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The Effects of Epinephrine and Nor-Epinephrine on the Blood Picture in the Rat

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GASS — EFFECTS OF EPINEPHRINE

THE EFFECTS OF EPINEPHRINE AND NOR-EPINEPHRINE

ON THE BLOOD PICTURE IN THE RAT

By

George H. Gass

A Thesis

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This thesis, directed and approved by the candidate's committee, has been accepted by the Graduate Committee of the University of New Mexico in partial fulfillment of the requirements for the degree of

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THE PROBLEM

It has long been known that various stresses and stimuli elicit responses in the animal body, and since the stating of Cannon's "emergency function" (1929), the adrenal medullary hormones have been credited with exciting many of the instantaneous responses of the animal body.

The secretion credited with initiating these phenomena was believed to be the adrenal medullary hormone, epinephrine. However, with the discovery of a second adrenal medullary hormone, nor-epinephrine (Stolz, 1904; Auerbach et al, 1949; von Euler et al., 1949; Goldenberg et al., 1949; Tullar, 1949), there have been numerous attempts to separate the various effects of these two secretions and to ascribe the proper response to the hormone involved.

The path by which the adrenal medullary hormones produce their responses appears to be by stimulating the adenohypophysis, which in turn affects the adrenal cortex, eliciting an increased production of adrenal cortical hormone. Such effects are said to be mediated by the pituitary adrenal axis (O'Connor and Verney, 1945; Long, 1947; Sayers et al., 1948).

The effects of adrenaline on the blood picture have been previously studied (Dougherty et al., 1943; Hills et al., 1948; Hungerford, 1949; Recant et al., 1950; Samuels et al., 1950; Samuels, 1951), and there is general agreement that adrenal medullary hormones will elicit a lymphocytopenia, eosinopenia,

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The effects of adrenaline on the blood picture have been previously studied (Dougherty et al., 1943; Hills et al., 1948; Hungerford, 1949; Recant et al., 1950; Samuels et al., 1950; Samuels, 1951), and there is general agreement that adrenal medullary hormones will elicit a lymphocytopenia, eosinopenia, and an increase in hematocrit values and hemoglobin. Samuels (1951) has shown that one obtains either a leucocytosis or a lymphocytopenia and eosinopenia, depending upon the time after treatment that the blood is studied. Since no comprehensive studies have been made on the relative effects of nor-epinephrine and epinephrine on the blood picture, such studies were undertaken in this investigation.

The experiment was designed to determine: (1) whether nor-epinephrine has effects on the blood elements different from those seen after epinephrine treatment; (2) whether the dosage of hormone employed will affect the type of response obtained; and (3) whether the demedullated rat responds to adrenal medullary hormones in the same pattern as the intact rat.

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HISTORY

The first anatomic description of the adrenal glands was made by Eustachius in his book entitled "De Glandulis Quae Renibus Incubent" in 1563 (Best and Taylor, 1950). Except for various bizarre theories, it was not until 1855, when Thomas Addison contributed the first physiological observation of these glands, that their importance was finally recognized (Turner, 1948).

Observations on the color reaction peculiar to the adrenals was reported by Vulpian in 1856 (Stolz, 1904). He observed that the juice of the adrenal gland gave a color reaction peculiar to the adrenals and that by the use of ferric chloride the cells of the medulla differed from those of the outer cortex in their staining properties.

The effects of the adrenal gland extract upon the blood pressure and its resulting rise when injected intravenously, was discovered by Oliver and Schaffer (1895) when they observed an immediate rise following the intravenous injection of an extract from the adrenal medulla.

The term "epinephrine" was first used by Abel in 1899. It had previously been separated as an active principle by Abel and Crawford in 1897, when they obtained a crude product from an aqueous extract by precipitation with benzol chloride and NaOH (cited by Aldrich, 1905).

Pure crystalline l-adrenaline was obtained in 1901 by

Aldrich (1901) and Takamine (1901). Both investigators used similar techniques. Aldrich proposed the empirical formula $C_9H_{13}O_3N$ for adrenaline as a result of data compiled from combustion analysis and nitrogen determinations.

The structural formula was arrived at by Freedman in 1904 (cited by Aldrich, 1905). Epinephrine, in conjunction with its non-methylated amine (nor-epinephrine or arterenol), was first synthesized by Stolz (1904).

The presence of nor-epinephrine in the adrenal medulla was proven conclusively by Goldenberg *et al.* (1949) by the use of paper chromatography. He reported that nor-epinephrine made up 12 to 18 percent of the adrenal medullary extract, running up to 50 to 90 percent in the case of chromaffin tissue tumors. Auerbach *et al.* (1949), Tullar (1949) and von Euler *et al.* (1949) showed its presence by colorimeter and pharmacological methods.

Investigations of the properties of epinephrine and nor-epinephrine reveal many similarities, both physiologically and chemically (Long, 1947; Hoppe *et al.*, 1949; Luft *et al.*, 1950).

The hormones secreted by the adrenal medulla are believed by Long (1947) to stimulate the pituitary adrenal axis. Three pathways through which the adrenal medullary hormones may act in causing a release of the cortical hormones are: (a) direct action on the pituitary causing an elaboration of ACTH, Aldrich (1901) and Takamine (1901). Both investigators used similar techniques. Aldrich proposed the empirical formula $C_9H_{13}O_3N$ for adrenaline as a result of data compiled from combustion analysis and nitrogen determinations.

