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.

8147 C

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.

can be effectively administered by simple sublingual application, whereas morphine is very poorly absorbed. The diacetyl derivative of morphine is absorbed fairly well, whereas the monomethyl derivative is absorbed very poorly. Since all 4 of these drugs are closely related both chemically and pharmacologically, the explanation for this phenomenon of selectivity might reasonably be expected to depend on physical differences. The most prominent suggestion is that of a correlation with the oil-water distribution coefficient. This relationship has been extensively developed for other problems of cell permeability,[3, 4] and also has been described as being the decisive factor in absorption through the oral mucosa.[5] However, for this latter aspect of the correlation, the only previous demonstration of the principle is the fact that glycerol trinitrate is readily soluble in oils and only sparingly soluble in water. The present report presents a study of this relationship for a series of common drugs which have more limited oil solubilities.

In Table I the ratio of sublingual doses to similarly effective subcutaneous doses is compared with the fat-water solubility coefficient of the same drug. The sublingual/subcutaneous ratios, which have been previously described[1, 2] are not to be considered as natural constants in the same sense as solubility figures, but simply as approximate expressions of their absorption behavior. The oil-water solubility coefficients are usually considered equivalent to the distribution ratios of the same drugs in a 2-phase system made up of equal volumes of oil and water.[6] All the figures for oil solubility and one of those for water solubility (dilaudid) were determined for the purposes of this correlation. With the exception of the oil solubility of cocaine these data were not available in the literature. The figures for water solubilities, with the one exception were obtained from the literature. Since the 2 sources of data, the U. S. Dispensatory and a special study by Kolthoff,[7] are based on different conditions, both are quoted in separate columns of the table. The figures reported by Kolthoff cannot be compared directly with those in the U. S. Disp. because of a difference in the temperatures of determination. Special interest may be attached to the results

[3] Meyer and Gottlieb (Meyer and Pick), Die experimentelle Pharmakologie, 1933.

[4] Beutner, Physical Chemistry of Living Tissues and Life Processes, 1933.

[5] Meyer and Gottlieb, *loc. cit.*, 6.

[6] Hill, A. E., in A Treatise on Physical Chemistry, edited by H. S. Taylor, 1930, **1**, 477.

[7] Kolthoff, *Biochem. Z.*, 1925, **162**, 289.

obtained by Kolthoff because of the unique titration method involved in their determination. According to the U. S. Disp., the solubility of cocaine in olive oil is 80 mg. per cc.

Method for Determination of Solubility in Olive Oil. The general procedure was to obtain a saturated oil solution of the alkaloid at 25°, to extract a definite volume of this saturated solution with aqueous acid and to determine the quantity of the alkaloid in the acid extract by precipitating with phosphotungstic acid. Another procedure, used for ascertaining the approximate order of solubility, consisted in stirring weighed quantities of the alkaloids with successively increasing volumes of oil until clear solutions were obtained. In both these procedures, the solutions were stirred with a series of motor-driven stirring shafts operating at 1,000-1,500 R.P.M. All alkaloids except apomorphine were oven-dried at temperatures of 90-115°.

According to the first procedure, all mixtures were stirred 300 minutes or more although approximate saturation was obtained in 100 minutes for those cases in which this point was determined. Suspended solids were removed from the saturated oil solutions by centrifuging and the clear solutions were extracted by shaking with M/10 HCl in amounts and instalments depending on the concentration of the various alkaloids. The volumes were so adjusted as to have about 1 mg./cc. of alkaloid in the total acid extract. The alkaloids were precipitated from the extract with an excess of phosphotungstic acid made up as follows: Sodium tungstate 100 gm., disodium phosphate 75 gm., water 500 cc., and con. nitric acid 70 cc. After centrifuging in calibrated tubes, the volumes of the precipitates were estimated by matching with precipitates of equal volume obtained by dissolving weighed amounts of the same alkaloid in M/10 HCl and precipitating and centrifuging at the same time. Each determination of concentration in the extracts represented several series of such precipitations. The whole performance was carried out 2 to 4 times for each drug.

In the second procedure mentioned above, weighed quantities of dried alkaloids were stirred with increasing volumes of oil until the solutions became clear, 150 minutes of stirring being considered sufficient for equilibrium with each successive volume of oil. Clear solutions were obtained with cocaine, strychnine, atropine, and heroin and the results corresponded fairly well with those obtained by the other procedure. With the other drugs indicative results were obtained but the operations were not carried to complete solution. For instance, morphine and dilaudid proved very insoluble.

