THE ACTION OF EPINEPHRINE ON THE BLOOD VESSELS OF CORTISONE-TREATED ANIMALS [1]

HENRY T. SUGIURA
Division of Anatomy, Hahnemann Medical College, Philadelphia, Pennsylvania

TWELVE FIGURES

There have been innumerable reports in the literature on the physiological and pharmacological effects of cortisone, both in human and animal investigations. This report presents an interesting aspect of cortisone action, which has not been mentioned in the literature, that may have some bearing in diseases of the vascular system. The vasoconstrictive action of epinephrine is a well known and documented phenomenon (Goodman and Gilman, '41). It is the purpose of this paper to report on the effect of epinephrine on the blood vessels of cortisone-treated hamsters.

METHODS

Two methods of study were employed. (1) Hamsters of approximately 120 gm body weight were injected intraperitoneally with 25 mg of cortisone acetate (Merck) for three consecutive days. Control animals were injected with 1 ml of sterile saline solution for the same period of time. Four to 6 hours after the last dose of cortisone, the animal was moderately anesthetized with nembutal (3 mg/100 gm body weight), one cheek pouch everted and pinned across a window in a cork board somewhat in the manner described by Fulton, Jackson and Lutz ('47). With transmitted light and a dissecting microscope at 60 diameter magnification the vessels were directly observed and measured with an ocular micrometer. While

[1] This investigation was supported (in part) by U. S. Public Health Grant H-1591.

under direct observation, the hamster was injected intraperitoneally with a dosage of epinephrine known to cause vasoconstriction in a normal untreated hamster (0.16 ml/100 gm body weight of 1 : 1000 epinephrine hydrochloride). Control animals were studied in the same manner. (2) Excised pieces of the cheek pouch tissue, or segments of femoral artery were taken

TABLE 1

NON-CORTISONE TREATED (Controls)			CORTISONE TREATED (Experimentals)		
Animal	Diam. of artery (microns)		Animal	Diam. of artery (microns)	
	Before epinephrine	After epinephrine		Before epinephrine	After epinephrine
1C	42	17	1E	58	42
2C	58	25	2E	33	25
3C	33	16.5	3E	33	17
4C	58	30	4E	25	16.5
5C	33	8.3	5E	50	33
6C	42	15	6E	42	33
7C	42	20	7E	41.5	34
8C	58	17	8E	33	25
9C	33	8.5	9E	58.5	41
10C	25	8.3	10E	42	33
11C	35	9	11E	31	23
			12E	52.5	34.5
			13E	27	18.5
			14E	42	38
Average	41.7	15.4	Average	40.6	29.5
Average % reduction: 63%			Average % reduction: 27%		

from both control and cortisone-treated hamsters. The exterior surface of the tissues were washed several times in warm mammalian Ringer's solution and gently teased out flat. The blood vessels were observed before and after adding 2 drops of 1 : 1000 epinephrine solution to the Ringer's solution bathing the excised tissue.

RESULTS

Table 1 summarizes the results. In the control group of 11 hamsters, that had received physiological saline solution intraperitoneally instead of cortisone, there was an average of 63%

reduction in the diameter of the arteries occurring within 3–5 seconds after the intraperitoneal injection of epinephrine. The vessels did not return to their original diameter for at least 30 minutes (table 1, figs. 1 and 2).

In contrast to the controls the experimental group of 14 hamsters pretreated with cortisone showed an average of 27% reduction in the diameter of the arteries (table 1). This reduction did not become evident until, at least, 5 minutes after the administration of epinephrine. Furthermore, the slight vasoconstrictive effect lasted only 10–12 minutes (figs. 3 and 4).

The in vitro studies were done as outlined in the second procedure. Figure 5 illustrates a darkened blood-filled artery from a control hamster cheek pouch before epinephrine was introduced in the solution bathing the tissue. Figure 6 shows this same artery one minute after adding 2 drops of epinephrine. The artery had markedly constricted and forced the blood cells from the cut ends of the vessel. A reduction in its diameter is also apparent. Following the same procedure with tissue from a cortisone-treated hamster, figures 7 and 8 show the relative ineffectiveness of epinephrine to constrict the artery. The vessel shows minimal constriction; retains its blood cells in its lumen and remains quite visible.

Using a muscular artery from another region of the animal, identical results were obtained. Figures 9 and 10 illustrate isolated segments of femoral artery before and after epinephrine application from a control hamster. The "X" in figure 10 points to regions of early constriction which becomes progressive along the vessel. Figures 11 and 12 are greatly enlarged views of an isolated segment of a femoral artery from a cortisone-treated animal. One can note a very slight reduction of arterial diameter in figure 12, the vessel having been photographed 5 minutes after epinephrine application.

