# ALTERED REACTIVITY TO EPINEPHRINE IN THE HYPERSENSITIVE RABBIT

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PLATE 36

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The purpose of this paper is to report a series of experiments concerning an altered reactivity of the skin of hypersensitive rabbits when epinephrine is injected into it following a challenge intravenous injection of specific antigen.

In 1956 Thomas (1) reported a series of experiments illustrating an altered skin reactivity to epinephrine in rabbits following intravenous injection of bacterial endotoxin. He found that epinephrine produced "hemorrhagic necrosis" when injected into the skin of rabbits at any time during a period of 4 hours following an intravenous injection of endotoxin. If the animals were rendered "tolerant" by repeated injections of endotoxin the epinephrine lesion did not occur. Evidence was given that the lesion was the result of an altered reactivity to epinephrine rather than due to the direct effect of the endotoxin. He pointed out certain dissimilarities between the epinephrine lesion following endotoxin injection and the Schwartzman phenomenon, and certain characteristics seemed to differentiate it from the Arthus reaction.

At the same time, Zweifach, Nagler, and Thomas (2) reported an altered reactivity of the vessels of the rat meso-appendix when epinephrine was applied topically following intravenous endotoxin injection. Analogous results were obtained using the perfused, isolated rabbit ear. This hyperreactivity became evident within 30 minutes and lasted for a period of 6 hours following the injection of endotoxin.

This paper concerns a skin lesion produced by epinephrine which possesses certain gross and microscopic similarities to the lesion reported by Thomas (1). Like the lesion in the endotoxin-treated rabbit, it results from the local injection of epinephrine (or norepinephrine). The mechanism differs in that the material injected into the hypersensitive rabbit is specific antigen instead of endotoxin. Other differences will be pointed out later.

## *Materials and Methods*

The pilot work for this series of experiments was carried out on two male rabbits which had been sensitized to horse serum. It was observed that if 100 micrograms of epinephrine was injected into the skin of the hypersensi-

tive rabbit immediately after a challenge dose of 5 ml. of horse serum had been injected intravenously, a rather striking delayed reaction occurred at the site of the epinephrine injection. Later in the work a similar reaction was found to be produced by norepinephrine. These lesions are illustrated in Fig. 1. The intensity and size of the epinephrine lesion appeared to be directly proportional to the intensity of the Arthus reaction. Later in the work it was found that if the animal experienced anaphylactic shock following the injection of the antigen no significant epinephrine lesion occurred.

The characteristic epinephrine lesion in the skin of a rabbit with a 4+ Arthus reaction, after 24 hours, is 2.5 to 3.0 cm. in diameter and of an irregular, circular to oval shape. When oval the long axis is oriented in a longitudinal direction. The most marked lesion consists of an elevated, dark blue rim 0.25 to 0.5 cm. in diameter which is surrounded by a zone of intense hyperemia. The central zone, which comprises the greater portion of the lesion, is non-elevated and blanched or gray-blue in color. This central zone may, in some instances, subsequently slough. The least sensitive may react with only hyperemia and petechial hemorrhages or with a faint gray-blue mottling, while the intermediate group usually develop a deep blue, non-elevated, irregular lesion. The gross evolution of the typical lesion occurring within the skin of a 4+ sensitive rabbit consisted of an initial area of blanching at the site of the injection of the epinephrine which seemed to gradually subside. At approximately 14 hours there appeared an irregular 2.5 x 3.5 cm. longitudinally oriented, dark blue, non-elevated lesion. The lesion at this stage bore distinct resemblance to the epinephrine lesions reported by Thomas (1). By the end of approximately 17 hours following the injection of epinephrine the center of the flat, bluish area began to blanch, and about it there was a slightly elevated, edematous, dark blue rim. At the end of 20 hours the features of the 17 hour lesion were enhanced and the blue rim was surrounded by a zone of intense hyperemia. The central blanched area appeared depressed as compared with the elevated, bluish rim. No further progress was observed after 22 hours, and the lesion gradually faded over a period of days or a week or two. The center sometimes sloughed. The lesions in the less sensitive animals, of course, did not evolve in this manner, and the degree appeared to be roughly in proportion to the degree of intensity of the Arthus reaction, as will be shown later.

