

## OBSERVATIONS WITH REGARD TO THE ACTION OF EPINEPHRIN ON THE CORONARY ARTERY.\*

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### PLATE 64.

The observations here reported were made partly in the course of twenty-five successful experiments concerning the vasoconstricting substances of blood serum (Janeway and Park (1)), partly in the course of a smaller number of experiments on the excised coronary artery performed directly in preparation for this work. The method employed has been the excised ring method of Meyer (2).

Previous investigators of the reaction of the coronary artery to epinephrin have used both perfusion and the excised strip or ring method of Meyer. Using the former, Schäfer (3) obtained no effect capable of definite interpretation. von Langendorff (4), despairing of his ability to overcome the great obstacle to the perfusion method, *i. e.*, excitation of cardiac contraction, abandoned that method and first applied the excised ring method to the study of the effect of epinephrin on the coronary. Wiggers (5) avoided excitation of the cardiac muscle by the perhaps questionable expedient of using an unoxygenated sodium chlorid solution as a perfusion medium; he obtained constriction. By the perfusion method Campbell (6) had at times no effect, at other times slight constriction. Brodie and Cullis (7) reported constriction of the coronary when they perfused with a dilution of epinephrin so small as not to augment cardiac contraction, but relaxation of the coronary when the strength of epinephrin was increased beyond this point. On the other hand, by the use of the excised ring method, von Langendorff (8), Eppinger and Hess (9), Pal, de Bonis and Susanna (10), Cow (11), and Campbell (12), have all

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demonstrated that epinephrin relaxes the excised coronary ring. While, then, the investigators by the perfusion method have obtained conflicting results with epinephrin, those using the excised ring method have obtained a uniform effect, relaxation of the coronary. Recently, however, Barbour (13) has introduced disagreement even here. Though, like his predecessors, he obtained relaxation from epinephrin when he used the coronary of animals,—ox, sheep, and pig,—he found that epinephrin used upon the coronary artery of man has a constricting effect.

Barbour's (14) investigations into the reaction of the human coronary to epinephrin require especial mention. He performed nine successful experiments on the excised rings of human coronaries obtained from three subjects in the first few hours, in one case seven hours, after death. These nine experiments he regarded as being free from error. In six of the nine he obtained constriction of the excised ring, in three no effect at all. The number of his experiments is then rather small, and only two thirds of them were of a positive nature. Yet on the basis of these experiments he assumes the general conclusion that epinephrin constricts the human coronary artery.

It would be remarkable if epinephrin produced on the coronary artery of animals one effect and the opposite effect on the coronary of man. The volume of proof required to establish so notable an exception to what has appeared to be a general law—so far as the excised ring method is concerned—must necessarily be great. The human coronaries investigated by Barbour had lain in the body for from two to seven hours after death. Who knows how the coronary arteries of animals allowed to lie *in situ* a like length of time might react to epinephrin? This point is still to be determined. The human coronaries of Barbour's experiments were pathological; all three showed intimal proliferation and one of them, in addition, calcification. Dale (15) has demonstrated that ergotoxin may alter the action of epinephrin on peripheral vessels. Is it not possible that the receptive mechanism in these pathological vessels has in some way become deranged by the disease process, and the character of the response to epinephrin has altered in consequence? But most important of all, how does the normal

human coronary react to epinephrin? Surely not until this last question has been answered can the conclusion be accepted that epinephrin constricts the coronary artery of man.

METHOD EMPLOYED IN THESE EXPERIMENTS.

The method used in my experiments does not differ materially from the original method of Meyer. Rings of the coronary artery of the ox, about three to four millimeters thick, were used instead of strips. Usually two of these were fastened together tandem fashion and suspended in a glass chamber. The lower ring was fastened to the floor of the chamber, the upper ring was connected to the short arm of a lever. The long arm of this lever recorded on a drum. The rings were bathed in Locke's fluid, which was kept constantly oxygenated and at a temperature of about 37° C. Epinephrin was introduced into the glass chamber containing the Locke's solution, either directly from a pipette or by a system of syphonage which involved withdrawal of the Locke's fluid and substitution of the desired dilution of epinephrin in Locke's fluid. The initial tonus was overcome by the use of weights. For his carotid strips Meyer used a stretching weight of eighty-six grams, which at the end of about twenty minutes was reduced to a lifting or permanent weight of about fifty grams. The best stretching weight for the ox coronary ring of about three millimeters diameter and three to four millimeters thickness is thirty grams, which is reduced at the end of fifteen minutes to a lifting load of about twenty grams.

Barbour employed a still different method to overcome the initial tonus of his coronary rings. He used a small weight, but depended chiefly on the sudden relaxation which occurs in the coronary ring when the temperature is elevated to about 42° C. In the experiments performed by the writer, the greatest pains were taken to prevent any such variation of temperature as Barbour intentionally employed.