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(b) epinephrine may act directly on the adrenal cortex causing a release of the cortical hormones, or (c) in accordance with Sayers et al. (1947), a stimulation of the metabolism of the peripheral cells will increase the demands for the cortical hormones and result in a lowering of the level of circulating cortical hormones in the blood, which stimulates the secretion of ACTH.

A direct relationship between the release or injection of pituitary ACTH and the stimulation of the adrenal cortex is shown by the depletion of its ascorbic acid stores, and the inverse relationship of cortical hormone administration to the secretion of pituitary ACTH has been shown by Sayers et al. (1948). That epinephrine acts peripherally to increase the tissue utilization of 11-oxysteroids, leading to lowered plasma levels and activation of the anterior pituitary to release ACTH has been shown by Sayers et al. (1949).

Taylor et al. (1949) has demonstrated this thesis of peripheral-humoral concept by showing that patients with adrenal cortical insufficiency have, in the blood, adrenotrophic activity and conclusively proved that adrenotrophic activity was not present in normal or hyperfunctional cortices of man.

Recent et al. (1948) has shown that a small dose (0.3 mg.) of epinephrine administered subcutaneously into a test subject with a resulting decrease of 50 percent in the number of

circulating eosinophils suggests an intact functional pituitary-adrenocortical system. This "epinephrine test" is dependent upon the enumeration of the eosinophils both before and at four hours after the injection. The results of this test may be applicable in determining hypopituitary states (Recent et al., 1950; Sayers, 1950), and Addison's disease (Dougherty et al., 1947; Hungerford, 1949; Spiers et al., 1949; Recant et al., 1950; Gordon et al., 1951).

Epinephrine affects the leucocyte counts, causing (1) a resulting decrease in the total leucocyte count, (2) a decrease in the absolute number of lymphocytes, and (3) an increase in the absolute number of polymorphonuclear cells (Dougherty et al., 1943; Thorn et al, 1948; Almy et al, 1949; Hungerford, 1949; Humphreys et al., 195; Madison, 1950; Pellegrino et al, 1950; White et al, 1950; Danford et al, 1951).

The effect on the lowering of the number of formed elements is not immediate, and is actually preceded by an increase in the number of circulating leucocytes. This effect has been described as a "biphasic cellular response to epinephrine", which is divided into a "primary phase" and a "secondary phase" (Samuels, 1951). The "primary phase" is characterized by a leucocytosis (Gabrilove et al, 1949; Luft et al, 1950; Samuels et al., 1950; White et al, 1950). This leucocytosis appears within five minutes after the injection of epinephrine in the human (Samuels, 1951). It exhibits a

maximal effect at 17 minutes, after which it subsides toward the normal. The "secondary phase" became apparent two hours after the injection of epinephrine. This phase evidenced a 15 percent reduction of lymphocytes and a 42 percent reduction in eosinophils, while the neutrophilia remained.

The "primary phase" is believed to be due to a release of leucocytes from the spleen by some investigators (Doan et al, 1946; Krache et al., 1949). However, this theory has been criticized by White et al. (1950), on the basis of observations that the increase of the different types of circulating leucocytes was not constant and also that splenectomy did not alter the type of responses.

The effects of nor-epinephrine on the leucocytic picture are less clear. A decrease in the number of circulating eosinophils, due to the administration of nor-epinephrine, was found by Humphreys et al. (1950) to be one-sixth that of epinephrine. Pellegrino et al. (1950) showed that, although a 35 to 48.6 percent fall in circulating eosinophils in man resulted at four hours after epinephrine administration, these results were not present with nor-epinephrine. Madison (1950) states that epinephrine is a potent eosinopenic agent, whereas nor-epinephrine is devoid of any significant effect. He reported a 47.2 to 54.9 percent fall in eosinophils with epinephrine, while nor-epinephrine caused a fall which was slightly less than that caused by the injection of saline alone.

However, Luft et al. (1950) while reporting a biphasic response with epinephrine, has shown a leucocytosis with nor-epinephrine, which tends to parallel the "primary phase" of epinephrine, but continues to rise after the "secondary phase" has become apparent. Continuous intravenous injection of epinephrine causes an increase in blood lactic acid and blood sugar, as well as a rise in blood pressure of rats (Cori, 1930).

Epinephrine causes a vasoconstriction of the renal, mesenteric, and femoral vascular beds (Ahlquist, 1948) and also elevates the systolic and diastolic pressure (DeLargy et al., 1950).

DeLargy et al. (1950) reported that the elevation of the systolic and diastolic pressure by nor-epinephrine was greater than that produced by epinephrine. Sutton et al. (1950) showed a systolic and diastolic pressure elevation, with bradycardia. Humphreys et al. (1950) disagrees with the increase in diastolic pressure. DeLargy et al. (1950) reports that epinephrine increases heart rate.

Hahn et al. (1942) reports a definite increase in the venous hematocrit values in the dog produced by the intravenous injection of epinephrine. Sutton et al. (1950) has shown an increase in hematocrit values in the human with nor-epinephrine.

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Sutton *et al.* (1950), by the use of radioactively tagged phosphorus (P_{32}), reported an increase in the large vein hematocrit values in humans, with no increase or decrease in the actively circulating red cell mass.

