and disappeared entirely. This must have been true for the original males as well, since it was known from previous culture work and controls of the experiment described that they consistently failed to survive as long as the females.

The recovery of over 600 worms could not possibly be accounted for without the intercalation of a second generation of sexual forms, since it was known from previous *in vitro* culture work with this species that the maximum number of offspring per female was 80 and the average 60. Thus 4 first generation females could not conceivably produce more than 320 and probably would not produce over 240 offspring. Considering 60 offspring as an average per female then one would expect 600 from the 4 females of the first generation and the 6 females of the second generation, a figure closely corresponding to the number actually recovered.

It is believed that this continued propagation as demonstrated on culture media occurs under suitable natural conditions. As far as is known this is the first demonstration of continued propagation of the free-living phase of any species of *Strongyloides.*

## 8146 C

## Absorption of Drugs Through the Oral Mucosa. II.

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The relative effectiveness of certain drugs by the sublingual method of administration has been previously reported.[1] In this earlier communication, approximate ratios were determined for effective sublingual doses and the similarly effective subcutaneous doses. In the present report, a similar ratio for 4 other drugs is described. These latter figures were determined principally for the purpose of studying the correlation between oral absorbability and certain fat-water solubility relationships. The general method of experimentation was the same as previously described. All drugs were used in the form of the hydrochloride salt and the dosage expressed on this basis.

*Cocaine.* Using excitement effects as the criterion of absorption,

[1] Walton and Lacey, *J. Pharm. and Exp. Therap.*, 1935, **54**, 61.

the sublingual/subcutaneous ratio in dogs was approximately 2 to 1. Twelve experiments were carried out with sublingual doses ranging from 15 mg./kg. to 50 mg./kg. These experiments included 3 trials with esophagotomized dogs in which a 5% tannic acid solution and suction drainage was used to prevent absorption from cut surfaces. The most satisfactory results were obtained following the intravenous injection of 1 mg. atropine sulphate to paralyze salivary secretions. Four trials were made with subcutaneous doses ranging from 15 to 30 mg./kg. These results agreed well with the more extensive observations described by Eddy[2] and Sollmann and Hanzlik.[3]

*Thebaine* (Paramorphine). Using reflex hyperexcitability in dogs as the criterion of effect, the sublingual/subcutaneous ratio was found to be greater than 4 to 1. Ten mg./kg. subcutaneously gave definite effects of increased reflex hyperexcitability which passed off in 120 minutes. Such effects were obtained at dosages which did not affect the Thiry fistula tracing. Five trials were made with sublingual dosages of 15 to 30 mg./kg. and 5 trials were made with subcutaneous doses of 5 to 10 mg./kg. The drug was of some theoretical interest because its chemical structure suggested a favorable fat-water solubility relationship.

*Emetine.* Using emesis as a criterion of effect, the sublingual/subcutaneous ratio in dogs was found to be greater than 6 to 1. With sublingual doses from 6 to 36 mg./kg. no vomiting occurred except in one case where there was considerable swallowing (5 trials, 2 with the maximum dose). Subcutaneous doses of 6 mg./kg. caused vomiting in each of 3 trials. These latter results are in good agreement with the more extensive observations of Eggleston and Hatcher with intravenous doses.[4]

*Diacetylmorphine.* Using the motor stimulant effect on Thiry fistulae which is characteristic of morphine derivatives, the sublingual/subcutaneous ratio was approximately 3 to 1. The results given in Table I were obtained according to a procedure previously described.[5] The expression of results by means of + symbols is modified here by the use of fractional values for these same symbols. It is considered that this is in keeping with the order of accuracy of this method of expression.

The subcutaneous effects are in agreement with the statement of

[2] Downs and Eddy, *J. Pharm. and Exp. Therap.*, 1932, **46**, 195.

[3] Sollmann and Hanzlik, An Introduction to Experimental Pharmacology, 1928, 279.

[4] Eggleston and Hatcher, *J. Pharm. and Exp. Therap.*, 1915, **7**, 233.

[5] Walton and Lacey, *J. Pharm. and Exp. Therap.*, 1935, **54**, 53.

TABLE I.
Effects Produced by Diacetylmorphine on Motor Activity of Thiry Gut.

| Subcutaneous | | | Sublingual | | |
|---|---|---|---|---|---|
| Dose mg./kg. | Effect | Time for Max. Effect, Min. | Dose mg./kg. | Effect | Time for Max. Effect, Min. |
| 0.10 | 2.0+ | 1.5 | 0.20 | 1.8+ | 4.0 |
| 0.10 | 2.7+ | 1.5 | 0.40 | 2.6+ | 4.0 |
| 0.20 | 3.7+ | .7 | 0.50 | 3.6+ | 6.5 |
| 0.40 | 4.5+ | 1.5 | 0.50 | 4.0+ | 5.0 |
| 0.40 | 4.6+ | 1.0 | 1.00 | 3.6+ | 7.0 |
| 0.60 | 10.0+ | 1.0 | | | |
| 1.00 | 5.2+ | 1.0 | | | |
| 3.00 | 13.5+ | 1.5 | | | |

Plant and Miller[6] that such effects are similar to those produced by morphine. Three sublingual trials with an esophagotomized dog gave prompt spastic effects in the dosage range used above. These effects could not be evaluated, however, because the control periods were irregular. Eight trials with human subjects in dosages ranging from 12 to 35 mg. showed no clear effects, except in 1 of 3 trials at this maximum dosage. The absorption is evidently not sufficient for this method to serve as a practical method of administration.

*Summary.* The ratios of sublingual doses to similarly effective subcutaneous doses have been described for 4 drugs. These approximate ratios are as follows: Cocaine, 2; diacetylmorphine, 3; thebaine, greater than 4; emetine, greater than 6.

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## Absorption of Drugs Through the Oral Mucosa. III. Fat-Water Solubility Coefficient of Alkaloids.

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It has been shown that the absorption of drugs from the mouth is strictly a selective process.[1, 2] With even a closely related group of drugs, such as the common alkaloids, marked differences are exhibited by the individual members. Apomorphine, for instance,

[6] Plant and Miller, *J. Pharm. and Exp. Therap.*, 1923, **21**, 202.

[1] Walton and Lacey, *J. Pharm. and Exp. Therap.*, 1935, **54**, 61.

[2] Walton, R. P., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1486.