

## THE CONSTRICTING INFLUENCE OF ADRENALIN UPON THE HUMAN CORONARY ARTERIES.\*

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The direct action of adrenalin upon the blood-vessels of the heart has hitherto been observed only upon the lower animals. Two classes of experiments have been made; namely, those with various modifications of the perfusion method, and those with isolated rings of artery (after Meyer (1)).

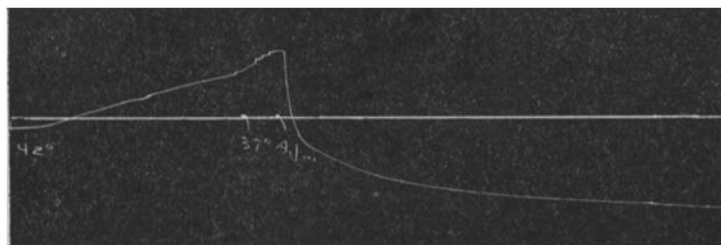
By perfusion of isolated hearts, neither Schäfer (2) nor Langendorff (3) were able to prove a vasomotor influence. Elliott (4) perfused a single vessel on a resting strip of cat's ventricle and observed an increased flow after adrenalin. Wiggers (5) believes he has proved that vasoconstriction results from adrenalin perfusion. Campbell (6) obtained, as a rule, no effect, but in some cases there was slight constriction. Brodie and Cullis (7) have recently concluded that very small doses (not large enough to alter the heart action) produce vasoconstriction only, while with larger doses (augmenting heart action) this effect is soon superseded by vasodilatation. This latter effect, however, they cannot entirely ascribe to metabolites from the heart, and they therefore conclude that the coronaries possess constrictors and dilators, both of sympathetic origin (8). Bond's (9) perfusion experiments on the living dog, while inconclusive as to vasomotor action, indicate that, in this animal at least, changes in the rate of coronary flow are parallel to changes in general arterial blood pressure.

By Meyer's method with isolated rings of arteries, Langendorff, Pal (10), de Bonis and Susanna (11), Cow (12), and Campbell have all demonstrated vasodilatation.

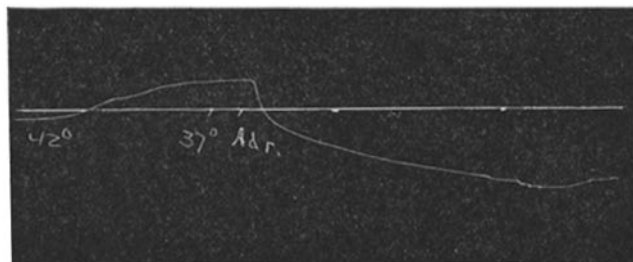
Before taking up our results with human coronary arteries, our experiments upon the arteries of animals may be mentioned.

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We have made twenty-five such experiments upon the coronary arteries of the calf. Eleven were without marked effect; two because the portion of the vessel was suspended longitudinally, and the other nine because they were made upon the short main stem of the left coronary. The explanation of the absence of effect will appear in a later paper dealing with the anatomical structure of various blood-vessels.<sup>1</sup> Of the fourteen remaining experiments, all showed a definite dilatation varying from 2 to 12.6 per cent. of the vessel's circumference. In all these, the tissue was from the



TEXT-FIG. 1.<sup>2</sup> Coronary artery of calf. Adrenalin dilatation after heat contraction. Kymographion rate: 1 cm. = about four minutes.



TEXT-FIG. 2. Coronary of calf. Adrenalin after heat contraction.

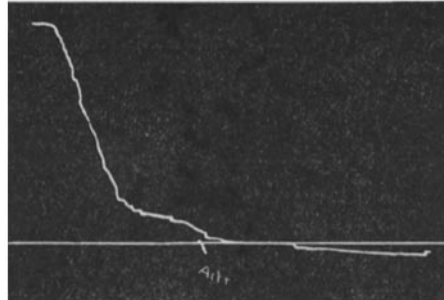
descending branch of the left coronary. Among similar experiments on other animals, we obtained from a sheep's coronary a relaxation of 17 per cent., and from a pig's coronary, a relaxation of 7 per cent.

Text-figures 1 to 4, from the calf, show that the effects of tempera-

<sup>1</sup> Barbour, *Arch. f. exper. Path. u. Pharmacol.*, 1912 (in press).

<sup>2</sup> All the tracings have been reproduced full size, with the exception of text-figure 5 which has been reduced one half.