Both in vitro and in vivo studies show that epinephrine and nor-epinephrine accelerate coagulation (Waldron, 1950).

MATERIALS AND METHODS

Hormones in aqueous solution were injected subcutaneously and, although the total dosage varied, the ratio of volume per unit of body weight injected was kept constant (0.1 cc./ 100 gms. of body weight). The hormones were supplied by Sterling Winthrop in crystalline form and dissolved in distilled water to proper concentration prior to use. Animals receiving no hormone treatment were injected with distilled water, but otherwise they were subjected to the same procedures as the experimental rats.

In the first series of experiments, six normal rats were divided into three groups of two each. The animals were then used as follows: Group 1, serving as controls, was injected with distilled water; rats of Group 2 were injected with _l_-epinephrine bitartrate; and animals of Group 3 were injected with _l_-arterenol bitartrate monohydrate (nor-epinephrine).

Blood samples were taken by cutting the tip of the tail and allowing the requisite amount of blood to drop into a depression on a glass plate which had previously been coated with paraffin. A small drop of heparin (Heparin Sodium, Upjohn) was placed in the depression prior to the time of withdrawal of the blood and allowed to dry. Since such a procedure results in negligible volume change, it was not necessary to correct for dilution factors. The animals were tested once each week, and no signs of anemia were evident in

any of the animals, although they were used repeatedly for a period of several weeks.

Six drops of blood sufficed for each of the experiments. The blood was well mixed with the heparin to prevent coagulation.

Five tests were performed on each sample of blood thus taken. They were as follows:

1. Erythrocyte count. 0.9 percent NaCl solution was found to be the most efficient diluent. The method was to fill both sides of the counting chamber and make two erythrocyte counts on each sample. By making duplicate counts, the error was reduced.

2. Leucocyte count. 0.1 N HCl was found to facilitate counting of the leucotytes, and more consistent counts were arrived at by the use of this diluent than others, i.e., Turk's diluting fluid. Again, both sides of the chamber were filled and two counts made.

3. Hematocrit determination. This determination was made by filling three capillary tubes three-fourths full of the blood being tested. One end of these tubes was then sealed with a microburner and the tubes placed in the air centrifuge and spun at approximately 25,000 RPM for seven minutes. (No greater concentration of the erythrocytes was effected by a longer rotation time.) The tubes were removed from the centrifuge, and the volumes of the formed elements

were measured with a steel ruler measuring accurately to 0.01 inch. Only the results obtained from two of the tubes having results most closely related were used, unless all three tubes gave very little difference in measurement.

4. Hemoglobin. The hemoglobin was determined by placing 0.02 cc. of the blood sample in a tube containing 5 cc. of 0.1 N HCl and allowing this to remain at room temperature for 30 minutes. At the end of this time the quantity of acid hematin was determined by use of a Klett-Summerson Photoelectric Colorimeter, and a prepared standard, which contained a concentration of 14.4 grams of acid hematin per 100 cc. of blood. By comparison of the colorimeter reading of the unknown sample with the known sample, the amount of hematin was calculated.

5. The absolute number of neutrophils, lymphocytes, eosinophils, and monocytes was determined by count of 200 cells from stained smears. By using an additional drop of blood from the tail of the rat, a smear was made and the slide stained with Wright's stain.

An additional test for serum proteins was performed only upon conclusion of the experiments, due to the quantity of blood required. The requirement of a large sample necessitated a cardiac puncture and the withdrawal of at least 0.5 cc. of blood. The syringe used for the cardiac puncture was previously prepared for this purpose by coating

the inside of the barrel with 0.02 cc. of heparin and allowing it to dry, so as not to affect the fluid volume.

A sample of this blood was then placed in a centrifuge tube and spun at 2,500 RPM's for five minutes, at which time it was removed and the serum drawn off with a Guthrie pipette controller, which contained a falling drop pipette calibrated to deliver with great accuracy two successive drops containing exactly 1/100 ml. each. By means of the Guthrie pipette controller, one drop of the serum was allowed to fall through a bromobenzene-xylene mixture, and the time for it to fall 30 cm. was clocked with a stop watch. This liquid mixture is immiscible with body fluids.

One drop of a standard solution was also allowed to fall through the bromobenzene-xylene mixture and timed. This standard was prepared by adding K_2SO_4 to distilled water, 33.91 grams K_2SO_4 per 1,000 ml. of water at 20° C. This has a specific gravity of 1.0269. The falling times for both the serum and the standard were then corrected for temperature and the serum protein calculated by the use of the Eimer and Amend Alignment Chart for Specific Gravity, and applying the result from this chart to the formula of Weech et al. (1936) for plasma proteins.

The intact rats were tested using an injection of 10 micrograms per 100 gms. of body weight, both for epinephrine and nor-epinephrine. Eight tests using epinephrine were

conducted at this concentration, and six tests using nor-epinephrine were also conducted at the same concentration. The concentration was then doubled (20 γ/100 gms. of body weight) and the test repeated for a total of six tests, again using both hormones.