DISCUSSION AND CONCLUSIONS

These experiments seem to indicate that cortisone in some manner altered or blocked the response of the smooth muscle

cells in the peripheral blood vessels to the action of epinephrine. The in vitro studies also show that blood vessels in excised pieces of tissue reacted similarly to those of the intact animals. Hence the author concludes that cortisone had modified the smooth muscle cell in its reaction to epinephrine. Other possible mechanisms of cortisone action must also be mentioned. There may have resulted an increase in the amount of amine oxidase or in its activity, thus hastening the breakdown of epinephrine. However, the in vitro experiments would cast doubt on the latter possibilities. The reaction time or the degree of contraction was not changed significantly on comparing the results of the in vivo and in vitro experiments.

How cortisone affects the smooth muscle cells of the peripheral blood vessels, in order to reduce their normal sensitivity to epinephrine, is still unknown. Cortisone also inhibits or reduces the formation of new blood vessels as demonstrated admirably by Ashton and Cook ('52). Whether there is any connection between cortisone/epinephrine action on the peripheral blood vessels and wound healing (Ragan et al., '49; Howes et al., '50) or the formation of new blood vessels remains to be investigated.

SUMMARY

Epinephrine administered in vasoconstrictive dosages failed to cause a marked decrease in arterial diameter in the cheek pouch and femoral arteries of hamsters pretreated with large doses of cortisone. Both in vivo and in vitro studies were performed. Some possible mechanisms of action of cortisone on the blood vessels relative to the epinephrine response are discussed.

LITERATURE CITED

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PLATE 1

EXPLANATION OF FIGURES

1 Cheek pouch of control hamster. Artery and vein. In vivo, transmitted light. × 50.

2 Same view as 1 taken one minute after intraperitoneal injection of epinephrine. Note the marked constriction of the artery. × 50.

3 Cheek pouch of cortisone-treated hamster. Artery and vein. In vivo, transmitted light. × 50.

4 Same view as 3 taken 5 minutes after intraperitoneal injection of epinephrine. Note the slight degree of contraction of the artery. × 50.