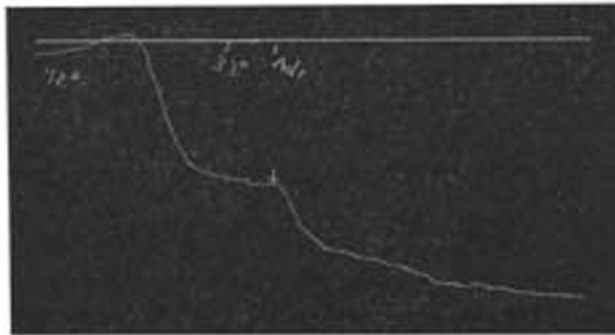
ture and of adrenalin have not been confused. In text-figures 1 and 2, heating to 42° C. was followed by contraction; in text-figure 4, by relaxation. In all three cases, however, the effect of adrenalin was constant. Text-figure 3 illustrates the fact that adrenalin pro-



TEXT-FIG. 3. Coronary of calf. Adrenalin has minimal or no effect on the main stem of the artery.

duces little or no effect upon the main stem of the left coronary artery.

Although Schlayer (13) states that human arteries are not responsive post-mortem to the action of adrenalin, Cow has successfully used peripheral arteries from amputated limbs. The extension



TEXT-FIG. 4. Coronary of calf. Adrenalin dilatation after heat relaxation.

of this work to the human coronary was undertaken by us and we were fortunate in securing, through the kindness of Professor Aschoff, material from the four cases in table I.

TABLE I.

	Date.	Age.	Pathological diagnosis.	Hours post-mortem.	Histology of coronary arteries.
I.	Dec. 15, 1911	24	Tubercular peritonitis	4	Thickened intima
II.	Dec. 20, 1911	60	Aneurysm; syphilitic aortitis	6 <sup>3</sup>	Thickened intima
III.	Dec. 29, 1911	34	Ileus; intestinal resection; peritonitis	2½	Thickened intima
IV.	Jan. 17, 1912	54	Carcinoma of the esophagus; fibrinous pericarditis; hemopericardium	7	Thickened intima with calcification

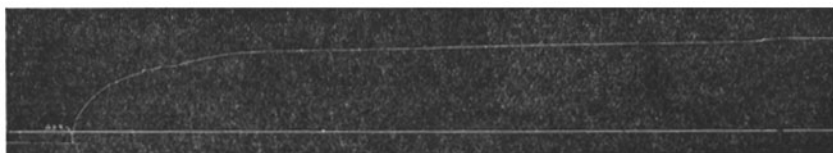
*Method.*—In each case, while the thoracic organs were still warm, a portion of the left coronary artery was removed and placed immediately in a thermos bottle containing Ringer's solution at 37° to 38° C. The tissues remained in the bottles at this temperature until the beginning of the experiments.

For each experiment, a ring from two to four millimeters in width was cut from the artery and suspended between two glass hooks. The lower hook was a prolongation of a stationary glass rod; the upper was suspended by a thread from the short arm of a lever at a point eight millimeters from the axis. The writing arm measured 270 millimeters. This magnified the curves about thirty-four times. The tissues were constantly under tension from a weight hung on the opposite side of the axis. The kymographion rate was about one centimeter in four minutes, and the vessel preparation was suspended in a bath containing 100 cubic centimeters of Ringer's solution, which was in turn surrounded by a large water bath. Oxygen was caused to bubble slowly through the Ringer's solution which was kept at a temperature of 42° C. for the first fifteen or twenty minutes. The tonus removal thus obtained was manifested, as a rule, in the human coronary arteries by a sudden extensive relaxation several minutes after the application of the weight tension and the raising of the temperature. When the lever was again writing a level curve, the temperature was lowered to 37° to 38° C. This latter change never caused an appreciable change in the height of the curve. One dose of 0.000625 of a gram of synthetic adrenalin (1:1,000 suprarenin) was given in 25 cubic centimeters of additional Ringer's solution. The total 125 cubic

<sup>3</sup> Tissues did not respond; see below.

centimeters of solution then contained adrenalin in the proportion of 1 : 200,000 (as used by Langendorff.)

In our first few experiments with human coronaries, we used one cubic centimeter of blood serum to protect the adrenalin against oxidation, for Trendelenburg (14), in his work on the quantitative estimation of adrenalin, has clearly demonstrated that serum has this property, and by its use we find that our adrenalin solutions keep colorless even after exposure to oxygen and heat for several hours. In the course of many experiments on calves' arteries, it has never masked the characteristic adrenalin reactions. Beginning with experiment 88, however, serum was not added until some minutes after the adrenalin action, thus removing the remotest objection to its use.