In the second series of experiments rats with the adrenal medulla removed were used. The medullae were removed by nicking the adrenal capsule with a scalpel and pressing out the contents, allowing only the capsule and some adhering cortical tissue to remain. These demedullated rats were not used until at least 30 days after the operation to allow time for a regeneration of the cortex (regeneration is limited to the cortex). For this series eight rats were divided into four groups of two each. Two groups received 10 γ/100 gms. of body weight of epinephrine or nor-epinephrine. Since demedullated rats were thought to be more susceptible to a smaller quantity of the adrenal-medullary hormones than normal rats (Eversole, 1952), this minimum concentration of the adrenal-medullary hormone was used. In the other two groups of demedullated rats, the dose was increased to 100 γ/100 gms. of body weight of epinephrine or nor-epinephrine. The testing procedure was the same for demedullated rats as for intact ones.

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Only male rats from the colony of the Department of Biology, University of New Mexico, which were accustomed to being handled, were used for these experiments. The rats used were mature individuals of 350 grams or greater. All animals were fasted for 18 hours prior to the tests. All food was removed at this time, but they were allowed water.

For each test the rat served as its own control. Blood studies were conducted prior to the administration of either distilled water, epinephrine, or nor-epinephrine. After these studies were performed, one of the above agents was administered, and after a lapse of 45 minutes, the tests were repeated. This gave an additional control, besides those administered distilled water only, as well as giving an excellent method of comparison of the effects of epinephrine and nor-epinephrine.

The standard error used in the tables showing the effects of adrenal medullary hormones on RBC's, WBC's, hemoglobin and hematocrit values was calculated according to the formula: $S.E. = \pm\sqrt{d^2/N(N-1)}$ where the d^2 is the sum of the variances and N is the number of individual animals used.

For determining the statistical significance, the "T" value was calculated according to the formula: $T = M_1 - M_2 / \sqrt{(SE_1)^2 - (SE_2)^2}$ where SE is the standard error of a group whose mean is M. If "T" was equal to 2 or more, the variation of that group was considered to be significant.

Sprague-Dawley rats were used for these experiments.

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For each test the rat served as its own control. Blood studies were conducted prior to the administration of either distilled water, epinephrine, or nor-epinephrine. After these studies were performed, one of the above agents was administered, and after a lapse of 15 minutes, the tests were repeated. This gave an additional control. Besides those administered distilled water only, as well as giving an excellent method of comparison of the effects of epinephrine and nor-epinephrine.

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RESULTS

Control Animals

A decrease in RBC's, WBC's, hemoglobin and hematocrit values was evidenced in the controls in the 45 minute period between the first and second cutting of the tail for the blood samples (Tables 1, 2, 3, and 4). At the end of 45 minutes, this decrease was statistically significant ($T > 2$) for both the RBC's and WBC's.

Intact Animals

Nor-epinephrine

Comparison of the results obtained before and after injections for any one type of treatment indicate that, as seen in Table 1 and Figure 1, the administration of nor-epinephrine inhibits the decrease in number of either WBC's or RBC's. A lower dose appears to be more effective in preventing the decrease in white blood cells than a higher dose; however, the higher dose was more effective in elevating the red cell count.

As shown in Table 1, the blood cell counts after injection of distilled water are consistently lower than the counts obtained after the injection of nor-epinephrine. When comparisons are made in this manner, nor-epinephrine appears to cause a significant increase ($T > 2$) in both the white and red blood cell counts.

In other words, nor-epinephrine inhibits the fall in

red and white blood cells that occurs in water injected animals, and, in the case of the RBC's, nor-epinephrine not only inhibits the fall, but causes a slight increase in the number of these blood elements.

Nor-epinephrine caused a slight increase in the hematocrit values and hemoglobin (Table 2), but these effects were less marked than those seen in the case of the blood cells.

Epinephrine

At 10γ/100 gms. of body weight, epinephrine was less effective than nor-epinephrine in eliciting any changes in the blood constituents, the only significant finding being on the RBC's, preventing to some extent the decrease that appeared in the control animals. The drop in WBC's was the same after epinephrine injection as that seen in water injected animals.

Epinephrine at 20γ/100 gms. of body weight again showed a significant deviation from the controls only in the RBC count. There appeared to be a slightly greater decrease in the number of circulating WBC's at this level, but not of a significant degree.

Demedullated Animals

Nor-epinephrine

As seen in Figure 2, nor-epinephrine at 10γ/100 gms. of body weight gave a pattern of response very similar to that seen in intact animals. Nor-epinephrine prevented a red and white blood cells that occurs in water injected animals, and, in the case of the RBC's, nor-epinephrine not only inhibits the fall, but causes a slight increase in the number of these blood elements.

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Nor-epinephrine

As seen in Figure 2, nor-epinephrine at $10\gamma/100$ gms. of body weight gave a pattern of response very similar to that seen in intact animals. Nor-epinephrine prevented a fall in both white and red blood cell levels, and it caused a significant elevation in hematocrit values. Contrary to the expected results, nor-epinephrine was no more effective in the demedullated rats than in the intact ones.

Increasing the dose of nor-epinephrine to 100γ/100 gms. of body weight was no more effective in causing changes in the blood picture than was the smaller dose. The larger dose, if anything, appeared to be less effective in inhibiting the drop in WBC's than the lower one.

Epinephrine

In conjunction with the expected increased sensitivity of demedullated animals to adrenal medullary hormones, the results on the WBC's at the 10γ level showed a distinct correlation; there was a marked inhibition of the expected fall in these cells. However, there were no significant effects on the RBC's and hemoglobin.

