

## Comparative Reactivity of Isolated Surviving Coronary Arteries to L-Epinephrine and L-Norepinephrine.\* (18159)

DURWOOD J. SMITH AND JOSEPH W. COXE. (Introduced by William S. McCann.)

From the Departments of Medicine and Physiology, University of Rochester School of Medicine and Dentistry and the Clinics of the Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y.

The comparative reactivity of isolated surviving coronary arteries to l-epinephrine and l-norepinephrine has not been determined. Recorded observations on the coronary flow response to norepinephrine include the perfused hearts of rabbits(1), cats (1,2) and dogs(3) as well as the dog heart-lung preparation(2) and the dog using the rotameter(4). All of these studies have demonstrated an increase in coronary blood flow associated with a concomitant increase in heart rate and amplitude of contractions(1-3). As pointed out by Folkow(3), in these studies it is difficult to determine whether true vasodilation has occurred, or whether the observed increase in coronary flow is due solely to the increased activity of the heart muscle. By these present studies of the isolated coronary arteries we have endeavored to determine whether l-norepinephrine and epinephrine have a direct vasodilating action on these vessels.

**Experimental Procedure.** The coronary arteries of healthy slaughtered swine were examined by the angioplethysmographic technique of Smith and Syverton(5,6). The vessels were removed and mounted in the plethysmograph and perfused with Tyrode's solution until the arterial wall had assumed a cer-

tain degree of tone. The artery was then tested with l-epinephrine (Winthrop-Stearns) and l-norepinephrine (kindly supplied by Winthrop-Stearns) by injecting test doses of usually 50  $\gamma$  of the drugs into the perfusate. This provided a stimulus of 5 parts per million for 15 seconds under these experimental conditions. Variation in the dosage down to  $1 \times 10^{-8}$  did not change the type of reaction observed. Volume changes of the artery were recorded as a measure of constriction or dilation.

**Results.** Eleven coronary arteries which had during perfusion assumed a certain degree of tone have been tested with l-norepinephrine. In each instance vasodilation resulted. Fig. 1 illustrates a typical experiment (No. 728). In 4 instances it was possible to compare the degree of vasodilation produced by l-epinephrine and l-norepinephrine in the same vessel by measurement of the areas of the reactions recorded by a planimeter. These measurements expressed in square centimeters are recorded in Table I.

**Discussion.** l-epinephrine and l-norepinephrine cause vasodilation of the isolated surviving coronary arteries of swine. In those instances when it was possible to compare the effects of similar test doses of l-epinephrine

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1. March, D. F., Pelletier, M. H., Ross, C. A., *J. Pharmacol. and Exper. Ther.*, 1948, v92, 108.

2. Burn, J. H., Hutcheon, D. E., *Brit. J. Pharmacol.*, 1949, v4, 373.

3. Folkow, B., Frost, J., Uvnäs, B., *Acta physiol. Scand.*, 1949, v17, 201.

4. Wegria, R., Ward, H., Frank, C. W., Dreyfuss, F., to be published.

5. Smith, D. J., *Proc. Soc. Exp. Biol. and Med.*, 1950, v73, 449.

6. Smith, D. J., Syverton, J. T., Cox, J. W., to be published.

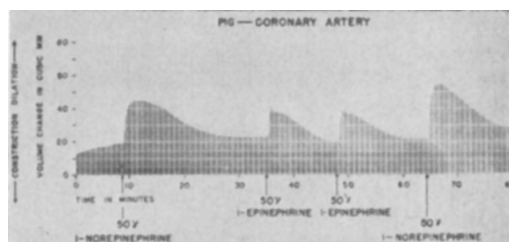


FIG. 1.

Exp. #728. Swine coronary artery. Comparative study of vasodilation produced by similar (50  $\gamma$ ) test doses of l-epinephrine and l-norepinephrine.

TABLE I. Comparative Vasodilation of Coronary Arteries to L-epinephrine and L-norepinephrine.

| Exp. | L-epinephrine | L-norepinephrine |
|------|---------------|------------------|
| 714  | 1.7           | 3.5              |
| 728  | 4.0           | 10.0             |
| 728  | 4.3           | 10.5             |
| 729  | 2.2           | 5.8              |

and L-norepinephrine the nor compound produced vasodilation about  $2\frac{1}{2}$  times greater than L-epinephrine as measured by this technique. The molecular weight of norepinephrine is 92.3% that of epinephrine hence these studies were not accomplished on a strictly equimolecular basis, yet the differ-

ence in reactivity far exceeds the probable difference attributable to differing molecular weights.

*Summary.* 1. L-norepinephrine and L-epinephrine produce vasodilation of the isolated surviving coronary arteries of swine.

2. L-norepinephrine produces about  $2\frac{1}{2}$  times the degree of vasodilation produced by L-epinephrine in the same artery in the same dose. This difference exceeds the anticipated difference attributable to differing molecular weights.

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### Comparative Study of the Ketogenic Activity of Certain Niacin Compounds.\* (18160)

R. G. JANES.

*From the Department of Anatomy, State University of Iowa College of Medicine, Iowa City, Ia.*

Normal rats, when fed on a niacin deficient diet, probably synthesize sufficient niacin or niacin-like compounds to carry on normal metabolic processes, providing the diet contains adequate amounts of protein(1-3). However, when excessive amounts of niacin are given to diabetic rats or to normal fasting rats, a marked ketonuria is produced, resulting presumably from some alteration in the metabolism of fat(4-5). The present work is concerned with a comparison of the ketogenic action of niacin, niacinamide and the alcohol of

niacin (Roniacol) in the non-fasting diabetic rat.

*Experimental.* Twenty-one adult male rats of the Long-Evans strain, 8 to 10 months of age, were used. After the rats had been fasted for 48 hours, diabetes was produced by a single subcutaneous injection of 125 mg of alloxan/kg body weight. All of the rats were diabetic for at least 2 months before the experiment was started and most of the animals showed a severe diabetes. Qualitative urinary acetone body determinations were made daily by the sodium nitro-prusside method, which gave an estimation of the degree of ketonuria. In the conditions of this experiment, each rat acted essentially as its own control.

*Effect of niacin compounds when 10% fat diet was used.* Initially, the animals were given the basal diet<sup>†</sup>(5) for several days in order to determine a baseline for the excretion of urinary acetone bodies. After this was established they were fed an experimental diet which consisted of the basal diet with 0.1%

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1. Heidelberger, C., Abraham, E. P., and Lepkovsky, S., *J. Biol. Chem.*, 1948, v176, 1461.

2. Hurt, W. W., Scheer, B. T., and Deuel, H. J., Jr., *Arch. Biochem.*, 1949, v21, 87.

3. Rosen, F., and Perlzweig, W. A., *J. Biol. Chem.*, 1949, v177, 163.

4. Janes, R. G., and Myers, L., *PROC. SOC. EXP. BIOL. AND MED.*, 1946, v63, 410.

5. Janes, R. G., and Brady, J., *Am. J. Physiol.*, 1949, v159, 547.

<sup>†</sup> The basal synthetic diet contained 10% fat, 18% protein, 70% carbohydrate with essential vitamins and minerals.