TEXT-FIG. 5. Case 1. Constriction of human coronary after adrenalin. Under observation for nearly two hours.

#### CASE I.

*Experiment 77.*—(Text-figure 5.) A ring from the descending branch of the left coronary artery, 2.5 cm. from the aorta. Adrenalin was added simultaneously with 1 c.c. of rabbit serum to protect the adrenalin against oxidation. Immediate contraction (15.7 per cent.) was maintained for nearly two hours.

*Experiments 78 and 79.*—Rings from the same artery, two hours later. The response to heat and tension were very slight. No response to adrenalin. Tissues dead.



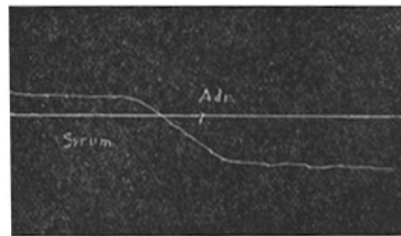
TEXT-FIG. 6. Case 3. Serum and adrenalin were both added before the removal of tonus.

## CASE II.

*Experiments 80, 81, and 82.*—Rings from the left coronary artery. Tissues respond weakly to heat and tension. No response to adrenalin. Tissues dead.

## CASE III.

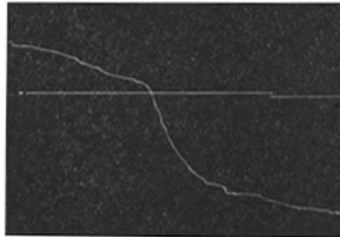
*Experiment 84.*—(Text-figure 6.) A ring from the descending branch of the left coronary artery, about 2.5 cm. from the aorta. To protect against oxidation, 1 c.c. of serum from the same cadaver was added about two minutes before the adrenalin. Sudden dilatation about five minutes after the addition of adrenalin.



TEXT-FIG. 7. Case 3. Serum was added before, and adrenalin during the removal of tonus.

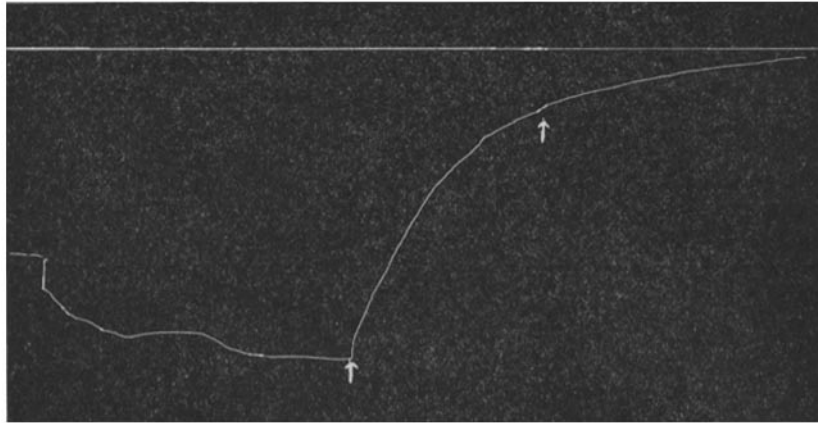
*Experiment 85.*—(Text-figure 7.) A ring from the distal portion of the same artery. Similar dilatation follows serum alone. Adrenalin was given during relaxation. This experiment rules out adrenalin as the cause of relaxation.

From the following experiment, as well as from later ones, it will be seen that this relaxation was simply the removal of tonus by heat, and was probably shortened by the administration of adrenalin.



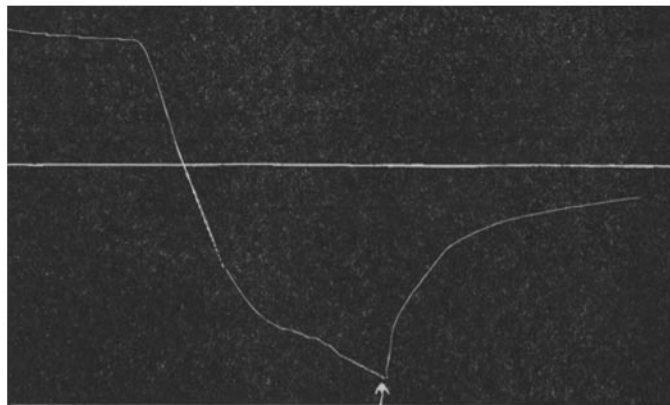
TEXT-FIG. 8. Case 3. The usual sudden removal of tonus by heat and tension alone.

*Experiment 86.*—(Text-figure 8.) Main stem of the same artery, close to the aorta. Nothing was added to Ringer's solution. Dilatation occurred after several minutes. This was misinterpreted as contamination, and the experiment was abandoned.