Histologically, at 22 hours, which was approximately the age of maturity in the gross, the lesion was characterized by a central area within which there was little detectable alteration; there were scattered granulocytes and mononuclear cells, some of which resembled plasma cells. The vessels of this zone, for the most part, did not appear altered, but there was an occasional small artery which demonstrated beginning necrosis of its wall. Within the area of vascular necrosis and about the vessels there were increased numbers of granulocytes. The connective tissue fibers appeared separated as if "displaced" by non-visible fluid. Surrounding this zone of relatively little alteration there was a zone of cellular infiltrate qualitatively similar to that within the central portion but more concentrated. Within this zone small arteries undergoing fibrinoid necrosis of their walls were fairly numerous, and the small veins appeared moderately dilated and engorged. The third, and outermost, zone was composed of numerous dilated and engorged small vessels, the majority of which appeared to be veins and capillaries. The congestion gradually lessened and finally disappeared as one approached the surrounding unaltered tissue. There was an occasional artery within the outer zone which was undergoing fibrinoid necrosis. An occasional vessel contained a thrombus. Numerous neutrophils were present about these altered vessels, but neutrophils were infrequent in the intervening tissue. Focal microscopic hemorrhage was beginning to occur within the outer two zones of the lesion.

At 41 hours the same changes present at 22 hours persisted and were greatly enhanced. There might be a crust of fibrin and red cells upon the skin surface. There were focal areas of necrosis of the epidermis, underlying which there was usually a focus of granular, eosinophilic material containing nuclear debris. Interstitial hemorrhage was widespread, and the exudate was greatly increased in all zones of the lesion. Many small vessels in all zones were greatly dilated and engorged and numerous small arteries demonstrated fibrinoid necrosis of their walls. The majority of these latter vessels were filled with eosinophilic, hyaline thrombi. The zones, as described in the 22 hour lesion, were discernible in the 41 hour lesion and the relative differences in degree of alteration were maintained, although the number of cells was increased. In spite of the fact that externally the lesion did not appear to progress after 22 hours, vascular thrombosis and necrosis, and cellular exudation and hemorrhage increased considerably afterward. The reaction did not seem to be distinguishable from the Arthus reaction histologically.

Female rabbits of mixed stock were used. At the beginning of the experiments the animals were approximately 12 weeks old and weighed between 3.0 and 4.2 kilograms each. They were maintained on a diet of Purina rabbit pellets and water.

The antigen was S-6 pooled horse serum purchased from Cappel Laboratories, West Chester, Pennsylvania. The epinephrine hydrochloride was a 1:1000 solution prepared by Eli Lilly and Company, Indianapolis. The norepinephrine (levophed bitartrate) was in 4 ml. ampules of 1:1000 solution and prepared by Winthrop Laboratories, New York. The heparin was in 3 ml. ampules in a strength of 100 mg. per ml. and prepared by Eli Lilly and Company. The dilutent was sterile non-pyrogen triple distilled water produced by Pharmaseal Laboratories, Glendale, California. The chlorpromazine (thorazine) was prepared by Smith, Kline, and French Laboratories, Philadelphia. The ephedrine was in 1 ml. ampules containing 0.05 gm. of ephedrine sulfate and prepared by Eli Lilly and Company.

The experiments were controlled by using one site of skin on the hypersensitive rabbit where only dilutent (sterile triple distilled water) was injected and, also, using control (non-sensitized) rabbits into the shaved skin of which was injected the same test substance, in the same quantity, that the sensitized rabbits received. A site was also used in the controls where only dilutent was injected.

The Arthus reaction was used in grading the degree of hypersensitivity, and this grading was based on a scale of four, much the same as that used by Opie (3). The degree of sensitivity was thus determined at varying intervals during the course of the experiments.

The intensity of the skin reactivity to the epinephrine was graded on a scale of four for convenience of tabulation. Mild hyperemia and edema as well as a discrete 1 cm. or less gray-blue nodule without a rim of hyperemia and edema were regarded as negative reactions, since this degree of reaction was noted in both control rabbits injected with epinephrine and at control sites of hypersensitive rabbits where only dilutent was injected. A discrete gray-blue focus measuring more than 1 cm. in diameter, with or without edema, was classed as 1+, a discrete blue-black lesion as 2+, a gray-blue center with elevated rim of bluish to red color as 3+ and a flat, gray-blue to blanched, non-elevated center surrounded by an elevated dark blue rim bordered by a zone of hyperemia as 4+. Because the lesion varied in size under certain circumstances the diameter was included in some instances as a second means of quantitation.