It is worthy of mention that the coronary artery as it is found in the slaughtered animal always presents a wide lumen, in contrast to the peripheral artery which is regularly in a constricted state but with the cut ends flaring out in bell-shaped fashion. These facts

would seem to indicate an essential difference in the tonus character of the two kinds of vessel. Attention should also be directed to the difference in behavior of the two during the course of any experiment. The coronary artery is much less subject than the peripheral to unaccountable fluctuations in tone.

#### EXPERIMENTS PERFORMED.

As already stated, Brodie and Cullis (16) found in their perfusion experiments that epinephrin in dilutions too small to augment heart action nevertheless constricted the coronary artery. By experiments made on six ox coronaries, I have attempted to determine whether very dilute solutions of epinephrin may produce a primary constriction, but have invariably found that the primary effect of threshold values of epinephrin is relaxation.

Rings of the coronary were subjected to a series of solutions of epinephrin, beginning with 1 to 200,000,000 and increasing in strength. In every experiment the first distinguishable effect of epinephrin on the coronary was relaxation at 1 to 50,000,000, appearing as a barely perceptible temporary depression of the tracing line (plate 64, figure 1). Perhaps it would have been possible to demonstrate an effect from a solution even more dilute, by increasing the sensitiveness of the coronary ring as described later. Meyer's threshold values for epinephrin on the ox carotid were in the neighborhood of 1 to 90,000,000.

Though there is no need of further proof that epinephrin relaxes the coronary artery of the ox, certain observations in regard to the nature of this relaxation are of interest. By the simple procedure of varying the lifting load, the quantitative effect of epinephrin on the coronary artery can be made to vary within wide limits. When, for example, the stretching load of thirty grams was reduced to a lifting load of twenty-nine grams (instead of the usual lifting load of twenty grams), it was found that epinephrin produced a relatively small relaxation, for the obvious reason that the coronary rings were already in a much relaxed condition on account of the heavy lifting load. But when, on the other hand, the stretching load of thirty grams was reduced to a lifting load of only two grams, the relaxing effect of epinephrin was again small, although the rings

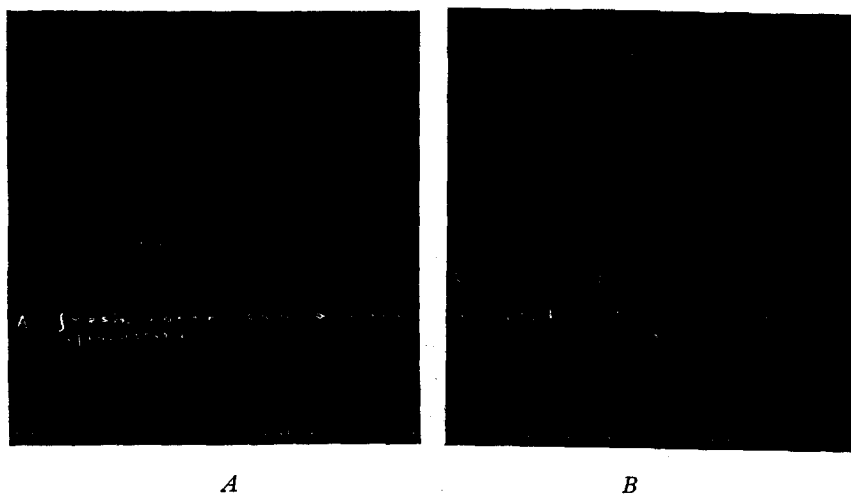
after their release from fourteen fifteenths of the original load had undergone marked shortening and were in a state of tonus ideal for the action of epinephrin. In the latter instance the rings failed to react maximally, not because they had been insufficiently affected by the epinephrin, but because a weight sufficient to produce elongation was lacking.

In a strict sense, then, the action of epinephrin on the ox coronary cannot be regarded as being dilatory, as no spontaneous increase in the diameter of the vessel occurs under its influence. The action seems analogous to the effect of epinephrin upon the intestinal musculature, and seems to be inhibitory. It cannot be thought of, however, as producing a complete abolition of tone, for if tone were completely abolished by epinephrin, as great a degree of relaxation would be produced by a light as by a heavy weight. The action on the coronary, therefore, seems to be in the nature of a sudden lowering of tone, so that the musculature offers but feeble resistance to any relaxing force. Epinephrin produces a very considerable temporary weakening of the arterial muscle, but does not completely paralyze it.

In this connection the work of Kepinow (17) is of interest. His experiments indicated that the combined action of epinephrin on the receptive substance and hypophysis extract on the contractile substance produced an effect on the peripheral vessel greater than the sum of their single effects. On the other hand, there is no doubt that epinephrin seriously impairs the effect of certain substances, which constrict the coronary by direct action on its smooth muscle. Epinephrin in sufficient dosage may hide the constrictor effect of these stimulants of smooth muscle entirely, or modify it to a great extent.

