their full astringent action has also been shown in many cases to be erroneous. The ones that most nearly correspond to the theoretical requirements are the acetic esters of tannin, of which there are two varieties on the market. While he found considerable difference in the individual specimens the best of them approached very closely to the ideal requirements. The hydrolysis of acetyl-tannin in the presence of sodium bicarbonate is, however, so slow that when taken by the mouth the most of the drug would be well down in the intestinal tract before its full astringency would be developed. For this reason it was deemed advisable to admit to the Pharmacopœia not only this derivative, but one of the albumin tannates whose astringent action is most marked in the duodenum.

REFERENCES.

Eggleston and Hatcher, *Journ. Pharmacol. and Exper. Therap.*, 1919, xiii, 433.
Closson, *Journ. Mich. State Med. Soc.*, 1914, xiii, 587.
Lambert, *Journ. Exper. Med.*, December, 1916.
Leech, *Journ. Amer. Med. Assn.*, 1920, lxxv, 1120.
Pilcher and Sollmann, *Journ. Lab. and Clin. Med.*, Feb. 1923, viii.
Power, *Journ. Chem. Soc.*, 1905, lxxxvii, 838 and 884.
Rock, *Bull. No. 1057, U. S. Dept. Agricult.*, 1922.
Smyth, *Amer. Journ. Pharm.*, April 1923.
Sollmann, *Journ. Pharmacol. and Exper. Therap.*, 1921, xvii, 63.
Takeda, *Arch. Internat. de Pharmacod. et de Therap.*, 1911, xxi, 203.

FURTHER STUDIES OF THE RELATIVE RATES OF ABSORPTION OF DRUGS FROM THE LYMPH SAC AND THE MUSCLES OF THE FROG.

BY C. D. HIGLEY AND M. S. DOOLEY.*

In a previous communication[1] it was shown that the digitalis group of substances, as measured by their intensity of action upon the heart, are absorbed more rapidly and evenly from the muscles of the frog than from the lymph sac. Strychnine is also absorbed more readily from the muscles, as judged by the observation that convulsions come on much sooner, from a given sized dose, than if the drug is acting from the lymph sac. Also it was found that the minimal convulsive dose of strychnine, when given intramuscularly, is not sufficient to cause convulsions in the frog when administered by the other method.[1] The present paper relates the results of experiments upon the question of whether this difference holds, when other drugs are introduced by the two methods. Of course only those drugs that induce some definitely measurable outward change in the frog can be used for this purpose. Epinephrin happens to be one of these. Its dilating effect upon the pupil of the frog from systemic administration, as demonstrated by Meltzer,[2] has been used as a basis of comparison.

DESCRIPTION OF METHOD.

The animals were fastened upon a frog board, and, as soon as the pupil maintained a constant diameter, injections were made into the muscles of the thighs or into the lymph sac as a given experiment required. During the first five minutes thereafter readings were taken of the vertical diameter of the pupil at half-minute

* Department of Pharmacology, Syracuse University College of Medicine, Syracuse, N. Y.

intervals, during the next five minutes at one-minute intervals, and at five-minute intervals thereafter until recovery. From the time of injection to the onset of dilatation is designated the latent period. The dosage and the time required to reach maximum pupil diameter for each method, as well as the duration of the effects, were tabulated throughout.

To demonstrate that our method had no appreciable influence upon the size of the pupil, a short series of experiments was undertaken, using normal salt solution in the same volume of dosage.

DISCUSSION.

It will be evident to the reader that, if by one method of administration the pupil undergoes more prompt dilatation than by the other, the drug has reached the eye in adequate concentration in less time by that method. Hence the rate of absorption has been more rapid. The factors mentioned, such as the time to reach maximum diameter, and the duration of the effect, are taken into account as of value, but the chief emphasis is laid upon the length of the latent period as a basis for our conclusions.

The accompanying tables and curves represent the average values derived from two series of experiments. One was carried out with maximum doses, according to Meltzer,[2] and one with approximately minimum doses, as nearly as we could determine. The drug was made up in normal salt solution, and 0.1 cc of a 1 to 10,000 solution or 0.001 mg. for each 20 Gm. of frog was injected, and, as in the experiments previously reported,[1] from a Luer tuberculin syringe. This was the standard dose in the first series for both intramuscular and for injections into the lymph sac. The dilution in the second series was 1 to 100,000 and the dose varied from 0.1 cc to 0.2 cc, or an approximate average of 0.00054 mg. per 20 Gm. of frog.

TABLE I.

	Lymph sac.	Intramuscular.	Per cent.
Normal diameter	2.10 mm.	2.14 mm.	
Latent period	3.10 min.	1.08 min.	187
Period of increasing pupil diameter	6.85 min.	14.00 min.	104.3
Maximum increase of pupil diameter	1.55 mm.	1.55 mm.	
Duration of maximum pupil diameter	20.90 min.	27.30 min.	30.6

TABLE II.