Codeine dissolved to give a fairly clear solution which became cloudy on further stirring. Possibly the codeine underwent decomposition to the more insoluble morphine.

The order of accuracy of the oil solubility determinations was considered sufficient for the purposes involved. Apomorphine presented a special problem because of its highly unstable character. A quantity of the alkaloid was obtained in a sealed ampoule (through a special courtesy of Merck and Co.) and ordinary precautions taken to prevent its oxidation. The water solubility of dihydromorphinone (dilaudid) was determined by stirring an excess of alkaloid with boiled, distilled water and estimating the concentration by precipitation with phosphotungstic acid as before.

The oil-water distribution coefficient of nicotine was determined at 40° by stirring 5% solutions in water with equal volumes of oil and 5% solutions in oil with equal volumes of water. The nicotine in the aqueous layers was determined by titration. The average coefficient thus obtained by 3 trials was 2.6 and is lower than would be expected from its relatively high oral absorption.[8,9] This divergence may be due to the highly irritant nature of the alkaloid or to its extreme oil solubility (complete miscibility).

TABLE I.

Drug	Oil solubility mg./cc. 25° C.	Water solubility, mg./cc. (Kolthoff) 15° C.	Water solubility, mg./cc. (U. S. Disp.) 25° C.	Oil-water sol. coeff. (Kolthoff)	Oil-water sol. coeff. (U. S. Disp.)	Ratio sublingual to subcu. dose
Cocaine	45.0	1.2	1.6	37	28	2
Apomorphine	1.8	0.09	—	20	—	2
Diacetylmorphine	10.0	—	0.6	—	17	3
Strychnine	3.2	0.09	0.15	35	21	4
Thebaine	8.0	0.7	—	12	—	4+
Emetine	10.0	1.1	—	9	—	6+
Atropine	14.0	1.6	2.1	9	7	8
Morphine	0.05	0.15	0.3	0.3	0.15	10
Dihydromorphinone	0.4	—	(2.0)	—	0.20	15
Codeine	16.0	—	8.0	—	2.0	15+

Although the correlation shown in Table I is by no means regular, the nature of the data involved is such that no high degree of regularity can be expected. The feature which is clearly demonstrated by the table is that certain drugs which are poorly absorbed have relatively low oil-water solubility coefficients and closely related drugs which are well absorbed have relatively high coefficients.

It may be concluded that the oil-water solubility coefficient is an

[8] Franke and Thomas, PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 1177.

[9] Franke and Thomas, *J. Pharm. and Exp. Therap.*, 1933, **48**, 199.

important factor in the selective oral absorption of these drugs. Other factors which may be significant are relative potency, degree of local vasoconstriction, irritation and alkalinity or acidity. It is also probable that absorption is favored by high oil solubility independent of the oil-water distribution coefficient, as is the case with nicotine.

8148 P

Peripheral Course of Pain-Fibers Supplying Coronary Arteries and the Myocardium.

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In decerebrate animals intra-arterial injection of an irritating solution results in stimulation of pain-elements associated with the small blood-vessels. The stimulation is evidenced by reflex activity of a pseudoaffective nature (Moore and Porter[1]). On injection of a coronary artery the reflex effects include arching of the back, movements of the extremities, snapping of the jaws, tossing of the head, and increased respiratory excursions. Attempts to prevent such activity by surgical neurectomy have provided information regarding the course of the pain-fibers concerned.

The experiments were performed upon cats. After guillotine decerebration, etherization was discontinued, the thorax was entered under artificial respiration, the pericardium opened and a thread passed beneath the stem of one or other coronary artery proximal to its bifurcation. Injection of 0.75 cc. 20% lactic acid distal to the thread caused instantaneous and very marked reflex activity associated with a rapidly progressing, black infarction of practically the entire wall of that half of the heart (Fig. 1). The injection was followed in 5 or 10 seconds by acute dilatation of both chambers.

Injection of the left coronary artery caused immediate and marked reflex activity in each of 17 animals in which the left thoracic sympathetic trunk was intact, although these animals had been subjected to unilateral or bilateral cervical sympathectomy or vagotomy. In contrast were the results in 10 animals in which the left thoracic

[1] Moore, R. M., and Porter, E. L., *Am. J. Physiol.*, 1934, **109**, 76.