenously, is bound to be neutralized by the buffers of the blood in a very short time, the conclusion that its toxic action must be limited to a few minutes seems to be logical. There are also indications that alloxan is not only neutralized but actually decomposed or disposed of in some way within a few minutes. Leech and Bailey[2] found that alloxan injected intravenously can be demonstrated in the blood for only 5 min after the injection.

That the toxic effect of alloxan takes place within a few minutes after injection could be proven by the following experiments:

Thirteen dogs were laparotomized under ether anesthesia, and that part of the pancreas which lies free in the duodenal mesentery was exposed, and its blood supply temporarily interrupted by placing two rubber-protected soft clamps along its both sides. Now a diabetogenic dose (60 to 100 mg/kg) of alloxan was injected rapidly into a leg vein. The clamps were removed one to 6 min after the termination of the injection, and the circulation to the clamped portion was reestablished. The abdominal wound was closed. The animals made a good recovery, and not a single one of them developed any sign of diabetes even temporarily. Ten or 14 days after the first operation the animals were relaparotomized or killed, and biopsies were taken from both the clamped and the untouched splenic portion of the pancreas. Sections were stained with chrome hematoxylin and phloxin,[3] and the

* This work has been supported by grants from the Douglas Smith Foundation for Medical Research of the University of Chicago, and from Eli Lilly and Co., Indianapolis.

1 Goldner, M. G., *Bull. N. Y. Acad. Med.*, 1945, **21**, 44.

2 Leech, R. S., and Bailey, C. C., *J. Biol. Chem.*, in press.

3 Gomori, G., *Am. J. Path.*, 1941, **17**, 395.