Although a challenge dose of 5 ml. of serum was used initially, smaller amounts were used subsequently after it was found that less antigen would also produce a lesion of approximately equal intensity.

## RESULTS

*1. The Effect of Varying the Challenge Dose of Antigen and the Relationship of the Size and Intensity of the Lesion to the Grade of the Arthus Reaction.*—

Five hypersensitive rabbits of varying degrees of sensitivity were used. Four experiments were carried out on each rabbit. A different quantity of serum was used as the challenge dose in each experiment. The challenge dose in each instance was followed within 30 minutes by an intracutaneous injection of 100 micrograms of epinephrine. The results are listed in Table I.

The data in Table I seem to indicate that the amount of circulating antigen (challenge dose) to as little as 1 ml. of serum has only slight influence on the

TABLE I

*The Effect of Varying the Amount of Serum Injected Intravenously*

| Rabbit No. | Arthus grade | Challenge dose of serum | Epinephrine lesion | |
|---|---|---|---|---|
| | | | Grade | Size |
| | | *ml.* | | *cm.* |
| 1-1 | +++ | 5 | +++ | 3 x 6 |
| 1-2 | + | 5 | Neg. | — |
| 1-4 | ++++ | 5 | ++++ | 3 x 6 |
| 1-5 | ++++ | 5 | ++++ | 3 x 6 |
| 1-7 | ++ | 5 | Neg. | — |
| 1-1 | +++ | 4 | ++ | 2 x 5 |
| 1-2 | + | 4 | Neg. | — |
| 1-4 | ++++ | 4 | ++++ | 3 x 6 |
| 1-5 | ++++ | 4 | ++++ | 3.5 x 3 |
| 1-7 | ++ | 4 | ++ | 3 x 1.5 |
| 1-1 | +++ | 3 | ± | 4 x 4 |
| 1-2 | + | 3 | + | 3 x 3 |
| 1-4 | ++++ | 3 | ++++ | 2 x 3 |
| 1-7 | + | 3 | ++ | 2 x 3 |
| 1-1 | +++ | 1 | +++ | 2.5 x 2.5 |
| 1-2 | + | 1 | + | 2.5 x 2.5 |
| 1-4 | ++++ | 1 | ++++ | 3 x 3 |
| 1-7 | + | 1 | ++++ | 2.5 x 2.5 |

size and intensity of the epinephrine lesion. The results in this table also demonstrate a fairly constant correlation between the grade of the Arthus reaction and the grade and size of the epinephrine lesion.

*2. The Effect of Intradermally Injected Epinephrine in Absence of a Challenge Dose of Serum.*—

Six hypersensitive rabbits of varying degrees of sensitivity were used. 100 micrograms of epinephrine was injected into a shaved site of the skin of each. This was repeated on four different occasions for a total of twenty-four rabbit tests.

The reaction was negative or only equivocal in twenty-three of these tests. In one rabbit there resulted a grade ++ reaction on one occasion, but on a subsequent test the reaction was negative. The only explanation apparent for the one epinephrine lesion was the possibility of residual circulating antigen. It was concluded that an epinephrine lesion does not occur in the skin of the hypersensitive rabbit in the absence of circulating antigen, residual or injected.

TABLE II

*The Effect of Varying the Amount of Locally Injected Epinephrine on the Lesion*

| Rabbit No. and Arthus reaction | Amount of epinephrine | Epinephrine lesion | |
|---|---|---|---|
| | | Grade | Size |
| | μg. | | cm. |
| 1-1 | 200 | ++ | 4 |
| Arthus +++ | 100 | ++ | 4 |
| | 50 | ± | 3 |
| | 20 | Neg. | — |
| 1-2 | 200 | ++ | 3 |
| Arthus + | 100 | ± | Poorly defined |
| | 50 | Neg. | — |
| | 20 | Neg. | — |
| 1-4 | 200 | ++++ | 2.5 x 3 |
| Arthus ++++ | 100 | +++ | 2 x 3 |
| | 50 | ++ | 1 |
| | 20 | Neg. | — |
| 1-7 | 200 | ++ | 2 x 3 |
| Arthus +++ | 100 | ++ | 2 x 3 |
| | 50 | ++ | 2 |
| | 20 | Neg. | — |

*3. The Effect of Varying the Quantity of Epinephrine Injected into the Skin.*—

In order that the influence of the quantity of epinephrine injected locally might be investigated, each rabbit was given 1 ml. of serum intravenously to desensitize it followed by 3 ml. intravenously 24 hours later. The latter was followed within 30 minutes by 200, 100, 50, and 20 micrograms of epinephrine, respectively, into four separate designated sites of the shaved skin. The lesions were read after 24 hours and the results tabulated in Table II.

