THE EFFECT OF THE PARENTERAL INJECTION OF EPINEPHRIN ON LEUKOCYTE COUNTS IN NORMAL SUBJECTS AND IN PATIENTS WITH ADDISON’S DISEASE.

By Jacques L. Gabriolove, M.D., Mario Volterra, M.D., Mildred D. Jacobs, A.B., and Louis J. Soffer, M.D.

It has been known for many years that the parenteral administration of epinephrin induces marked temporary changes in the white blood cell picture. The mechanism responsible for these changes is still obscure. Interest in this phenomenon, however, has recently been revived since Dougherty and White have demonstrated that the administration of adrenotrophic hormone of the anterior hypophysis or whole adrenal cortical extract results in the destruction of lymphoid tissue with the production of a lymphocytopenia. Long and his group have shown that the injection of epinephrin into experimental animals causes stimulation of the anterior hypophysis with increased secretion of adrenotrophic factor, which in turn stimulates the adrenal cortex. In view of this observation, it was thought desirable to study the effect of epinephrin on the leukocyte count in normal subjects and in patients with Addison’s disease, the latter being the closest clinical analogue of the bilaterally adrenalectomized animal.

The lymphocytopenia resulting from adrenal cortical secretion is presumed to be part of the reaction to stress involved in the adaptation syndrome. Pincus et al. have used this phenomenon to study reactions to stress in the human as a measure of adrenal cortical secretion.

Conversely, it has long been known, as recently emphasized by De la Balze and co-workers, that patients with Addison’s disease have a lymphocytosis associated with a reduction in the total white blood cell count, as well as a decrease in the number of neutrophiles.

Previously published studies with epinephrin have almost invariably been short period experiments, usually for less than two hours, since the problem being investigated dealt, for the most part, with the role of the spleen in the ensuing leukocytosis. The administration of epinephrin results initially in a leukocytosis, associated with a sharp increase in the absolute and relative number of lymphocytes. These changes disappear within an hour and are followed by a neutropenia. More recent studies on the effects of epinephrin on the lymphocyte count in normal and adrenalectomized dogs have shown that the former develop a lymphocytopenia which is not observed to occur in the totally adrenalectomized animals.

METHODS

Ten normal subjects and 11 patients with Addison’s disease were studied. Seventy-five hundredths cc. of a 1 to 1,000 aqueous epinephrin solution (0.75 milligrams) was administered subcutaneously. Blood for total white blood cell counts and differential studies was obtained from the finger before the administration of epinephrin as well as at fifteen minutes, one hour, two hours, three hours, four hours,
and five hours following the injection. Smears were stained with Wright's stain and one hundred cells were counted. All tests were performed at approximately the same time of day, from 8 to 9 A.M. to 1 to 2 P.M. Because of the fear of hypoglycemia in the patients with Addison's disease, all subjects were allowed to eat prior to the test and at luncheon time (about 12 noon). All patients experienced palpitation, apprehension, tachycardia, and nervousness as the result of the administration of epinephrin.

The diagnosis of Addison's disease had been established in each instance on the basis of adequate clinical and laboratory evidence. All the patients presented the classic clinical picture, and each had been in acute adrenal insufficiency, either occurring spontaneously or induced by salt deprivation, on at least one occasion. The characteristic blood electrolyte pattern demonstrating a low serum sodium and chloride and elevation of serum potassium was manifested by every patient of the group selected for study. The members of the group were treated with desoxycorticosterone acetate. None received whole adrenal cortical extract.

![Graph](image)

**Fig. 1**—The total white count following the subcutaneous administration of 0.75 cc. of 1/1000 epi-nephrine. Broken lines denote normal subjects. Continuous lines denote patients with Addison's disease.

**RESULTS**

In both normal subjects and in patients with Addison's disease, the total white blood cell count (fig. 1) exhibits a diphasic character with a high early peak and a low late peak. The peaks occur at fifteen minutes to one hour and at three to four hours. The minimum count is noted at two to three hours. In the normal subjects, as opposed to the patients with adrenal hypofunction, the total white blood cell count is initially higher, and maintains a higher level throughout the test. In addition, in normals, the second peak is much higher than it is in patients with Addison's disease.

In both normal subjects and patients with Addison's disease, the absolute neutrophile count exhibits a diphasic curve. The early peak occurs in fifteen minutes to one hour and is low. The minimum count is noted in one to two hours. The second
Fig. 1.—The absolute neutrophil count following the subcutaneous administration of 0.75 cc. of 1/1000 epinephrine. Broken lines denote normal subjects. Continuous lines denote patients with Addison's disease.