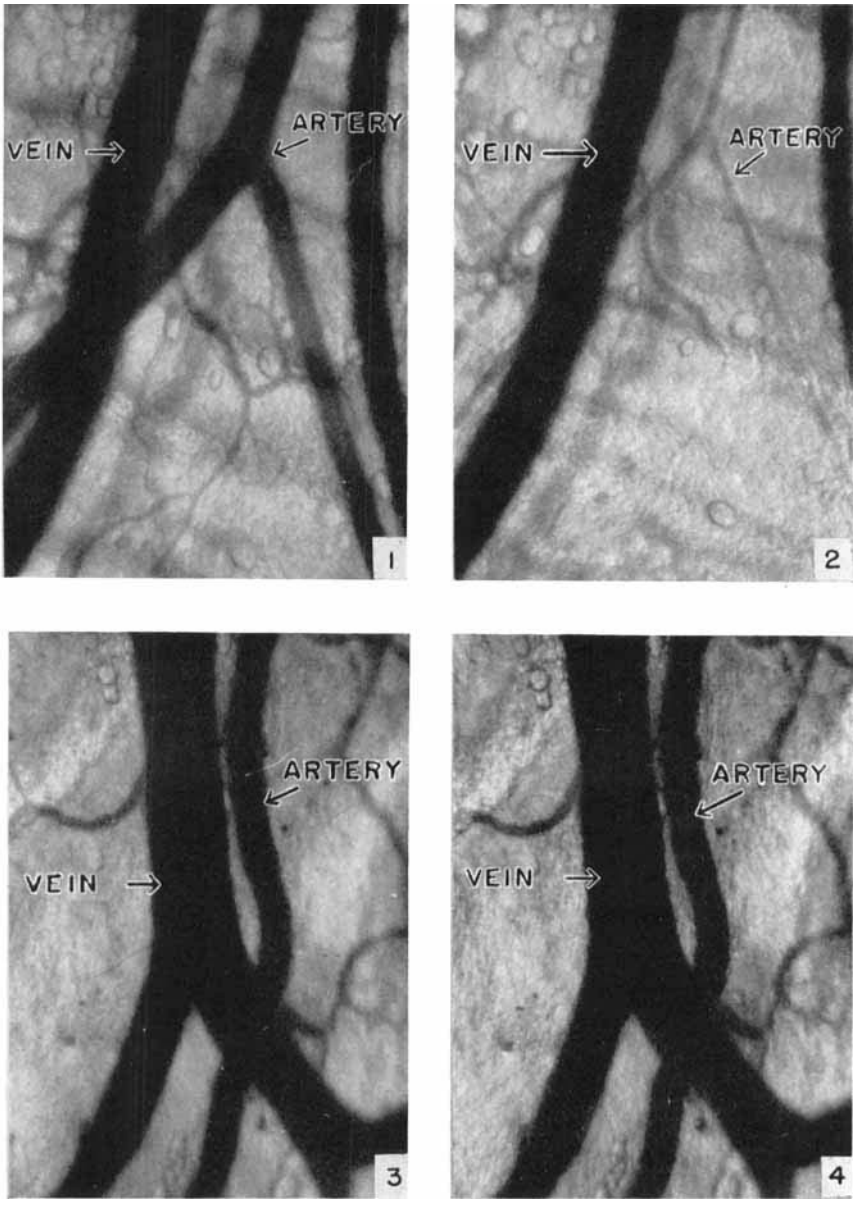
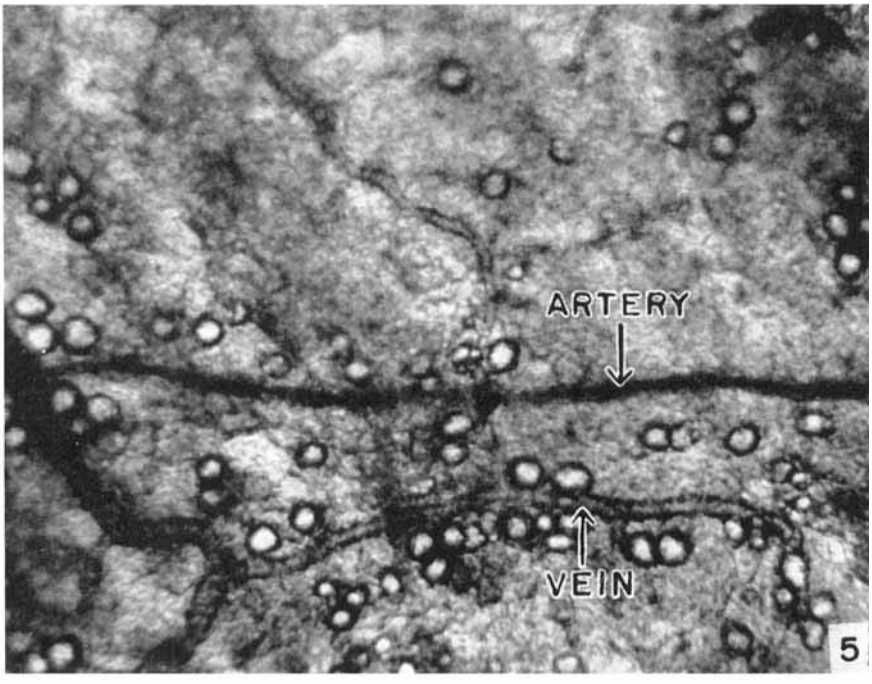

VEIN
ARTERY
1
VEIN
ARTERY
2
ARTERY
VEIN
3
ARTERY
VEIN
4

PLATE 2

EXPLANATION OF FIGURES

5 Control hamster cheek pouch tissue. In vitro, transmitted light. × 30.

6 Same view as 5 taken one minute after adding epinephrine to Ringer's fluid bathing the excised piece of tissue. Note that the arterial contraction had forced the blood cells from the lumen. × 30.


