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## Rate of Elimination of Nicotine by the Rabbit.

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It is always advisable, and in some instances essential, for maximum therapeutic effectiveness and safety, to have fairly accurate information concerning the rate of elimination of drugs from the animal organism. For drugs which are excreted unchanged or in the form of some readily recognizable degradation product measurement of rate of elimination consists essentially of quantitative analyses of the excreta for the products sought. For other drugs whose fate in the body is less well understood the approach must be of a more indirect sort. Thus, with digitalis and the related glycosides, it is common practice to administer a fraction of the average lethal dose to suitable animals, then to ascertain after various time intervals how much additional drug must be administered to prove fatal. The difference between total amount of drug administered and average lethal dose represents the amount of drug eliminated from the organism in the period of time selected. For these drugs, which usually require from several days to a week or more for complete elimination, this method appears satisfactory. For certain others which seem to be practically completely eliminated within much shorter periods of time the method is not readily applicable. In his investigation of picrotoxin Dille[1] ascertained first the average convulsant dose of the drug for suitable test animals, then the amount of drug necessary after certain intervals of time to restore concentration within the organism to the convulsant level. Such an amount of picrotoxin Dille holds to represent the quantity eliminated during the interval since the initial convulsant dose was administered.

Kohn and Grimes[2] used a method somewhat similar to that of Dille in their studies on certain barbituric acid derivatives, and conclude that, at least for these substances, rate of elimination is proportional to the uneliminated residue. Mathematical formulae for calculating rate of elimination are presented by these authors. Others, among whom are Beck and Lendle,[3] Lendle,[4] Weese,[5] and

1 Dille, J. M., *J. Pharm. and Exp. Therap.*, 1938, **64**, 319.

2 Kohn, R., and Grimes, C., *Anesthesia and Analgesia*, 1939, **18**, 139.

3 Beck, A., and Lendle, L., *Arch. f. exp. Path. u. Pharmak.*, 1932, **164**, 188.

4 Lendle, L., *Arch. f. exp. Path. u. Pharmak.*, 1933, **169**, 585.

5 Weese, H., *Arch. f. exp. Path. u. Pharmak.*, 1936, **181**, 46.

Werner,[6] report studies in which essentially similar methods were used, varying in details according to individual needs.

The fact that relatively large portions of the populations of this as well as other countries frequently are exposed to nicotine through the use of tobacco, and the further fact that nicotine is a very interesting substance from the point of view of the pharmacologist, emphasize the necessity for additional information concerning this substance. Although several publications mention that relatively large quantities of nicotine are tolerated by the organism if administered sufficiently slowly—suggesting rapid elimination—no exact data on the subject have come to the attention of the author. The investigation of this subject was therefore undertaken. The term "elimination" is used here in its broadest sense; that is, to imply any process whereby the drug is rendered physiologically inactive, such as destruction, excretion, or conjugation. No attempt has been made in this investigation to ascertain the mechanism involved in elimination of nicotine.

*Material and Methods.* Male rabbits of mixed breeds weighing from 1200 to 1800 g were used in these experiments. Nicotine was administered as the acetate, although quantities are expressed in terms of the alkaloid. The solution injected contained 2 mg per cc, and all injections were made at the rate of 0.1 cc per second into marginal ear veins.

The various procedures described by the authors mentioned above presuppose a fairly accurate knowledge of the amount of drug required to produce a certain physiological reaction or end-point, whether this end-point be the onset of convulsions as with picrotoxin, paralysis of the respiratory center as with barbituric acid derivatives, or death of the animals as in the present investigation. Haag[7] found the average lethal dose (L.D. 50%) of nicotine for rabbits to be 6.2 mg per kg when administered intravenously. During the course of his investigation he observed that more consistent results were obtained when the rate of injection was made as nearly constant as possible. A rate of 0.1 cc per second proved to be satisfactory, so this precaution was observed throughout the present investigation. Sollmann and Hanzlik[8] report the M.L.D. as 10 mg per kg, but the percentage of animals succumbing to this dose was not mentioned.

*Results.* In the first series of experiments nicotine in doses of

6 Werner, H. W., *J. Pharm. and Exp. Therap.*, 1938, **63**, 39.

7 Haag, H. B., *J. Lab. and Clin. Med.*, in press.

8 Sollmann, T., and Hanzlik, P. J., *Fundamentals of Experimental Pharmacology*, Appendix G-I, p. 275, 1939.

1 mg per kg was administered at intervals of 1, 1½, 2, 3, 4, or 5 minutes until the animals died. The average amount of nicotine administered to the animals of a group less the average lethal dose (6.2 mg) indicates the average amount of nicotine eliminated by members of the group during the average period of time required for the animals to be killed. The amount eliminated divided by the number of minutes required gives the amount eliminated per minute. A second series of experiments was performed in which the size of the individual dose as well as the interval between doses was halved, although the amount administered per minute remained the same as in corresponding experiments of the first series. Thus, doses of 0.5 mg were administered at intervals of ½, 1, and 2 minutes. Also, 2 mg per kg were administered to another group at intervals of 2 minutes. Data obtained from these experiments are presented in Table I.