But even when the weighting of a given ring of ox coronary is constant, I have observed that the reaction of the artery to epinephrin may vary in the course of a single experiment, without change in experimental conditions. When the weighted ox coronary rings were kept suspended in a medium of Locke's fluid for from one to two hours, a gradual constriction occurred. The causation of this constriction requires further investigation; its explanation may possibly be found in a disturbed osmotic relation.

At any rate, it is a fact that when the constriction became well developed, the effect of epinephrin was greatly intensified. When previous to the constriction a given concentration of epinephrin had produced a fall of one centimeter in the curve, after the appearance of this constriction the same concentration of epinephrin produced falls of from three to four centimeters, almost to the base level of the previous relaxation curve (text-figure 1, *A* and *B*). Such



TEXT-FIG. 1A. INFLUENCE OF EXISTING TONUS OF CORONARY UPON ITS QUANTITATIVE RESPONSE TO EPINEPHRIN. *A* = strong epinephrin in Locke's solution introduced. From the point at which tracing is cut to resumption in text-figure 1B is an interval of three hours and ten minutes. During the first thirty minutes, dilatation remained unchanged; then gave place to a progressive, slow constriction (text-figure 1B.) Magnification,  $\times 7\frac{1}{4}$  (half size reproduction).

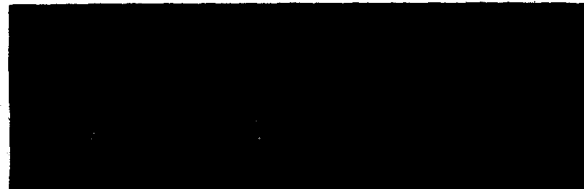
TEXT-FIG. 1B. Continuation of text-figure 1A. Relation to base line as in text-figure 1A. For forty-five minutes repeated washing with Locke's fluid. *C* = final washing with Locke's fluid. *A* = reintroduction of the same solution as at *A*, text-figure 1A.

variations in the degree of relaxation in the same artery from the same concentration of epinephrin, but at different times, illustrate the futility of attempting to measure the effect of epinephrin in terms of the circumference of the excised ring, or of comparing reactions in a quantitative way.

Dixon (18) has shown that apocodein inhibits the constrictor effect of epinephrin, but not the inhibitory (dilator) effect on the receptive substance. If, as Brodie and Cullis maintain, both constrictor and dilator sympathetic nerves are present in the coronary artery, any given effect of epinephrin on the coronary artery must be due to the summation of the antagonistic effects on both sets of nerve endings (receptive substances). If now the constrictor endings (the constrictor receptive substance) can be inhibited by apocodein, the relaxing effect of epinephrin should be increased; but such appears not to be the case. In four experiments performed by the writer and Dr. Charles Lieb, to clear up this point, the result was uniform. In none of these experiments was the relaxation produced by a given dosage of epinephrin more extensive after treatment of the vessel with apocodein than before such treatment



A



B

TEXT-FIG. 2. FAILURE OF APOCODEIN TO INFLUENCE THE RESPONSE OF THE CORONARY TO EPINEPHRIN. Experiment 2, series A, April 21, 1912. Ox coronary, four successive segments. Magnification,  $\times 15\frac{1}{2}$ .

A. Segments 1 and 3. Loads, stretching, 35 gm.; lifting, 20 gm. in Locke's fluid. 1. Fresh Locke's fluid introduced. 2. Epinephrin (adrenalin chlorid) to make 1:5,000,000.

B. Segments 2 and 4. Loads and all conditions as in the text-figure 2A. 1. Locke's fluid containing apocodein 0.1 per cent. 2. Epinephrin (adrenalin chlorid) to make 1:5,000,000. Note quantitative dilatation in A and B.

(text-figure 2, *A* and *B*). While the number of experiments is perhaps insufficient for dogmatic statement, the results obtained would seem to be a strong argument against the assumption of Brodie and Cullis.

## CONCLUSIONS.

1. Excised rings of the coronary artery of the ox properly weighted react to epinephrin by dilatation.
2. This reaction of the ox coronary is not an active dilatation, but is in the nature of a sudden lowering from a high to a relatively low degree of tonus. The tonus is not, however, entirely abolished by epinephrin.
3. The degree of relaxation produced by epinephrin is not constant. It depends on several factors other than the concentration of epinephrin used.
4. It is possible to increase the sensitiveness of the coronary artery to epinephrin.
5. There is no evidence of any primary constrictor effect on the ox coronary from epinephrin in most dilute solutions, nor can the existence in this artery of any constrictor mechanism of sympathetic origin be determined by the excised ring method.

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## EXPLANATION OF PLATE 64.

FIG. 1. THRESHOLD VALUES OF EPINEPHRIN. Tracing from ox coronary artery, 2 rings, showing the effects of increasing strengths of epinephrin (adrenalin chlorid special, Parke, Davis and Co.) from 1 : 100,000,000 to 1 : 5,000,000. L indicates substitution of Locke's fluid. Magnification  $\times 15\frac{1}{2}$ . Time in minutes.

