TABLE I.
Effects of Yeast Extract on Cocaine Anesthesia of Rabbit Cornea (0.05 M Cocaine · HCl).

Yeast extr. conc., %	pH	Avg duration of anesthesia, min.	No. of detns.	% decrease in duration of anesthesia
0	4.8	30.0	16	
1	6.1	27.0	8	10
5	6.2	24.0	8	20
5	4.8	13.5	14	55

35% of the theoretical value. When the 0.05 M cocaine hydrochloride solution containing 5% of yeast extract was adjusted to a pH of 4.8 with hydrochloric acid, an average anesthetic duration of 13.5 minutes was obtained, a decrease over the control of 55%. It is evident that the yeast extract lowers the corneal anesthetic activity of cocaine and that this lowering becomes striking when compensation is made for pH changes.

Experiments, too few for a detailed report, indicated that the yeast extract lowered the subcutaneous LD_{50} of cocaine for rats by about 20% when cocaine and yeast extract were injected simultaneously in equal dosage on opposite sides of the abdomen. Further work is being undertaken on local anesthetics and on other physiologically active compounds.

Summary. Addition of a yeast extract to cocaine hydrochloride solution reduces the corneal anesthetic potency, this reduction being especially notable when the pH of the treated solution is lowered to the level of the control solution. There is evidence that the subcutaneous toxicity of cocaine is also decreased by the extract.

14369

Angiotonin Myotropism

FREDRICK F. YONKMAN, ROBERT JEREMIAS, AND DON STILWELL.

From the Department of Pharmacology and Therapeutics, Wayne University College of Medicine, Detroit, Mich.

Page and Helmer[1] stated that angiotonin exhibited smooth-muscle stimulating properties since it constricted blood vessels of the perfused rabbit ear, caused contraction of isolated segments of rabbit ileum and elevated arterial tension in the pithed cat. Apparently no effort was made in their vascular experiments to determine if angiotonin acted myotropically or by way of sympathetic vasoconstrictor components. Another approach to this problem is afforded by the technic employed in our experiments involving sympatholysis.*

Method. Ten cats and 2 dogs were anesthetized either with urethane gastrically or pentobarbital intravenously and then prepared for the insertion of cannulæ into the trachea, femoral vein and carotid artery. In 4 experiments Wharton's duct was also cannulated to determine the effect of angiotonin upon submaxillary salivation. Salivary flow was recorded manometrically. Blood pressure was recorded from the carotid artery with a mercury manometer (Gorrell's plastic tube type) and all drugs were infused intravenously in physiologic saline solution.

Drugs were administered in the following order and usually in the following dosage in mg or cc per kg: Epinephrine HCl, 0.015 mg;

[1] Page, I. H., and Helmer, O. M., *J. Exp. Med.*, 1939, **71**, 29.

* We wish to acknowledge the cooperation in this project of Dr. Donel Sullivan of Detroit Receiving Hospital and Dr. Robert Byberg of Henry Ford Hospital, both former assistants in Pharmacology.

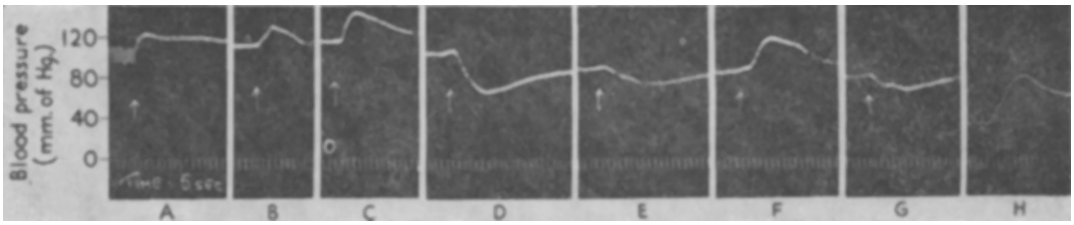

FIG. 1.