TEXT-FIG. 9. Case 3. The first arrow shows the point where adrenalin was added; the second arrow, where serum was added.

*Experiment 88.*—(Text-figure 9.) A ring from the descending branch of the same artery, about 2.5 cm. from the aorta. Heat ( $42^{\circ}$  C.) dilatation. Adrenalin added at the lower end of the heat curve gave 29 per cent. contraction. Serum added later had no effect.



TEXT-FIG. 10. Case 3. Adrenalin (arrow) added after strong heat dilatation.

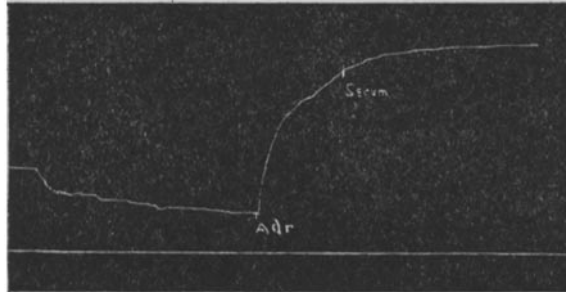
*Experiment 89.*—(Text-figure 10.) A small distal ring from the right coronary artery. Marked heat ( $42^{\circ}$  C.) dilatation. Adrenalin gave 36 per cent. contraction. Serum had no effect.

*Experiments 90, 91, and 92.*—Rings from the left coronary artery. Very weak heart response. No response to adrenalin. Tissues dead.

## CASE IV.

Small portions had to be taken from this vessel, as the larger proximal portions were calcified.

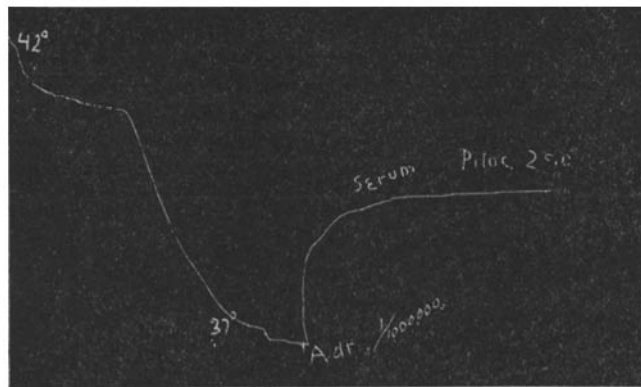
*Experiment 101.*—(Text-figure 11.) A ring from the proximal end of the



TEXT-FIG. 11. Case 4. Dilatation resulting from heating to  $42^{\circ}$ . Contraction followed immediately the adding of adrenalin. Serum added later was without visible effect.

side branch of the descending limb of the left coronary artery (about 3 cm. from the aorta). Heat dilatation ( $42^{\circ}$  C.) was steep but short. Adrenalin gave 24 per cent. contraction. Serum, from the same cadaver, was without effect.

*Experiment 102.*—(Text-figure 12.) A ring from the distal portion of the

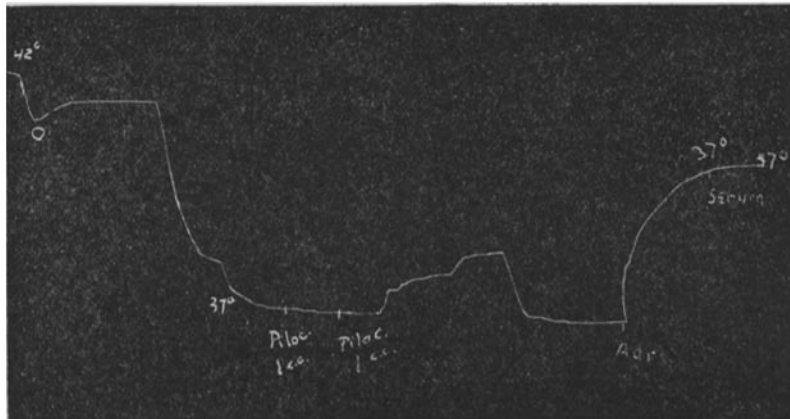


TEXT-FIG. 12. Case 4. Adrenalin after heat dilatation (dose 1:1,000,000). Pilocarpin was added later without effect.

left coronary artery. Strong heat ( $42^{\circ}$  C.) dilatation. Temperature lowered to  $37^{\circ}$  C., and adrenalin, 1:1,000,000, or 0.0001 of a gram, added before the curve became level, gave 18 per cent. contraction. Serum was without effect. Two c.c. of 0.5 per cent. pilocarpin had no effect.