ARTERY
VEIN
5

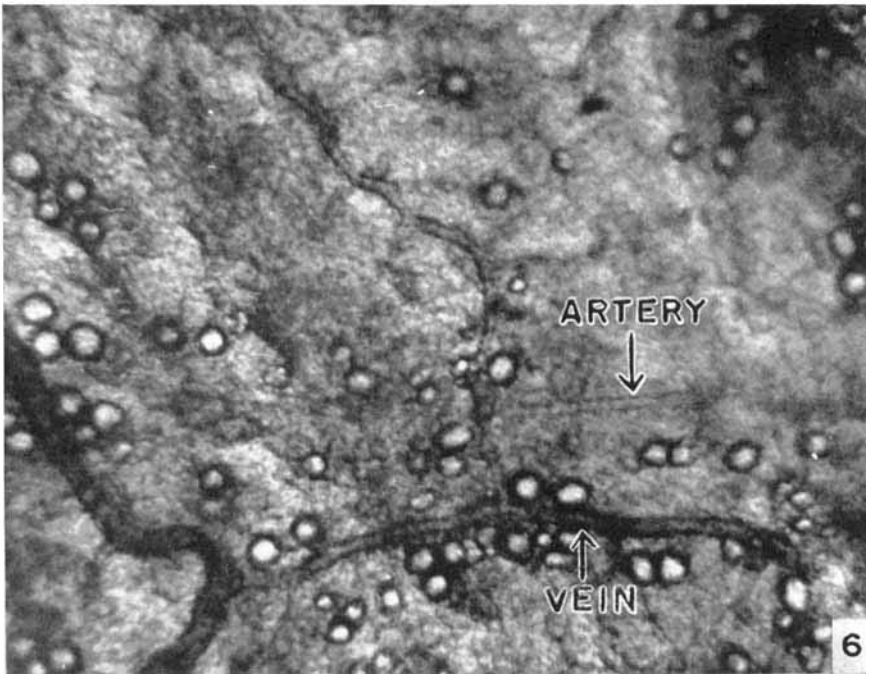
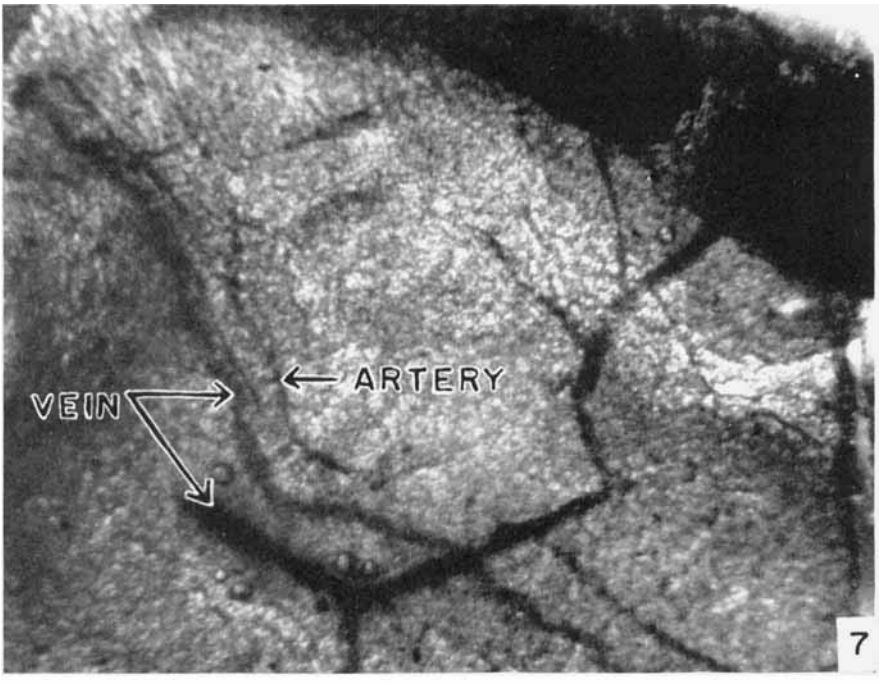

ARTERY
VEIN
6

PLATE 3

EXPLANATION OF FIGURES

7 Cortisone-treated hamster cheek pouch. In vitro, transmitted light. × 30.

8 Same view as 7 taken 5 minutes after epinephrine addition. Note that the artery has constricted only slightly and blood is still present in the lumen. × 30.