On the basis of the experiments on these four rabbits there appears to be a fairly direct relationship between the amount of epinephrine, up to a certain optimum dose (100 micrograms), and the intensity and size of the local reac-

tion. The lesion at the 200 microgram sites, when compared with the 100 microgram sites, did not appear proportionately increased, thus there appeared to be a maximum potentiality of reactivity. No reaction occurred at any sites where only 20 micrograms of epinephrine was injected.

*4. Effect of Varying the Time Interval of Injection of Epinephrine.—*

In order to determine the influence of the time interval between the intravenous injection of the antigen and the subsequent injection of the epinephrine, five sensitized rabbits were given 1 ml. of specific antigen intravenously which was followed by intracutaneous injection of 100 micrograms of epinephrine, respectively, into separate, designated sites of the skin at intervals of 15 minutes, 2 hours, 4 hours, 6 hours, and 24 hours. Each lesion was read after 24 hours (Table III).

TABLE III

*The Effect on the Grade and Size of the Lesion by Varying the Time Interval of the Epinephrine Injection*

| Rabbit No. | Arthus | 15 mins. | | 2 hrs. | | 4 hrs. | | 6 hrs. | | 24 hrs. | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Grade | Size | Grade | Size | Grade | Size | Grade | Size | Grade | Size |
| | | | *cm.* | | *cm.* | | *cm.* | | *cm.* | | *cm.* |
| 1-1 | +++ | +++ | 3.5 | +++ | 3 | +++ | 3 | Neg. | | Neg. | |
| 1-2 | + | ++ | 3 | ++ | 3 | ++ | 3 | Neg. | | Neg. | |
| 1-4 | ++++ | ++++ | 4 x 3.5 | ++++ | 3 | +++ | 3 | Neg. | | Neg. | |
| 1-7 | + | ++++ | 3 | +++ | 3 | ++ | 2.5 | ++ | 2.5 | + | 1 |
| 1-8 | ++++ | ++++ | 3.5 | +++ | 3 | ++++ | 4 x 3 | +++ | 3 x 2 | + | 1 |

The size and intensity of the epinephrine lesion remained constant at the 15 minute, 2 hour, and 4 hour sites, but only two rabbits displayed a lesion at the 6 hour sites. Since there was no appreciable change in the epinephrine lesion for as long as 4 hours and/or three injections of epinephrine, the question arose as to whether the time interval or the availability of circulating antigen, or both, were factors involved. In order to investigate this, these same five rabbits were given 1 ml. of specific antigen intravenously and nothing else; 24 hours later 100 micrograms of epinephrine was injected into the skin of each rabbit. Although there was some decrease in size and intensity of the lesions in relationship to the Arthus grade, a lesion occurred in each instance in relative proportion to its degree of sensitivity. Since the need for circulating antigen in the production of the epinephrine lesion has been shown and since the degree of sensitivity and amount of epinephrine injected locally remained constant in these two experiments, it appears that the circulating antigen disappeared or was greatly reduced during the evolution of the lesion. The only experimental variable in the two experiments was the total amount of epinephrine injected. On the basis of this, the conclusion was reached that,

in some way, the circulating antigen was utilized in producing the epinephrine lesion.

*5. Amelioration of the Reaction by Heparin.*—Thomas (1) has shown that heparin does not prevent or ameliorate the altered reactivity to epinephrine in rabbits injected with endotoxin, but Chase (4) writes that "heparin is able to mitigate the intensity of the Arthus reaction in cutaneous tissue (Gregoire, 1946)." In order to evaluate the effect of heparin on the reaction the following experiment was carried out:—

Each of five hypersensitive rabbits was given 20 mg. of heparin intravenously. Thirty minutes later each rabbit was given 1 ml. of horse serum intravenously, followed by 100 micrograms of epinephrine into the shaved skin. Twenty milligrams of heparin was subsequently injected intravenously into each rabbit at hourly intervals for four successive doses, except in the case of one rabbit which had begun to ooze from the needle punctures to such an extent that the last dose was omitted.

