

TABLE I.  
Mm<sup>3</sup> O<sub>2</sub> Consumed in 2 to 4 Hours by *Mustelus* Blood.

	In air	In CO	In air	In CO
Added	Nothing	Nothing	Methylene blue	Methylene blue
No. of exp.	15	12	9	8
O <sub>2</sub> consumed (in mm <sup>3</sup> )	23.3	14.4	35.2	20.1
" " %	100 ±	61.8 ±	151 ±	86.1 ±
	2.7%	7.2%	5.0%	4.3%

of respiration: (2) that in air methylene blue causes an increased O<sub>2</sub> consumption of 151% over the controls in 2 to 4 hours under the conditions of the experiment—this does not confirm Barron's conclusions that methylene blue has little or not effect upon the respiration of nucleated red blood cells; (3) that CO produces a decrease to 61% (it was not determined in these experiments whether this change in the manometric readings was due to residual oxygen remaining after the atmosphere was saturated with CO, or actual CO consumption); (4) that methylene blue counteracts this decrease, increasing the rate to 86%. This increased rate in CO is about the same in percent as that produced by methylene blue in air.

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### Oral and Intramuscular Ineffectiveness of "Hypotensive" Extracts.

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Administered intravenously in animals, the commonly used "hypotensive" extracts obtained from the pancreas, muscles and urine possess definite, though fleeting and complex, hemodynamic actions, with marked individual and species differences.<sup>1, 2</sup> However, the therapeutic claims for these extracts in circulatory disorders (Raynaud's disease, Buerger's disease, hypertension, angina pectoris, intermittent claudication, etc.) are based on oral and intramuscular administrations. Therefore, it was thought worth while to in-

<sup>1</sup> Lehman, A. J., and Van Winkle, W., Jr., *Arch. internat. de pharm. et de therap.*, 1938, **59**, 75.

<sup>2</sup> Van Winkle, W., Jr., and Lehman, A. J., *Arch. internat. de pharm. et de therap.*, 1938, **59**, 133.

investigate the oral and intramuscular absorbability of representative products.

*Absorption.* Six pigeons, 7 rabbits, 7 cats and 2 dogs were used. Anesthesia was obtained with pentobarbital, 35 mg per kg intraperitoneally. Blood pressure was recorded in the usual manner from the carotid artery. Intramuscular injections were made into the pectoral muscles of pigeons and gluteal muscles of mammals. The injected region was massaged to promote absorption. The criterion of absorption in mammals was a fall of blood pressure (depressor effect), and in pigeons, a rise (pressor effect). The two extracts used were padutin (kallikrein; pancreas or urine)\* and tissue extract No. 568 (pancreas),† in doses far exceeding those recommended as therapeutic.

Briefly, all animals reacted typically to intravenous injections of the extracts, in doses of 0.1 cc per kg, both before and after oral and intramuscular administrations. However, in no case was absorption of these extracts demonstrable after repeated oral and intramuscular administrations, as indicated by an absence of blood pressure changes and symptoms. More than one hour was allowed for any effects, and doses as high as 5 cc per kg were tried intramuscularly and orally, *i. e.*, 50 times the effective intravenous dose.

Direct absorption from the intestine (in the absence of destructive effects of digestive enzymes) was tested by injecting the extracts into ligated empty loops of small intestine of dogs and cats, using about a 20 cm length of jejunum. Two hours were allowed for absorption, and 2 cc per kg of the extracts were injected. Again, there were no demonstrable changes in blood pressure. At the end of 2 hours, the contents of the loop were removed and 1/10 of the volume was injected intravenously into the same animal. Invariably, the blood pressure fell about 50% in all animals receiving both extracts. Intravenous injection of the same volume of contents from another, and similar, intestinal loop containing 0.9% sodium chloride solution, as control, caused a fleeting and negligible fall of blood pressure of only about 6%. Intravenous injections of 0.2 cc per kg of the tissue extracts themselves produced falls of blood pressure equal in degree and duration to those after injection of contents from loops which had received the extracts. Accordingly, the tissue extracts remained practically unchanged, qualitatively and quantitatively, in the intestinal loops and there was no demonstrable systemic absorption.

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\* Marketed by Winthrop Chemical Co.

† Marketed by Sharpe and Dohme.

*Toxic and Fatal Doses.* Although gastrointestinal and intramuscular absorptions of the "hypotensive" extracts in high therapeutic doses were not demonstrable in anesthetized mammals and pigeons, a test was made for possible toxic effects in healthy and previously untreated pigeons. However, oral and intramuscular doses as high as 20 cc per kg produced no demonstrable effects in 11 pigeons and all the birds remained in good condition. The highest dose tried, or 20 cc per kg, was the equivalent of giving at once 1.4 liters of the extracts by the same routes to a 70 kg man, or about 300 to 1400 times a single recommended therapeutic dose.

Injected intravenously, the same pigeons used for tests of oral and intramuscular toxicity and other previously untreated pigeons (total 41) reacted to the extracts in percent mortality and dose per kg as follows: tissue extract No. 568: 100%, 12.5 cc; 60%, 7.5 cc; 33%, 5 cc; none, 2.5 cc; padutin: 100%, 10 cc; 60%, 9 cc; 40%, 8.5 cc; none, 7.5 cc. Death, in fatal cases, occurred within 5 minutes, preceded by tremors, emesis, increased respiration, opisthotonus, convulsions and coma; respiration stopped before the heart. Clearly, intravenous injections of these "hypotensive" extracts are capable of producing violent symptoms, and even death, but the doses would have to be beyond the therapeutic. In sensitive persons, however, the dose might be smaller. Such effects could conceivably occur from accidental intravenous injections in the intramuscular or hypodermic use of these extracts.

*Summary.* Two hypotensive extracts, namely Padutin and tissue extract No. 568, advocated in the treatment of important circulatory disorders, produced no demonstrable changes in blood pressure and no symptoms after oral and intramuscular administrations in very high (beyond therapeutic) doses in animals. Placed directly into ligated intestinal loops, both extracts remained unchanged and unabsorbed for 2 hours. All the animals reacted typically to control intravenous injections of both extracts. A range of fatal doses was determined intravenously only in pigeons, because very much larger doses given either by the oral or intramuscular route were without demonstrable effects. An experimental basis for the clinical use of the "hypotensive" tissue extracts, either orally or intramuscularly, is completely lacking. However, accidental intravenous injections, resulting from careless intramuscular or hypodermic uses, could conceivably cause alarming symptoms and even death. These extracts are undesirable, if not dangerous, for intravenous use.