VEIN
ARTERY
7

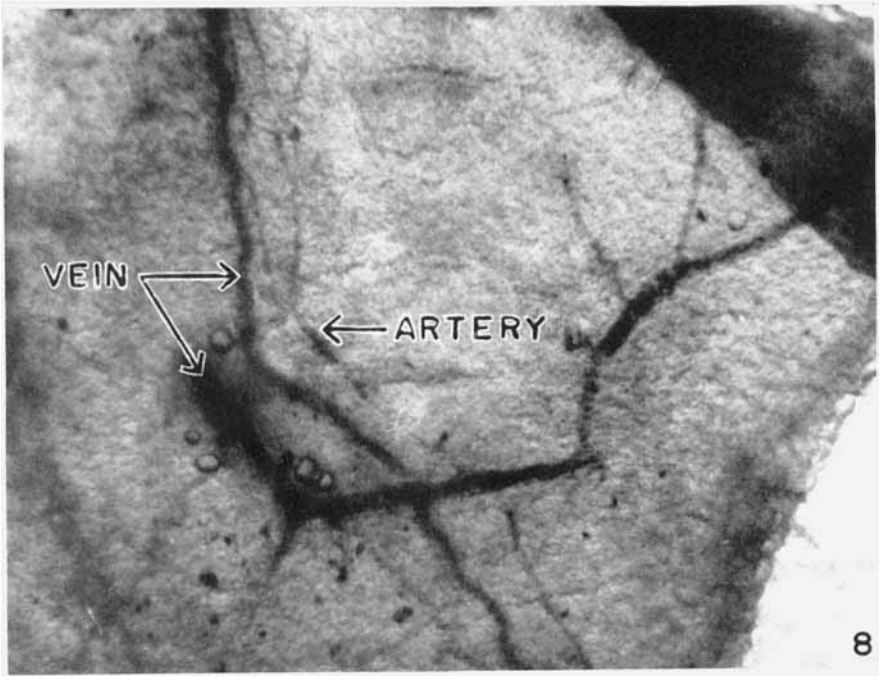
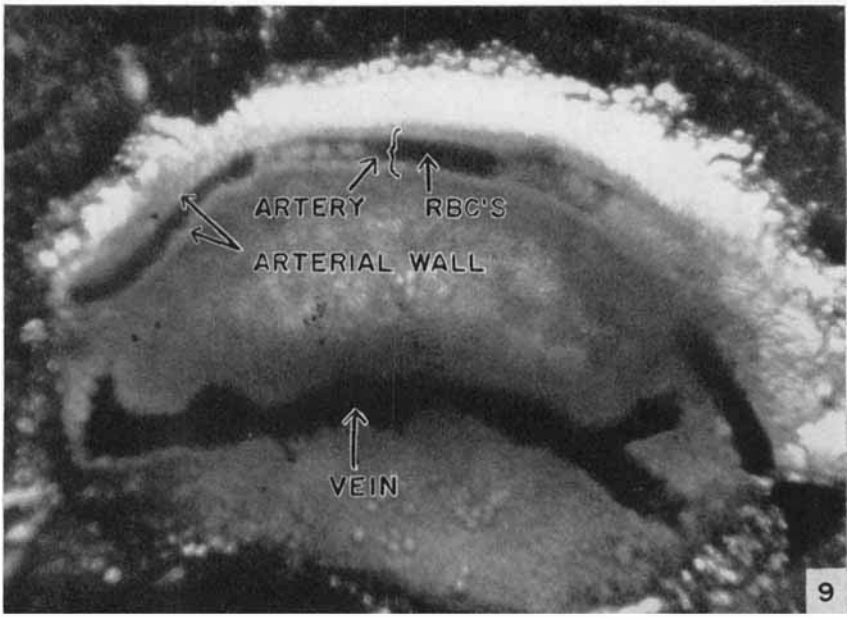

VEIN
ARTERY
8

PLATE 4

EXPLANATION OF FIGURES

9 Femoral artery and vein from a control hamster. In vitro, transmitted light. × 8.

10 Same view as 9 taken immediately after addition of epinephrine. Note the beginning arterial constrictions at regions marked "X." × 8.