No lesion was produced by the epinephrine in three rabbits, and a 1+ reaction was obtained in two, one of which did not receive the last dose of heparin. This experiment demonstrates that heparin prevents or considerably ameliorates the epinephrine lesion.

*6. Effect of Systemic Chlorpromazine on the Epinephrine Lesion.*—Thomas (1) has shown that chlorpromazine, dibenzyline, and cortisone prevent the epinephrine lesion in rabbits given endotoxin. The effect of chlorpromazine was investigated in the following manner:—

Each of five hypersensitive rabbits was given 5 mg. of chlorpromazine into the lumbar muscles. Approximately 30 minutes later each rabbit was given 1 ml. of horse serum intravenously, followed by 100 micrograms of epinephrine into a shaved site of the skin. This procedure was repeated on four of the rabbits, making a total of nine rabbit tests.

No amelioration of the reaction occurred in seven. One of the two in which the epinephrine lesion did not occur had a severe anaphylactic reaction and should be excluded; the remaining non-reactor displayed a typical lesion in a repeat of the experiment. On the basis of these experiments it was concluded that chlorpromazine neither prevents nor measurably ameliorates the epinephrine lesion.

*7. Comparison of the Local Skin Reactivity to Epinephrine with That of Injected Norepinephrine and Ephedrine and Topically Applied Xylene.*—Thomas (1) reported that norepinephrine produced a lesion similar to epinephrine in the skin of the endotoxin-injected rabbit but that ephedrine failed to produce a lesion. Xylene applied topically has been reported capable of evoking a mild Arthus reaction in the hypersensitive rabbit.

Each of six hypersensitive rabbits was given 1 ml. of horse serum intravenously to desensitize it followed by 4 ml. of serum intravenously 24 hours later. A shaved site of skin was divided into quadrants. 100 micrograms of epinephrine was injected into the skin of one quadrant, 500 micrograms of ephedrine into a second quadrant and xylene was applied topically, by brisk rubbing, to the skin of a third quadrant. The remaining quadrant was used as a control.

A lesion occurred at the site of the epinephrine injection in all rabbits as described previously in this paper; no lesion developed at the site of ephedrine in a single rabbit, and no lesion occurred at the site of application of xylene in a single animal.

A second experiment similar in all respects to the above was carried out on these same rabbits with the exception of the substitution of 100 micrograms of norepinephrine in the place of xylene, the use of 5,000 micrograms of ephedrine and the use of 1 ml. of horse serum as the challenge dose instead of the 4 ml. used previously.

A lesion developed at the sites of injection of the norepinephrine similar to that occurring at the epinephrine sites, but of slightly smaller size. No lesion occurred at the ephedrine site in spite of the large amount injected (Fig. 1).

The conclusion reached from these experiments was that norepinephrine, in an equal amount, produced a lesion similar to that produced by epinephrine. The failure of ephedrine to produce a lesion seems to indicate that more than simple vasoconstriction is involved in initiating the epinephrine lesion.

*8. Alteration of the Arthus Reaction by Epinephrine, Norepinephrine and Heparin.*—

A large area of the abdomen of five hypersensitive rabbits was shaved and divided into quadrants. Into the skin of each quadrant, respectively, was injected 1 ml. of horse serum + 100 micrograms of epinephrine, 1 ml. of horse serum + 100 micrograms of norepinephrine, 1 ml. of horse serum + 20 milligrams of heparin, and 1 ml. of horse serum only. The "serum only" site was used as a control, unaltered Arthus reaction. The reaction was photographed after 24 hours (Fig. 2).

The photograph illustrates an alteration of the Arthus reaction by epinephrine and norepinephrine which embodies certain gross similarities to the epinephrine lesion. When altered by these two agents the lesion possesses a large, flat, central area of blanching surrounded by a slightly elevated, blue-black rim. Heparin altered the Arthus reaction by slightly decreasing its total size and the size of the central blanched zone. Thus, it appeared that heparin injected locally exerts some degree of ameliorating influence on the Arthus reaction.