*Experiment 103.*—(Text-figure 13.) The ring employed was similar to the one in experiment 102. Oxygen turned on late caused a slight rise. There was a strong heat ( $42^{\circ}$  C.) dilatation. Two 1 c.c. doses of pilocarpin about three

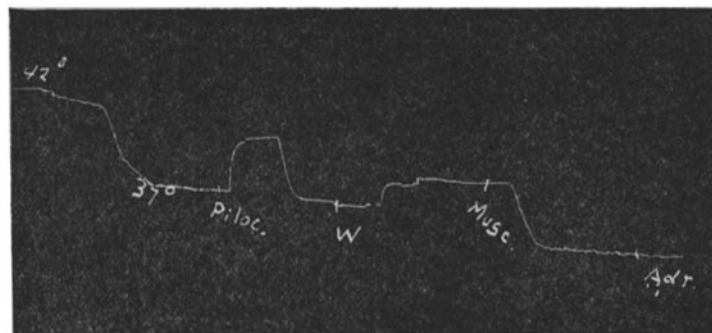


TEXT-FIG. 13. Case 4. O = Oxygen turned on late. Heat dilatation. Pilocarpin (two doses) was followed by temporary constriction. Adrenalin was followed by constriction.

minutes apart, were followed by an 8 per cent. contraction, in two sharp rises about three minutes apart. Then sharp relaxation to the first level. Adrenalin gave 20 per cent. contraction. Serum had no effect. Heating to  $47^{\circ}$  C. had also no effect.

*Experiment 104.*—The ring from the proximal portion of the descending branch of the left coronary artery was employed only after the calcified intima had been shelled out. There was a very strong tension curve, the media being probably much injured. Adrenalin gave minimal contraction.

*Experiment 105.*—(Text-figure 14.) The ring employed was similar to the



TEXT-FIG. 14. Case 4. Heat dilatation. Pilocarpin followed by temporary constriction. W = washout. Muscarin relaxation.

one in Experiment 102. After heat dilatation, 1 c.c. of 0.5 per cent. pilocarpin was given. After about one minute, there was a 7 per cent. contraction, which was sustained for three minutes, and then fell sharply.

The preparation was washed out in three changes of Ringer's solution. One c.c. of muscarin (0.1 per cent.) was added, and this was followed by a steep 8 per cent. dilatation. Adrenalin given later was without visible effect.

*Experiment 106.*—A similar ring. Sharp heat dilatation. No response to 0.2 of a gram of pituitrin. No response to adrenalin. Tissue presumably dead.

In all, twenty experiments were made upon rings cut from the coronary arteries of four human cadavers. Excluding experiments 78 to 82, 90 to 92, and 106, as pharmacologically dead, we have left eleven experiments upon surviving tissue from three cases.

Each of these three cases yielded at least one remarkably strong adrenalin contraction. Experiment 86, in which no adrenalin was added, must be discarded as unfinished, also experiment 104 (minimal contraction), as dealing with mutilated tissue. Of the remaining nine curves, six show typical adrenalin contractions varying in degree from 15.7 to 36 per cent. of the vessel's circumference, and four of these contractions occurred before the introduction of any substance other than adrenalin. In the three remaining experiments, adrenalin failed to act. In experiments 84 and 85, it was introduced before the tonus removal, and in experiment 104, the tissues had already responded to two drugs. The histological study of numerous coronary arteries from calves and human beings reveals no essential differences between the two species in the structure of muscle or elastic tissue in untreated arteries or in those treated with adrenalin. If we make the improbable assumption that the intimal proliferation observed in all our human cases is responsible for the reversal of adrenalin action, the results are of no less importance, for it is to this class of cases that the greatest therapeutic interest is attached.

Attention should be called to two observations that await the support of further evidence. The two results from pilocarpin are in accord, and the relaxation following muscarin is of interest in connection with Straub's (15) demonstration of muscarin as a relaxor of heart muscle (negative inotropic action).

Further studies will be made upon the pharmacology of isolated human vessels.

## CONCLUSIONS.

1. Adrenalin causes a marked constriction of the human coronary artery, although it undoubtedly produces a relaxation in some mammals; *e. g.*, calf, sheep, pig, etc.

2. The human coronary artery is probably provided with sympathetic vasoconstrictors.

3. If human blood-vessels are obtained in a warm condition within a few hours after death, they are often suitable for biological and pharmacological study.

It is with much pleasure that I acknowledge the advice and assistance of Professor Aschoff, Professor Straub, and Dr. Trendelenburg.

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