Administration of epinephrine at a dose level of 100γ/100 gms. of body weight indicated a much greater degree of activity than any of the lower dose levels used. There was a significant increase in the RBC's and WBC's. The WBC's were not only prevented from decreasing, but showed a considerable increase.

Leucocyte Changes

The use of the differential staining technique showed that there was little change in the relative lymphocyte and

neutrophil numbers at the various dose levels of nor-epinephrine and epinephrine.

The results obtained on the eosinophil numbers indicate, for the 10γ dose level, that either epinephrine or nor-epinephrine cause an increase in the blood elements. The administration of 100γ of either hormone to demedullated animals resulted in a decrease in the eosinophils.

Serum Proteins

Epinephrine and nor-epinephrine caused no significant change in the serum protein values over the values obtained for the water injected animals. The explanation of this is probably that determinations were made only on two cases in each instance.

DISCUSSION

It is quite evident from the above results that nor-epinephrine is considerably more effective in the low dosages than is epinephrine, as far as the effect on the blood picture of the intact rat is concerned. In demedullated animals, epinephrine was just as effective as nor-epinephrine in eliciting changes in the blood elements. The hormones tended to maintain a normal blood picture in the face of a procedure that tended to lower the hematocrit values, red cells, and white cells. Exactly how they do this is not understood.

It would be of interest to carry out experiments using lower dose levels of nor-epinephrine. One should not discard the possibility that dose levels lower than 10γ/100 gms. of body weight of nor-epinephrine might have even more significance.

Low dose levels of nor-epinephrine prevented the decrease in WBC's that was noted in the controls (Figure 1). Had the tail not been cut and a sample taken prior to injection, it is assumed that a leucocytosis would have resulted. A leucocytosis 45 minutes after the administration of nor-epinephrine would have agreed with the findings for epinephrine as reported by Samuels (1951). Samuels describes the effect of epinephrine on WBC's in humans as a biphasic cellular response in which he observed a lymphocytosis, eosinophilia,

and neutrophilia. This leucocytosis remained for four hours after the administration of epinephrine; however, he noted a lymphopenia and eosinopenia at the end of two hours.

An eosinopenia resulted from the administration of the highest dosage of nor-epinephrine and epinephrine which, in the rat, might favorably compare with Samuels' (1951) findings two hours after epinephrine administration in the human.

As was expected, the effects of epinephrine were more pronounced in the demedullated animals. At 10 γ /100 gms. of body weight, it prevented a decrease in WBC's that paralleled that found for nor-epinephrine at 10 γ in the intact animals. The activity of epinephrine at the highest dose level was considerable increased over any other dose level, either for epinephrine or nor-epinephrine. The highest dose levels of both epinephrine and nor-epinephrine caused an eosinopenia, This compares favorably with the findings of other investigators (Thorn et al., 1949; Humphreys et al., 1950; White et al., 1950; Samuels, 1951).

If one compares only the figures obtained after injection, it would seem that low doses of nor-epinephrine and high doses of epinephrine will cause an increase in RBC's, WBC's, hemoglobin, and hematocrit values. When the data are considered in this light there is agreement with the work of Hahn et al.,(1942), Hungerford (1945), Dougherty et al. (1943), Gabrilove et al. (1949), White et al. (1950), Pellegrino et al.

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(1950), and Samuels (1951). Since these experiments were controlled both by using control animals, and by prior tests on the animal itself before the administration of the hormone, the comparison of the results with both controls no longer shows the apparent increase in RBC's, WBC's, hemoglobin, and hematocrit values. The results do definitely show, however, that the shifts in the blood in water injected controls were prevented by treatment with medullary hormones; nor-epinephrine being more effective in the intact animal and epinephrine being just as effective as nor-epinephrine in the demedullated animals. Such findings indicate that the adrenal medullary hormones are of considerable importance in maintaining homeostasis in the circulating blood elements.

SUMMARY

1. A definite decrease in RBC's, WBC's, hemoglobin and hematocrit values takes place in the rat in a 45 minute period after cutting the tip of the tail and removing a blood sample.

2. Nor-epinephrine prevents, to some extent, this loss, or even increases the circulating formed elements. This effect is brought about by a dose level below the effective physiological dose of epinephrine. Less effect is evidenced by higher dose levels of nor-epinephrine.

3. The results of epinephrine parallel those found by other investigators, with the largest dose level (100γ / 100 gms. of body weight) having the greatest effect upon the circulating formed elements. A dose level of 10γ /100 gms. of body weight had no significant effect. A dose level of 20γ /100 gms. of body weight caused an increase in circulating red cells (hemoglobin and hematocrit values). No dose level below 100γ /100 gms. of body weight had any significant effect upon the number of circulating white cell elements.

4. Demedullated rats were more reactive to the low level of epinephrine than were intact animals.

5. Nor-epinephrine and epinephrine produced a change in the relative number of eosinophils, the duration of the change being dependent upon the dose level. The increase

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5. Nor-epinephrine and epinephrine produced a change in the relative number of eosinophils, the duration of the change being dependent upon the dose level. The increase

in eosinophils with low doses of the hormones was changed to a decrease in eosinophils by a dosage level of 100 γ/ 100 gms. of body weight. In other words, low doses caused an eosinophilia and high doses an eosinopenia.