## DISCUSSION

The epinephrine lesion in the hypersensitive rabbit, although bearing certain similarities to the epinephrine lesion produced in the endotoxin-treated ani-

mals reported by Thomas (1), differs in that it is prevented or greatly ameliorated by systemically administered heparin and is neither prevented nor lessened in degree by systemic chlorpromazine. Weil and Spink (5) showed that endotoxin shock had many features in common with anaphylactic shock but differed in that there was a lack of change of coagulability of the blood and a delayed toxic effect resulting in death after hepatectomy in endotoxin (anaphylactoid) shock. These reports seem to indicate that the effect of bacterial endotoxin on experimental animals has much in common with the effect of specific antigen on the hypersensitive animal. There are, however, distinct and undeniable differences.

This being true, there is a need to further classify the epinephrine lesion. There are several features that tend to identify the lesion with the Arthus-type of reaction: first of all, the epinephrine lesion as produced in the hypersensitive animal is a delayed reaction in the sense that the Arthus reaction is a delayed reaction. Secondly, a state of hypersensitivity is necessary for its production and, by implication, circulating antibodies must be present. If the Arthus reaction is a measure of circulating specific antibodies then the epinephrine lesion seems also to be a measure of the circulating antibodies since the intensity of the latter occurs in fairly consistent proportion to the degree of the Arthus response. Thirdly, the availability of the antigen, as well as antibody, has been shown to be necessary in order to produce the lesion. These are the same factors necessary for the production of the Arthus reaction. Fourthly, the histologic features of the Arthus reaction and the epinephrine lesion are similar qualitatively. Fifthly, heparin inhibits or greatly ameliorates the epinephrine lesion. Finally, epinephrine (or norepinephrine) alters the Arthus reaction in a manner that it resembles in the gross the epinephrine lesion.

No experimentally substantiated explanation can be given for the infrequent lack of correlation between the degree of the Arthus reaction and the size and intensity of the epinephrine lesion. The state of hypersensitivity is so dynamic that there is a possibility that it might have changed since the last Arthus test.

It has appeared that the so-called collagen diseases are associated in some way with the allergic or hypersensitive state, although the exact mechanism of the focal lesions has been difficult to explain in a manner that satisfactorily elucidates the varied anatomic manifestations of the entire group. There is evidence that a state of hypersensitivity together with circulating specific antigen are factors in producing the lesions in some cases. The epinephrine lesions reported in this paper also require a state of hypersensitivity and the presence of circulating specific antigen. The epinephrine lesion is one method of producing lesions in predetermined foci in sensitized animals which might be helpful in the study of the pathogenesis of this group of diseases. If an animal were in a state of hypersensitivity and specific antigen were introduced

into the circulation, then there may exist a situation whereby the epinephrine lesion might be produced if there were present a source of epinephrine (or norepinephrine), a means to propel it and a target. The unanswered question is: How could one cause sudden deposition of epinephrine from within the body on a given target? Were this hypothetical situation to exist there is a possibility that focal lesions, including a necrotizing arteritis, might be produced which would embody many of the attributes of those of the collagen diseases. Certainly, other unrecognized factors probably should be included in this postulation and the outstanding one seems to be that which determines the site or target. The latter might, in some way, be of the same general nature as that involved in the production of the renal lesions by injection of antikidney serum.

## SUMMARY

A series of experiments are reported which illustrate and characterize an altered state of reactivity of the skin of the hypersensitive rabbit to epinephrine (and norepinephrine). The requirements for the production of the lesion are: a state of hypersensitivity, circulating antigen and antibody and focal deposition of epinephrine or norepinephrine. The size and intensity of the reaction appear to be directly related to the amount of epinephrine injected (within certain limits) and to the degree of hypersensitivity as measured by the Arthus reaction. Although circulating antigen is required, the precise quantity does not seem to be as critical as does the amount of circulating antibody; a certain minimum amount is necessary, however. Experimental evidence is given which indicates the utilization of antigen in the production of the lesion. Data tending to identify this lesion with the Arthus reaction are given. The possibility of an analogous relationship between the mechanism of this experimental lesion and the necrotizing arteritis of the collagen diseases is postulated.