Cat, 2.7 kg, 12-16-42. Blood pressure reactions under urethane anesthesia. Time—5 seconds. All doses on per kilogram basis.

A. Section of vagi; B. epinephrine, 0.015 mg; C. angiotonin, 0.05 cc; D. ethyl yohimbine, 3 mg; E. epinephrine, 0.015 mg; F. angiotonin, 0.05 cc; G. epinephrine, 0.015 mg; H. pituitrin, 0.07 cc.

Angiotonin,† 0.05 cc; Ethyl Yohimbine HCl,‡ 3 mg; Angiotonin, 0.05 cc; Epinephrine HCl, 0.015 mg; Pituitrin, 0.07 cc.

Results. The typical reactions to the drugs employed differed quantitatively but were qualitatively uniform. Epinephrine and angiotonin caused the anticipated rises in arterial tension when injected prior to ethyl yohimbine but after the latter drug epinephrine produced its customary fall as has been previously reported.[2,3] Angiotonin, on the other hand, persistently effected a rise in arterial tension not unlike that produced before ethyl yohimbine and similar to that of pituitrin.

Angiotonin had no effect upon salivation and produced no pupillary reactions.

Discussion and Comment. Ethyl Yohimbine is an adrenolytic and sympatholytic§ agent and hence acts as a "medical scalpel" in relation to sympathetic vasoconstrictor neural components of the vascular system. This nullification of sympathetic vasoconstrictors extends likewise to the hypertensive state.[4] Sympathetic inhibition is evident from Fig. 1 in which the usual rise in arterial tension produced by epinephrine (B) is reversed by the yohimbine radicle (D). The sympathetic vasoconstrictor elements have been nullified by ethyl yohimbine, leaving the vasodilator mechanisms under the influence of epinephrine and resulting in a drop in arterial pressure (E). Angiotonin (F), however, still produces a rise in blood pressure which may be accounted for by either of two hypotheses: either (a) angiotonin acts directly upon smooth muscle components as do both soluble barium salts and pituitrin (H) or (b) angiotonin nullifies the vasoconstrictor paralyzing or sympatholytic action of ethyl yohimbine and acts adrenergically like epinephrine. The latter seems not to be the case since epinephrine (G), following ethyl yohimbine and angiotonin in the order named, still has its action "reversed." This indicates that a paralyzing action of ethyl yohimbine still persists *after* angiotonin has been injected and implies that this paralysis must have prevailed *during* its injection. In other words, sympatholysis prevailed during the second injection of angiotonin as well as during the second injection of epinephrine. Had it not, epinephrine should have produced its usual rise in tension as it did prior to ethyl yohimbine.

Since pituitrin and angiotonin both produce a rise in arterial tension during the adreno-

† Angiotonin was supplied to us by courtesy of Dr. Irvine H. Page of the Lilly Laboratory for Clinical Research, Indianapolis, Indiana, in solutions of such strength that 0.2 cc produced a rise of approximately 30 mm Hg. in the anesthetized dog weighing about 10 kilograms.

‡ Ethyl Yohimbine HCl was an 8-year-old sample but active and was originally supplied to us by Hoffmann-LaRoche Company through courtesy of Drs. A. G. Young and D. Worrall of Boston, Mass.

[2] Hamet, *C. R. Acad. d sc.*, 1925, **180**, 2074.

[3] Young, A. G., and Yonkman, F. F., *J. Pharm. and Exp. Therap.*, 1936, **57**, 150.

§ There has been some discussion regarding sympatholysis by Yohimbine and its congners and evidence supporting a true sympatholytic, as well as adrenolytic action, will be presented in another communication.

[4] Chase, H. F., Yonkman, F. F., and Lehman, A. J., *J. Pharm. and Exp. Therap.*, 1941, **72**, 6.

lytic or sympatholytic action of ethyl yohimbine it seems reasonable to believe that they act directly upon smooth muscle components and not upon ephinephrine-receptors in the vascular musculature.