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TABLE 1

EFFECTS OF ADRENAL MEDULLARY HORMONES ON RBC's AND WBC's IN INTACT RATS

Treatment /100 gms. body wt.	RBC's (10^5)		WBC's (10^3)	
	Before	After	Before	After
0.1 cc. Dist. H_2O	100.26 ±0.65 (10)	92.13 ±3.24* (10)	17.35 ±0.86 (10)	12.28 ±0.87* (10)
Nor-epinephrine 10γ	95.70 ±4.39 (6)	97.62 ±1.58 (6)	13.87 ±1.27 (6)	13.50 ±1.55 (6)
Epinephrine 10γ	89.90 ±2.03 (8)	89.01 ±1.70 (8)	19.96 ±1.79 (8)	15.00 ±0.76* (8)
Nor-epinephrine 20γ	95.70 ±4.48 (5)	103.27 ±7.22 (5)	20.63 ±2.08 (5)	17.34 ±1.58 (5)
Epinephrine 20γ	88.80 ±5.34 (6)	89.80 ±3.24 (6)	24.19 ±2.52 (6)	16.57 ±1.60* (6)

*Differs significantly from that value obtained prior to treatment

The figure enclosed in parenthesis is the number of cases considered in that group.

TABLE 2

EFFECTS OF ADRENAL MEDULLARY HORMONES ON HEMOGLOBIN AND HEMATOCRIT VALUES IN INTACT RATS

Treatment /100 gms. body wt.	Hemoglobin		Hematocrit Values	
	Before	After	Before	After
0.1 cc. Dist. H_2O	15.02 ±0.38 (10)	14.48 ±0.39 (10)	48.6 ±0.74 (10)	46.6 ±1.35 (10)
Nor-epinephrine 10γ	15.10 ±0.22 (6)	15.38 ±0.25 (6)	48.9 ±0.53 (6)	49.6 ±0.38* (6)
Epinephrine 10γ	15.28 ±0.18 (8)	14.85 ±0.24* (8)	48.7 ±1.02 (8)	48.1 ±0.94 (8)
Nor-epinephrine 20γ	14.94 ±0.40 (5)	15.09 ±0.59 (5)	49.0 ±1.20 (4)	49.2 ±0.99 (4)
Epinephrine 20γ	14.20 ±0.61 (6)	14.74 ±0.34 (6)	49.1 ±0.12 (5)	50.0 ±0.11 (5)

*Differs significantly from that value obtained prior to treatment

The figure enclosed in parenthesis is the number of cases considered in that group.

TABLE 3

EFFECTS OF ADRENAL MEDULLARY HORMONES ON RBC's AND WBC's IN DEMEDULLATED RATS

Treatment /100 gms. body wt.	RBC's (10^5)		WBC's (10^3)	
	Before	After	Before	After
0.1 cc. Dist. H_2O	100.26 ±0.65 (10)	92.13 ±3.24* (10)	17.35 ±0.86 (10)	12.28 ±0.87* (10)
Nor-epinephrine 10γ	101.24 ±3.96 (5)	103.07 ±2.88 (5)	19.16 ±1.57 (5)	18.64 ±1.95 (5)
Epinephrine 10γ	86.95 ±6.24 (5)	84.26 ±6.66 (5)	20.67 ±3.27 (5)	20.59 ±1.59 (5)
Nor-epinephrine 100γ	100.05 ±4.28 (5)	102.57 ±6.40 (5)	19.05 ±1.04 (5)	16.71 ±2.19 (5)
Epinephrine 100γ	90.41 ±3.87 (5)	97.95 ±2.61 (5)	19.05 ±1.57 (5)	21.64 ±0.86 (5)

*Differs significantly from that value obtained prior to treatment

The figure enclosed in parenthesis is the number of cases considered in that group.

TABLE 4

EFFECTS OF ADRENAL MEDULLARY HORMONES ON HEMOGLOBIN AND HEMATOCRIT VALUES IN DEMEDULLATED RATS

Treatment /100 gms. body wt.	Hemoglobin		Hematocrit Values	
	Before	After	Before	After
0.1 cc. Dist H_2O	15.02 ±0.38 (10)	14.48 ±0.39 (10)	48.6 ±0.74 (10)	46.6 ±1.35 (10)
Nor-epinephrine 10γ	16.20 ±0.28 (5)	16.00 ±0.31 (5)	49.1 ±0.36 (4)	50.9 ±0.58* (4)
Epinephrine 10γ	15.68 ±0.73 (5)	15.38 ±0.62 (5)	49.0 ±3.94 (2)	49.4 ±4.90 (2)
Nor-epinephrine 100γ	16.30 ±0.25 (5)	16.40 ±0.40 (5)	47.0 ±1.41 (3)	50.7 ±1.55 (3)
Epinephrine 100γ	15.53 ±0.29 (5)	15.44 ±0.23 (5)	48.4 ±0.51 (3)	49.8 ±0.00* (3)

*Differs significantly from that value obtained prior to treatment

The figure enclosed in parenthesis is the number of cases considered in that group.

TABLE 5

"T"*VALUES WHEN MEANS OF TREATED ANIMALS ARE COMPARED WITH MEANS OF CONTROL ANIMALS (INTACT ANIMALS)

	RBC	WBC	Hemoglobin	Hematocrit Values
Nor-epinephrine 10γ	T = 2.3 (6)	T = 3.3 (6)	T = 2.4 (6)	T < 2 (6)
Nor-epinephrine 20γ	T = 2.6 (5)	T = 2.2 (5)	T < 2 (5)	T < 2 (4)
Epinephrine 10γ	T = 2.5 (8)	T < 2 (8)	T < 2 (8)	T < 2 (8)
Epinephrine 20γ	T = 2.5 (6)	T < 2 (6)	T = 2.6 (6)	T < 2 (5)

*"T" values greater than 2 are considered to be of statistical significance.