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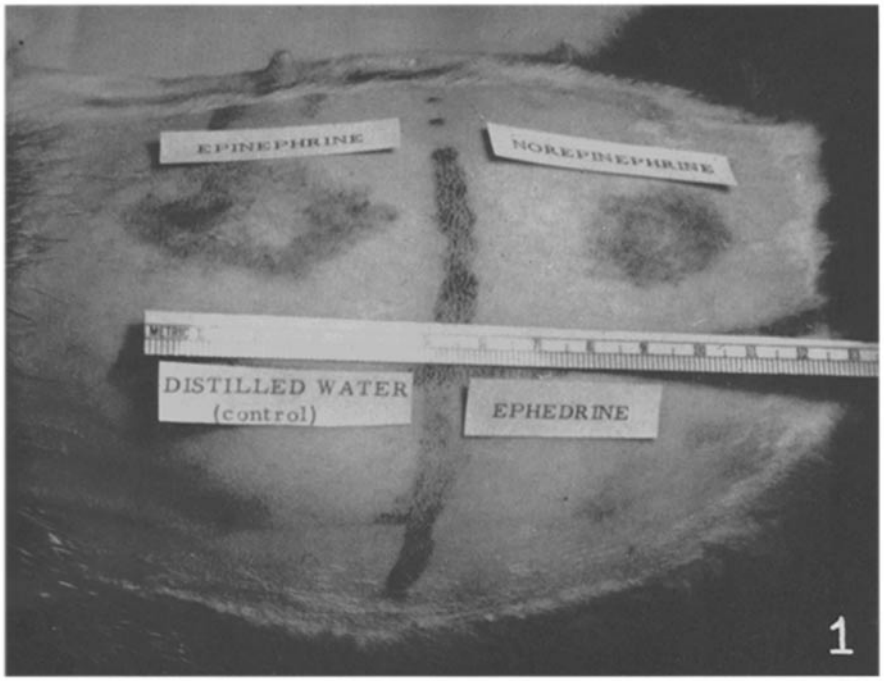
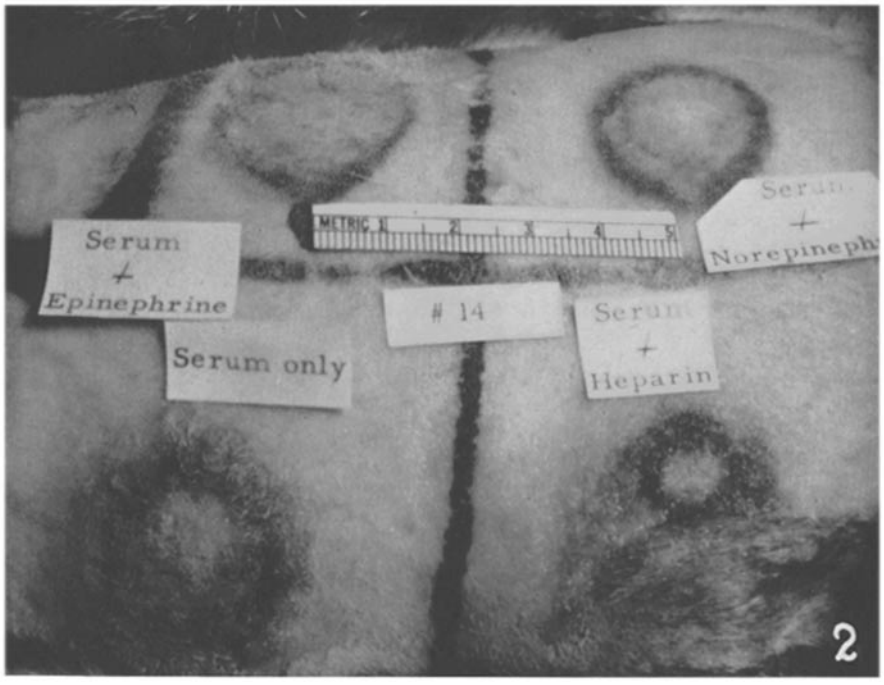
## EXPLANATION OF PLATE 36

FIG. 1. Twenty-four hour skin lesions produced by 100 micrograms of epinephrine and 100 micrograms of norepinephrine, respectively, in a rabbit with a 4+ Arthus reaction which had received 1 ml. of serum intravenously. The reaction to 500 micrograms of ephedrine and the control site are shown for comparison.

FIG. 2. Alteration of Arthus reaction by addition of 100 micrograms of epinephrine, 100 micrograms of norepinephrine, and 20 milligrams of heparin, respectively, to 1 ml. of horse serum at the designated sites. "Serum only" site is the unaltered Arthus reaction for comparison.




(Gatling: Reactivity to epinephrine in hypersensitivity)