Fig. 1 shows the curve obtained by plotting rate of administration against rate of elimination. It will be noted that rate of elimination is lowest when rate of administration also is lowest. Under these conditions apparently the mechanism for eliminating nicotine is not functioning at its greatest capacity. As the rate of administration is increased there is a corresponding increase in rate of elimination until a maximum is reached. This maximum occurs when the rate of administration is approximately 0.5 mg per kg per minute, or 1 mg per 2 minutes. A further increase in rate of administration results in a decrease in rate of elimination. It will be seen also that results obtained from the second series of experiments agree satisfactorily with those from the first. An additional group of animals received 2 mg per 2 minutes, with the result that the apparent rate of elimination dropped considerably below that established by the first and

TABLE I.

| Single dose, mg/kg | Dose interval, min | No. animals in group | Avg No. doses | Total administered, mg/kg | Total eliminated, mg/kg | Rate of elimination, mg/kg/min |
|---|---|---|---|---|---|---|
| 1 | 1 | 20 | 8.3 | 8.3 | 2.1 | .253 |
| 1 | 1½ | 20 | 12.0 | 12.0 | 5.8 | .322 |
| 1 | 2 | 20 | 19.3 | 19.3 | 13.1 | .339 |
| 1 | 3 | 10 | 23.7 | 23.7 | 17.5 | .246 |
| 1 | 4 | 10 | 27.0 | 7.0 | 20.8 | .193 |
| 1 | 5 | 10 | 31.6 | 31.6 | 25.4 | .161 |
| 0.5 | ½ | 10 | 17.0 | 8.5 | 2.3 | .271 |
| 0.5 | 1 | 10 | 33.3 | 16.67 | 10.47 | .314 |
| 0.5 | 2 | 10 | 51.6 | 25.8 | 19.6 | .190 |
| 2 | 2 | 10 | 3.6 | 7.2 | 1.0 | .139 |

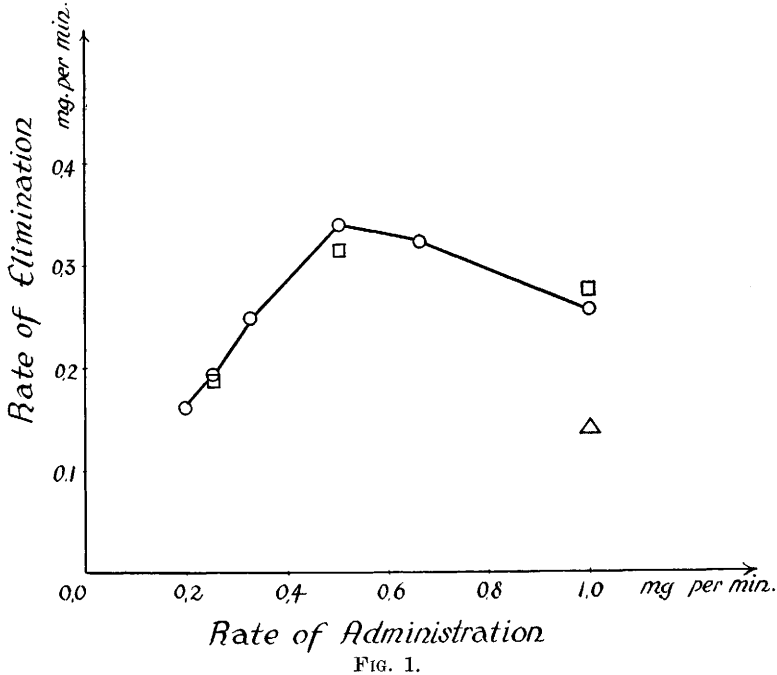


FIG. 1.

Relationship between Rate of Administration and Rate of Elimination.
○ = First Series. □ = Second Series. △ = 2 mg per 2 minutes.

second series of experiments. When one considers that such a dose represents nearly one-third the average lethal dose it is hardly surprising that such results were obtained. It is probable that these large doses so disturb physiological functions in the organism that elimination does not occur as rapidly as when doses of one-half the size or less are used.

*Conclusions.* When repeatedly administered in small doses the rate of elimination of nicotine seems to be proportional, within certain limits, to the rate of administration. When the optimum rate of administration is exceeded the rate of elimination is less than maximum, and ultimately reaches zero when the rate of administration is so rapid as to cause the end-point to be reached practically immediately.