The belief that epinephrine-receptors are not stimulated by angiotonin gains support by the failure of this substance to produce salivary flow or mydriasis in those cats which salivated profusely after epinephrine and cervical sympathetic nerve faradization.

The results of our vascular experiments confirm those reported by other workers[5] in that this hypertensive agent is unlike epinephrine. In their investigations a dioxane derivative, F 933, was employed as the sympatholytic agent and their angiotonin equivalent was known as pepsitensin which seems to be similar to the "hypertensin" of Braun Menendez and his co-workers.[6]

Conclusions. 1. Angiotonin (Page) has a true pituitrin-like action. 2. It contracts smooth muscle directly and not through the medium of adrenergic neural vasoconstrictor components. 3. Its action is not reversed by ethyl yohimbine as is that of epinephrine. 4. It exhibits no vasodilating action such as is characteristic of small doses of epinephrine. 5. It does not nullify the adrenolytic or sympatholytic action of ethyl yohimbine. 6. It has no effect upon cholinergically or adrenergically controlled salivation or pupillary responses.

[5] Alanso, O., Croxatto, R., and Croxatto, H., PROC. SOC. EXP. BIOL. AND MED., 1943, **52**, 61.

[6] Menendez, B., Fasciolo, J. C., Leloir, L. F., and Munoz, J. M., *J. Physiol.*, 1940, **98**, 283.

14370 P

Effect of Insulin, Glucose, and Glucose and Insulin on the Rate of Metabolism of Ethyl Alcohol.

RAYMOND GREGORY, PAUL L. EWING, AND VIRGINIA DUFF-WHITE.

From the Departments of Internal Medicine and Pharmacology, The University of Texas School of Medicine, Galveston.

Reports in the literature are not in agreement concerning the effect of insulin on the rate of metabolism of ethyl alcohol. Numerous reports indicate that insulin has no effect on the rate of metabolism of this substance.[1-7] Many reports claim, on the other hand, that insulin or insulin and glucose increase the rate of oxidation of ethyl alcohol.[3,8-14]

The conflicting reports in the literature, the fact that insulin or insulin and glucose have been used clinically in the treatment of acute alcoholism, and the theoretical unlikelihood that insulin would be so lacking in specificity

[1] Hirschfelder, A. D., and Maxwell, H. C., *Am. J. Physiol.*, 1924, **70**, 520.

[2] Fleming, R., and Reynolds, D., *J. Pharm. and Exp. Therap.*, 1935, **54**, 236.

[3] Goldfarb, W., Bowman, K. M., and Parker, S., *J. Clin. Invest.*, 1939, **18**, 581.

[4] Bohmer, K., *Deutsche Z. f. d. ges. gerichtl. Med.*, 1938, **30**, 205.

[5] Lang, S., and Von Schlick, B., *Z. Exp. Med.*, 1936, **99**, 81.

[6] Dontcheff, L., *C. R. Soc. Biol.*, 1939, **130**, 1406.

[7] Mirsky, I. A., and Nelson, N., *Am. J. Physiol.*, 1939, **127**, 308.

[8] Supniewski, J. V., *J. Biol. Chem.*, 1926, **70**, 13.

[9] Newman, H. W., and Cutting, W. C., *J. Clin. Invest.*, 1935, **14**, 945.

[10] Widmark, E. M. P., *Biochem. Z.*, 1935, **282**, 79.

[11] Bickel, A., *Deutsche Med. Wchnschr.*, 1936, **62**, 1209.

[12] Siegmund, B., and Flohr, W., *Klin. Wchnschr.*, 1937, **16**, 1718.

[13] Clark, B. B., and Morrissey, R. W., *Am. J. Physiol.*, 1938 (P), **123**, 37.

[14] Clark, B. B., Morrissey, R. W., Fazekas, J. F., and Welch, C. S., *Quart. J. Studies on Alcohol*, 1941, **1**, 663.