Eosinophilia in Addison's Disease

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This report describes studies on the mechanism of eosinophilia in blood and bone marrow of a patient with untreated Addison's disease.

CASE REPORT

A 21-year-old man was admitted to hospital because of diarrhea, vomiting, and abdominal pain. The illness had begun 3 years earlier when he first felt excessive fatigue and noticed areas of vitiligo. He had attacks of vomiting, lasting about a week, recurring every few months. He lost weight and had to give up his work. He had no history of allergies. On admission to hospital, he was dehydrated and thin, with generalized pigmentation including the palmar creases, but there was no pigmentation of mucous membranes. The tips of the fingers, skin over the hips, and nipples showed vitiligo. Systolic blood pressure was 70 mm Hg. He had no fever. A clinical diagnosis of Addison's disease was made.

Hemoglobin was 14 g%, leukocyte count 7000/mm³, with 800 eosinophils/mm³, ESR 28. ECG showed flat T waves in the chest leads. Urea was initially 68 mg/100 ml, and returned to normal after he was rehydrated. Blood electrolytes were normal. Chest X ray showed a small tubular heart. Plasma cortisol levels were low, 7–9 μg/100 ml, with no diurnal variation or increase after injection of 0.25 mg of an adrenocorticotropic hormone analog, Synacthen (Ciba). The serum contained γG antibodies to human adrenal tissue at a dilution of 1/20. There was no evidence of other endocrine disorder. There were no intrinsic factor antibodies, and the stomach produced normal amounts of acid in response to gastrin stimulation. The serum protein-bound iodine and vitamin B₁₂ levels were normal. The Mantoux test was negative at 1/1000. The stool did not contain parasites or ova.

Eosinophil production and half-life. Direct blood eosinophil counts were done by the method of Discombe (1) on venous blood before and after giving Synacthen, 0.25 mg intramuscularly, and cortisone, 25 mg orally, as shown in Fig. 1. There was no alteration in blood eosinophil counts in response to Synacthen; however, 25 mg of cortisone reduced the blood eosinophil count from 780 to 230/mm³ 4 hr later. When the patient began taking cortisone, 12.5 mg orally twice daily, the blood eosinophil level remained normal.

Bone marrow biopsies were done 6 hr before and 3 days after cortisone treatment was begun. The patient had given his full consent when the experimental character and nature of the biopsies had been explained. The bone marrow was taken from the sternum and put directly into a culture medium at 37°C containing 8 ml of Parker 199 (Wellcome), 2 ml of isotonic phosphate buffer at pH 7.4, 1 ml of 50% glucose, and 1 ml of unheated isologous fresh serum taken 1.5 hr before sternal puncture, with 1 unit of heparin/ml. Two microcultures of [³H]thymidine 15.6 Ci/m mole (The Radiochemical Centre, Amersham) in 0.1 ml of saline was added, and the marrow cells were left at 37°C for 0.5 hr with intermittent shaking. Cells were then washed

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four times and concentrated by centrifugation in a capillary tube, using a microhematocrit centrifuge (Hawksley). The layer of white cells was put in six drops of culture medium and centrifuged onto six slides using a Cytocentrifuge (Shandon, Ltd.). Autoradiographs were prepared using a dipping technique, and after 3 weeks the films were developed and the slides were stained with hemotoxylin and Biebrich scarlet at pH 9.5. Results of the bone marrow studies are shown in Table 1.

**COMMENT**

In this patient, steroids reduced the number of blood eosinophils within 4 hr by 70%. The rate of fall was exponential, which favors the concept of random loss of eosinophils from the blood irrespective of their age, as described by Thompson and van Furth (2) for mouse monocytes following an injection of steroids. Calculations by the method of van Furth and Cohn (3) indicated that during this 4-hr period, the half-life of eosinophils in the patient's circulation was 2.4 hr. Presumably the mechanism of this acute eosinopenic response is an intravascular shift of eosinophils or increased migration into tissues.

Marrow content of eosinophils declined by half, 3 days after steroids were begun, and the proportion of marrow eosinophils in DNA synthesis (S phase) declined by two-thirds. This is compatible with the possibility that steroids had decreased marrow eosinophil production, as the diminished labeling indicated fewer eosinophils in the cell cycle, possibly combined with S phase occupying a smaller proportion of the cell cycle time. Inasmuch as kinetic studies on rat bone marrow eosinophils have shown that alterations in production take 2 days to affect blood levels (4), it seems likely that the decrease in blood eosinophils in this patient came about by two actions of steroids: first, a direct effect on the circulating eosinophils and, later, a reduced

| Marrow Eosinophils | Before steroids | After steroids |
|--------------------|----------------|---------------|
| Eosinophils among 2000 nucleated marrow cells | 118 (5.9%) | 46 (2.3%) |
| Number of labeled eosinophils among 1000 marrow eosinophils | 110 (11%) | 40 (4%) |

*Marrow eosinophils before and 3 days after the patient with Addison's disease was treated with cortisone. Both the content of marrow eosinophils and their DNA synthetic activity were reduced.*
rate of eosinophil production. The effect on eosinophil production may be mediated through an action on lymphocytes, as other studies in this laboratory have provided evidence that eosinophilia is mediated by lymphocytes and that agents which affect body stores of lymphocytes can block the eosinophil response to parasitic invasion (5, 6).

An eosinophilia is occasionally found in Addison's disease. Hills et al. (7) found that 4 of 26 patients with untreated Addison's disease had eosinophil counts greater than 500/mm³. They assumed that the eosinophilia was due to the low levels of circulating steroids, but, if this is so, it is surprising that eosinophilia is not a constant feature of Addison's disease. Autoantibodies to adrenal tissue have been described in 50% of patients with Addison's disease (8, 9). West (10) described a patient with Addison's disease, due to tuberculosis, who had an eosinopenia. The patient described here had both an eosinophilia and adrenal antibodies, raising the possibility that an eosinophilia greater than 500/mm³ before treatment may occur in the autoallergic form of Addison's disease. We have been unable to find any other reports in which pretreatment eosinophil counts have been done in patients shown to have adrenal autoantibodies. Eosinophil counts after treatment has begun would not be helpful, as steroids affect the eosinophil count by the mechanism described in this patient.

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