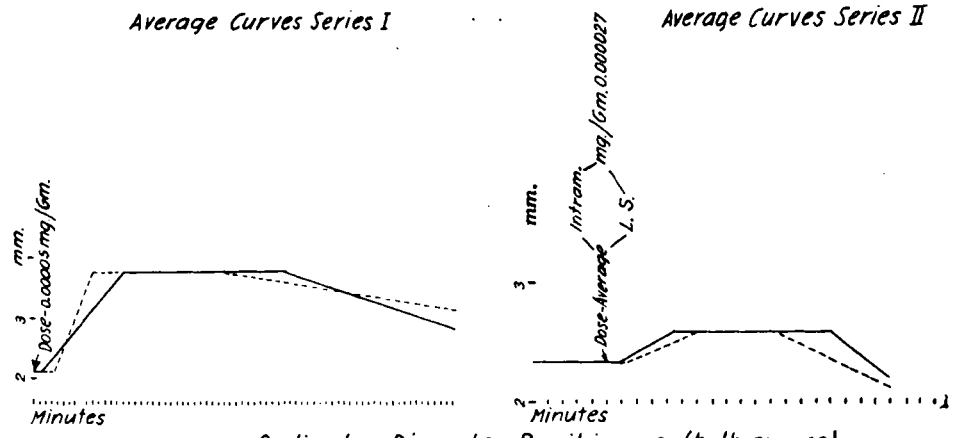
	Lymph sac.	Intramuscular.	Per cent.
Normal diameter	2.37 mm.	2.30 mm.	
Latent period	1.13 min.	0.75 min.	33
Period of increasing pupil diameter	4.56 min.	3.64 min.	25.2
Maximum increase of pupil diameter	0.26 mm.	0.28 mm.	
Duration of maximum pupil diameter	5.38 min.	8.68 min.	61.3

A summary of the results of the first series of experiments is shown in Fig. I, Table I, which are expressed in averages. The normal diameter of the pupil varied from 2.10 to 2.14 mm. The latent period for absorption from the muscles was 1.08 minutes, as against 3.1 minutes from the lymph sac, or 187% more rapid from the muscles. It required only 6.85 minutes for the maximum diameter to be reached in the case of the injections into the lymph sac, as compared with 14 minutes by the

other route, 104.5% faster in the case of the former method. While this was an unexpected result, yet it is felt that it does not constitute evidence against our contention of more rapid absorption from the muscles, as it is susceptible of more than one interpretation, whereas a shorter latent period signifies one thing only, more prompt absorption. The duration of maximum dilatation from intramuscular injections was 27.3 minutes as against 20.9 minutes for the other, 30.6% longer in the case of the former. Here again we have no satisfactory explanation for this relationship, unless it be that, owing to its well-known tendency to rapid loss of activity in the body, a less concentration of the drug reaches the eye from the lymph sac as the period of absorption continues. However this explanation may not apply in this instance.

Reference to the first set of curves in the figures will aid further in making these comparisons clear.

Epinephrin effects upon the frog's pupil.



Intramuscular curve—— Lymph sac curve- - - - -

In Figure I, Table II, involving the use of approximately minimum effective doses, the difference in the latent period was greatly reduced, but was still 33% shorter from intramuscular injections. The duration of the period when the pupil was increasing in diameter was shorter by 25.2%, than from injections into the lymph sac, the reverse of the effect of large doses in this respect, but the increase in diameter was the same by both methods. The duration of maximum dilatation for this series was longer in the case of the intramuscular injections by 61%, thus showing in this phase a similar time relation to that from large doses.

The curves, Series II, illustrate these various factors.

Viewing the results as a whole there are, as stated above, some facts that cannot be accounted for; some results which argue, so far as can be seen, until more can be known of their significance, neither for nor against our main contention, that absorption, in general, is more rapid from intramuscular injections. As was stated, the length of the latent period is taken as the real measure of this fact, and this has been found throughout, regardless of dose, to be shorter after intramuscular injections. One would expect the latent period to be longer for small doses, but this was found not to be so. Three possible explanations suggest

themselves: First, that of seasonal variation. The experiments with the larger doses were performed during the summer, at which time, in the case of the other drugs, such as the digitalis group, absorption is most difficult.[1] Second, another possible reason for it is the well-known styptic effect of epinephrin on the blood vessels locally. The stronger solutions might, in this way, retard their own rate of absorption, and thus not show the characteristic pupillary effect more promptly than a weaker solution which would not impede its own rate of absorption to as great a degree. Third, another factor operative in such a contingency, would be the well-known tendency for epinephrin to undergo rapid loss of activity, so that if its absorption should be interfered with in the manner suggested, that which enters the circulation would tend to be disposed of faster than additional amounts could enter, and thus the latent period would, of necessity, be lengthened until such time as absorption more than offsets elimination.

It is not intended in this connection to lay any particular emphasis upon the value of these experiments with reference to any action of epinephrin itself, but only in so far as they confirm our findings mentioned above with regard to the digitalis drugs.[1] If it is borne in mind that the official method of assay for the digitalis group requires that the drug be injected into the lymph sac, and that, as is well known, many samples cannot be successfully assayed by the method, on account of the fact that they are poorly absorbed from the lymph sac, the significance of our experiments becomes more apparent, as a further proof of the unreliable character of the present official method. However it may be stated that no such variability in the rate of absorption from the lymph sac was found in the case of epinephrin as in the case of digitalis.

In our previous article[1] on this question, we submitted much evidence to show that if the same size doses of digitalis were, instead, injected into the muscles a much more constant and positive result followed. Because of the very great pharmaceutical and therapeutic importance of the question involved, it seemed desirable to obtain still further evidence of the superiority of the intramuscular method in comparison with the official method. The results of the present experiments are offered, therefore, as further support of this fact developed in our earlier experiments.

REFERENCES.

[1] M. S. Dooley and C. D. Higley, JOUR. A. PH. A., 11, 911, 1922.
[2] Meltzer and Auer, *Am. Journ. Physiol.*, 11, 449, 1904.

THE STANDARDIZATION OF GELSEMIUM.*

BY PAUL S. PITTENGER.

Although the amount of Veratrum and Gelsemium prescribed and used by the present-day practitioner is very small as compared with Aconite and some other cardiac depressants, these drugs are still used in appreciable quantities.

As stated in a recent paper,† "It is the opinion of the author that any drug

* Scientific Section, A. Ph. A., Asheville meeting, 1923.

† Pittenger, "The Standardization of Veratrum," read before the Scientific Section of the Penna. Pharm. Association, Bedford Springs, Pa., June 1923.