ARTERY
RBC'S
ARTERIAL WALL
VEIN
9

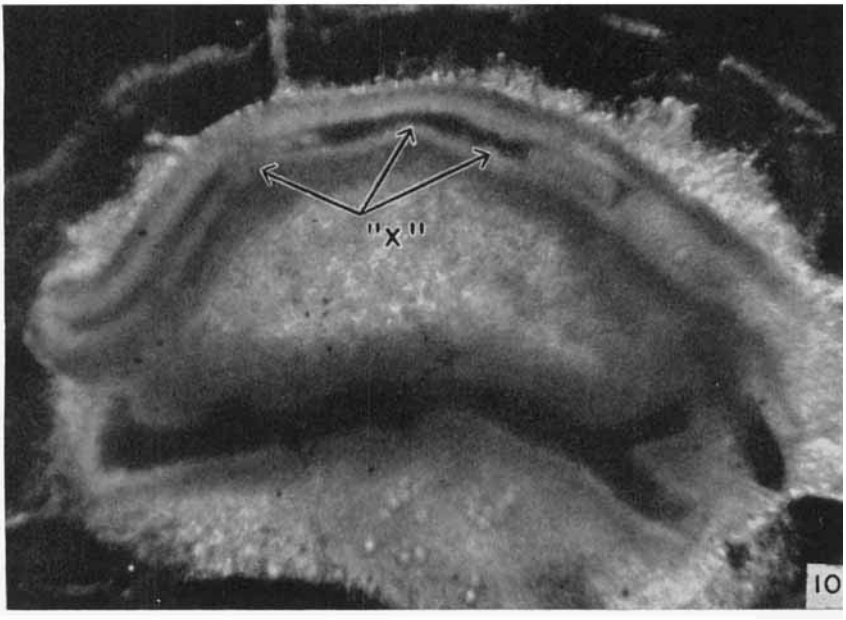
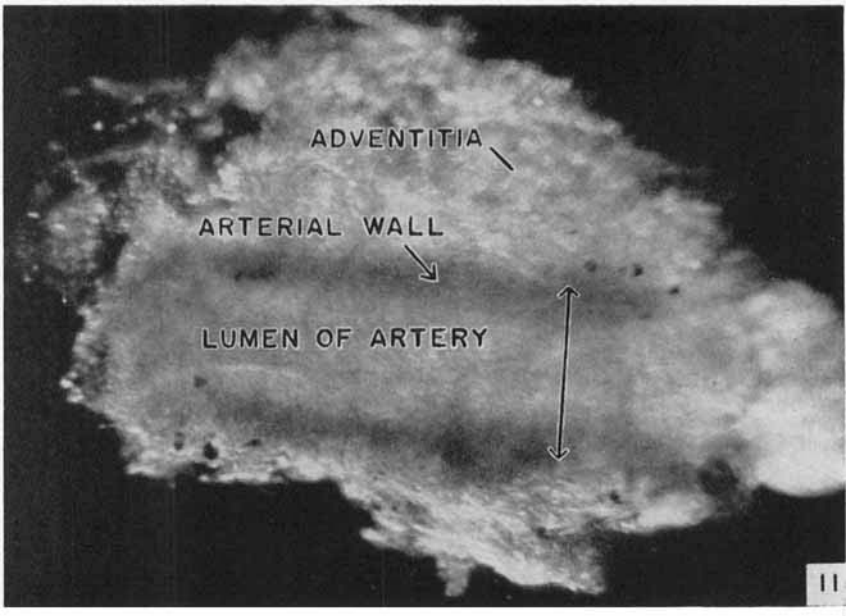

"X"
10

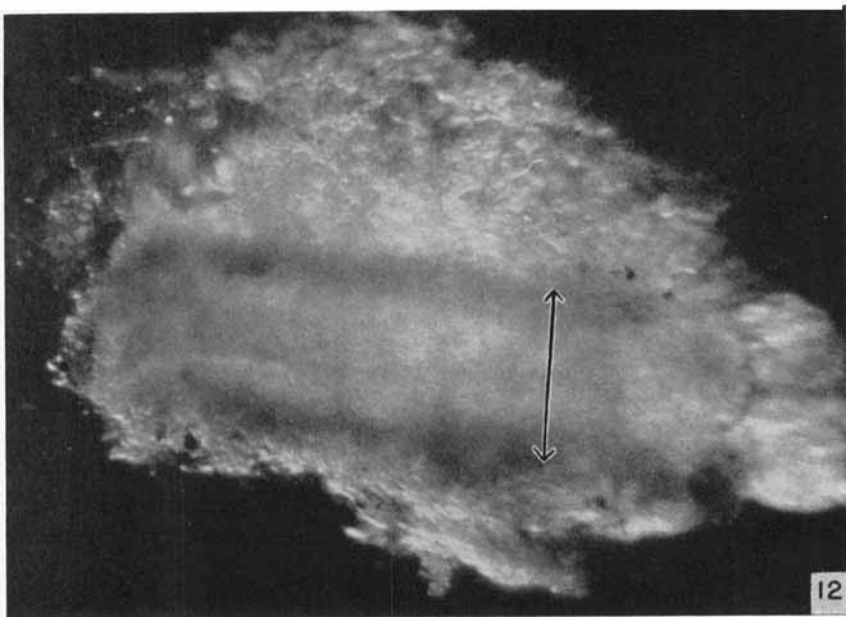
PLATE 5

EXPLANATION OF FIGURES

11 Femoral artery from a cortisone-treated hamster. In vitro, transmitted light. × 50.

12 Same view as 11 taken 5 minutes after adding epinephrine. Only a slight reduction in vessel diameter is discernible. × 50.


ADVENTITIA
ARTERIAL WALL
LUMEN OF ARTERY
11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