The figure enclosed in parenthesis is the number of cases considered in that group.

TABLE 6

"T"*VALUES WHEN MEANS OF TREATED ANIMALS ARE COMPARED WITH MEANS OF CONTROL ANIMALS (DEMEDULLATED ANIMALS)

	RBC	WBC	Hemoglobin	Hematocrit Values
Nor-epinephrine 10γ	$T < 2$ (5)	$T = 2.1$ (5)	$T < 2$ (5)	$T = 2.3$ (4)
Nor-epinephrine 100γ	$T < 2$ (5)	$T < 2$ (5)	$T < 2$ (5)	$T < 2$ (3)
Epinephrine 10γ	$T < 2$ (5)	$T < 2$ (5)	$T < 2$ (5)	$T < 2$ (2)
Epinephrine 100γ	$T = 3.8$ (5)	$T = 3.9$ (5)	$T < 2$ (5)	$T = 2.1$ (3)

*"T" values greater than 2 are considered to be of statistical significance.

The figure enclosed in parenthesis is the number of cases considered in that group.

TABLE 7

EOSINOPHIL CHANGES WITH ADRENAL MEDULLARY HORMONES

	PERCENT CHANGE
Nor-epinephrine 10γ Intact	32.8 (5)
Nor-epinephrine 10γ Demedullated	226.2 (5)
Nor-epinephrine 20γ Intact	-1.4 (5)
Nor-epinephrine 100γ Demedullated	-46.2 (5)
Epinephrine 10γ Intact	5.5 (7)
Epinephrine 10γ Demedullated	35.5 (5)
Epinephrine 20γ Intact	12.7 (6)
Epinephrine 100γ Demedullated	-38.5 (5)

The figure enclosed in parenthesis is the number of cases considered in that group.