Fig. 3.—The absolute lymphocyte count following the subcutaneous administration of 0.75 cc. of 1/1000 epinephrine. Broken lines denote normal subjects. Continuous lines denote patients with Addison's disease.
Fig. 4.—The percentage of the original absolute lymphocyte count following the subcutaneous administration of 0.75 cc. of 1/1000 epinephrine. Broken lines denote normal subjects. Continuous lines denote patients with Addison's disease.

Fig. 5.—The percentage of lymphocytes in the differential leukocyte count following the subcutaneous administration of 0.75 cc. of 1/1000 epinephrine. Broken lines denote normal subjects. Continuous lines denote patients with Addison's disease.
peak is more pronounced than the primary rise, and the second peak in normals is far greater than that noted in patients with adrenal insufficiency. In general, the absolute lymphocyte count in patients with Addison's disease is initially higher than in normals, and maintains this higher level throughout the test. The overlap is so great that no more pronounced lymphocytopenia in normals as contrasted to patients with Addison's disease can be demonstrated as a means of differentiation between the groups (figs. 2 and 3).

When the percentage of the absolute lymphocyte count at any time compared to the original absolute lymphocyte count is plotted against time, a diphasic curve is noted. Here, too, no definite evidence of more marked lymphocytopenia in the normal as opposed to the patient with Addison's disease is noted (fig. 4). Although we do not feel that the differential count per se in this test is of significance, we have plotted it merely to illustrate how the relative composition of the blood varies. The lymphocyte percentage in the patient with Addison's disease is initially higher than in the normal, and this higher percentage is maintained throughout the test. In both the normals and the patients with Addison's disease, the percentage of lymphocytes rises early and falls late (fig. 5).

With our technic, employing Wright's stain for differential study, no difference in eosinophilia is noted between the two groups. There is a slight late decrease in eosinophilia following the administration of epinephrin.

**DISCUSSION**

On the basis of the results obtained, no clear cut separation can be made in the reaction to epinephrin of the patients with Addison's disease from that of the normal individuals.

Several possibilities exist to explain why the expected altered reaction in the patients with Addison's disease as compared to normals was not encountered:

1. Seventy-five hundredths cc. of 1 to 1,000 epinephrin (0.75 mg.) is insufficient to result in stimulation of the anterior pituitary lobe to the secretion of increased amounts of adrenotropic hormone.

Long et al., working with animals, employed 0.02 milligrams of epinephrin per 100 grams of body weight. Comparable dosage would necessitate the use of 10 milligrams in a man weighing 50 kilograms. Malmejac et al., working with dogs, employed 0.1 to 0.2 milligram per kilogram of body weight, intravenously every five minutes for six doses. This is equivalent to 5 to 10 mg. every five minutes in a man weighing 50 kilograms. They found that with this dosage the lymphocytes fell to two-thirds the initial value.

2. The effect is not demonstrable within five hours.

This is rather unlikely, since White and Dougherty demonstrated the effect of adrenotrophic and adrenocortical hormone in one hour, even though the maximum effect occurred in nine hours. Long and Fry produced adrenal changes within two hours after the administration of epinephrin, while Malmejac et al. noted maximum effects in two to three hours.

3. In patients with Addison's disease there is still some responsive adrenal cortical tissue.
It is obvious that all grades of adrenal insufficiency both quantitatively and qualitatively exist. The lymphocyte effect is believed to depend on the carbohydrate regulating fraction of the adrenal cortex. It is possible that in clinical Addison's disease sufficient responding adrenal cortical tissue is present to react following the administration of epinephrin, with some resulting resemblance to the normal reaction.

4. The extraneous effects of epinephrin may mask its effect on the pituitary-adrenal relationship. This possible effect of epinephrin on contraction of the spleen, hemoconcentration, redistribution of formed elements in the blood may interfere with the detection of the effect being studied.

SUMMARY

Ten normal subjects and 11 patients with Addison's disease were studied as to their leukocyte response following the subcutaneous administration of epinephrin. The pattern of response was found to be similar in both groups, diphasic curves being noted. In general, the patients with Addison's disease differ from normal individuals in having: (1) a lower and less labile white count, (2) a lower and less labile neutrophile count, (3) a higher lymphocyte count, (4) a slightly lesser percentage fall in absolute number of lymphocytes, and (5) a higher lymphocyte percentage.

The use of this method to demonstrate adrenal cortical destruction is not feasible with the dosage of epinephrin employed in this study.

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