FIGURE 1

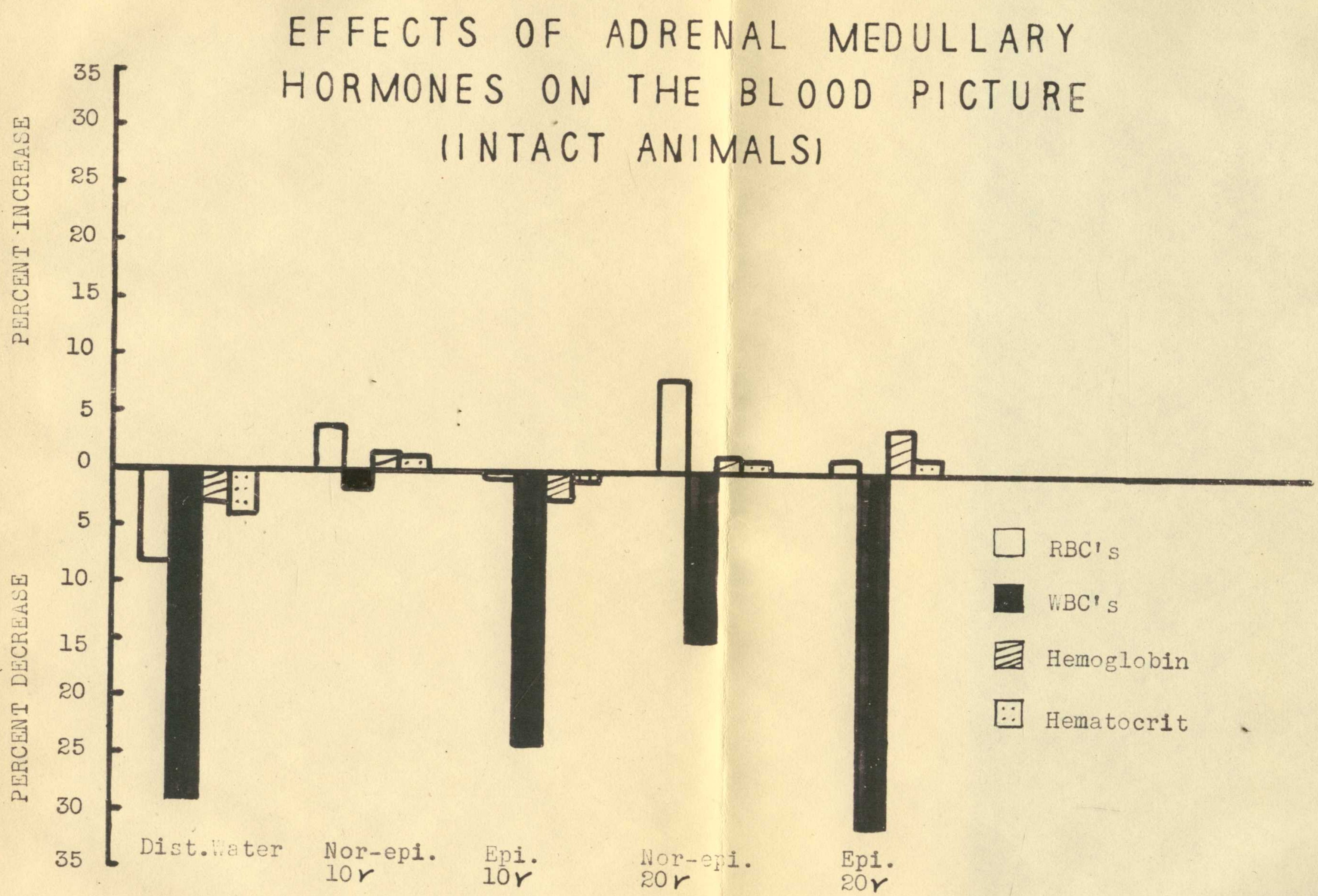
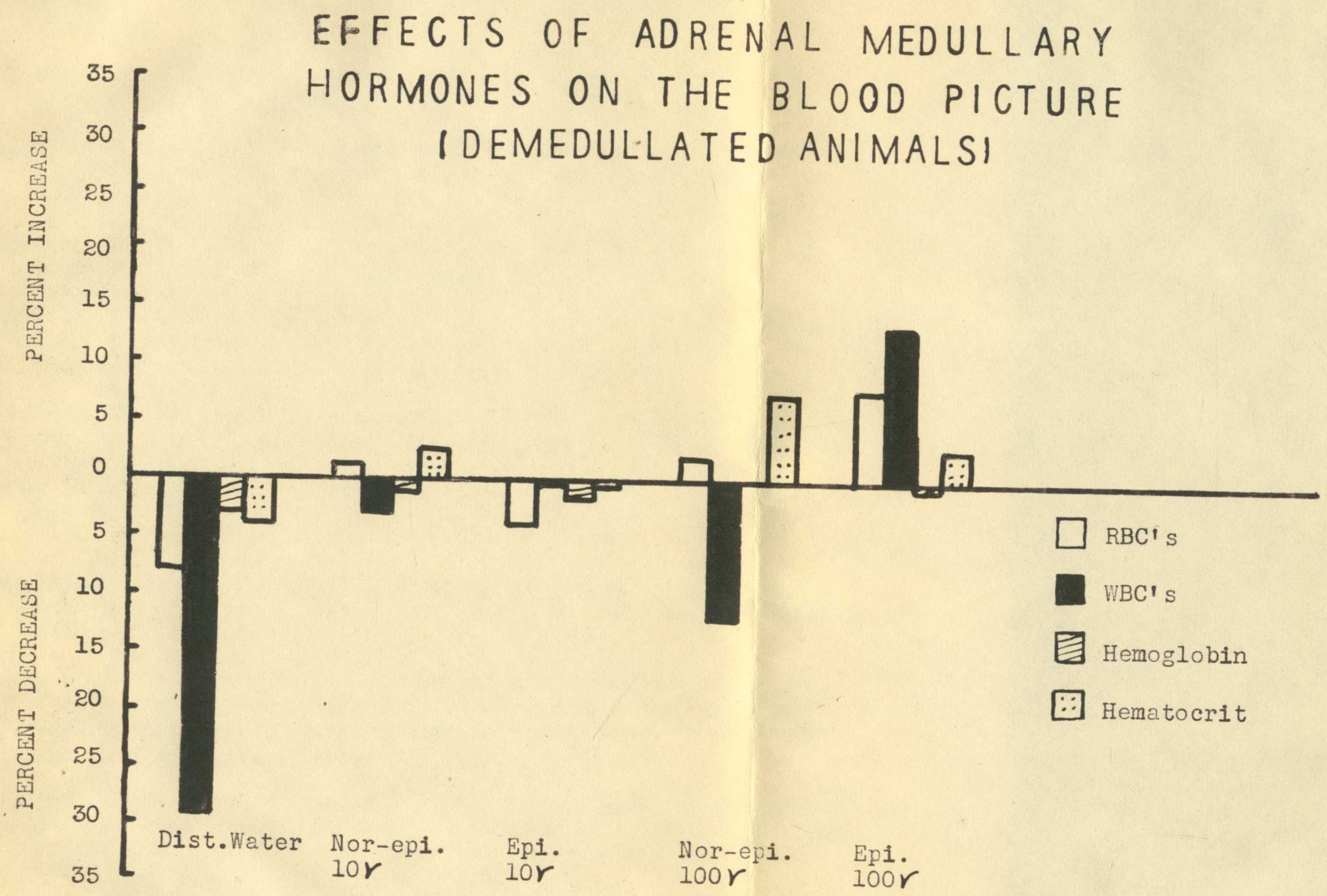

EFFECTS OF ADRENAL MEDULLARY HORMONES ON THE BLOOD PICTURE (INTACT ANIMALS)
PERCENT INCREASE
PERCENT DECREASE
35
30
25
20
15
10
5
0
Dist.Water
Nor-epi. 10γ
Epi. 10γ
Nor-epi. 20γ
Epi. 20γ
RBC's
WBC's
Hemoglobin
Hematocrit

FIGURE 2


EFFECTS OF ADRENAL MEDULLARY
HORMONES ON THE BLOOD PICTURE
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PERCENT INCREASE
PERCENT DECREASE
35
30
25
20
15
10
5
0
5
10
15
20
25
30
35
Dist.Water
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Epi. 10γ
Nor-epi. 100γ
Epi. 100γ
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