Hematologic Changes with ACTH and Cortisone Therapy of Rheumatoid Arthritis*

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Most physiologic processes are modified directly or indirectly by hormones. Although no "hemotrophic" hormone has been found, blood formation is frequently altered by endocrine imbalance, and the possibility exists that some blood dyscrasias of obscure etiology may be due to a disturbance of endocrine function. The capacity of ACTH and cortisone to produce profound changes in the peripheral blood of human subjects has been noted incidentally to the treatment of various disorders. However, the mechanism by which these changes are produced and the correlation of changes in the peripheral blood with changes in the bone marrow have not been clearly elucidated. It is the purpose of this study to present information on the changes in the peripheral blood, blood volume, and bone marrow of a group of patients with "mesenchymal disease,"† most of whom were anemic, and who were treated with either ACTH or cortisone. It is hoped that these studies may more clearly establish the role of ACTH and cortisone in the regulation of blood formation.

Materials and Methods

All hematologic observations were made on oxalated venous blood. Hematocrit determinations were done with Wintrobe tubes centrifuged at a relative centrifugal force of 1,800 g for 30 minutes. Reticulocyte counts were done by the method of Osgood and Wilhelm. Hemoglobin was determined colorimetrically by the method of Evelyn. Red cell counts were done in duplicate. Blood volume determinations were performed using the dye T-1824 according to the method of Gibson and Evelyn with a correction factor as described by Gibson et al. Eosinophil counts were done by the direct method. Total polymorphonuclear and lymphocytic leukocytes were estimated from 100 cell differentials with simultaneous total leukocyte counts. Sternal bone marrow aspirations were done with a 14 gauge needle, and smears were stained with Wright's and Giemsa's stains. Eosinophils and their precursors were counted on marrow smears and expressed as number per 1,000 granulocytes.

Submitted February 14, 1951; accepted for publication April 23, 1951.

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Some of these observations were reported at the Second Clinical ACTH Conference, Chicago, III., December 8, 1950, and at the American Federation for Clinical Research Meeting, Atlantic City, N. J., May 1, 1951.

* This investigation was supported in part by research grants from the United States Public Health Service to the Robert Breck Brigham Hospital, and the Atomic Energy Commission to the Massachusetts Memorial Hospitals. ACTH used in these studies was supplied through the courtesy of Dr. John R. Mote of the Armour Laboratories.

† The authors wish to acknowledge the valuable technical assistance of Mrs. Elmar Judd, Miss Mary F. Massol, Miss Emire Matheson, Miss Mary E. Summons and Miss Patricia Anthony.

† We use this term to include rheumatoid arthritis, scleroderma and periarteritis nodosa.

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Experimental Procedure

A total of 20 patients with rheumatoid arthritis or closely allied disorders, most of whom were anemic, were treated with either ACTH or cortisone. Included in this study were 17 patients with either adult or juvenile rheumatoid arthritis, 2 with scleroderma and 1 with periarteritis nodosa. Detailed hematologic studies were made before, during, and after the first course of therapy. These studies consisted of erythrocyte indexes, total leukocyte and differential counts and direct eosinophil counts at not less than weekly intervals. Daily reticulocyte counts were performed for the first 15 days, and then at intervals of 5 to 7 days. Bone marrow aspirations were done whenever possible on the first and last days of treatment, and, in a few instances, during the course of treatment. Blood volumes were usually performed on the first, tenth, and twenty-first days.

In all but 3 patients the first course of therapy consisted of twenty-one consecutive days of either ACTH or cortisone administered intramuscularly in divided doses at 6 hour intervals. The 3 exceptions (R.H., N.T., A.S.) were children who were treated for only fifteen days. Twenty-nine additional courses of therapy, ranging from four to fifty-three days, were administered to these same patients, and are reported in less detail (table 1). The usual ACTH dosage was 40 mg. a day for the adults, and 20 mg. a day for the children. Those adults receiving cortisone were given 100 mg. a day, while the children received 50 mg. a day. In all, 14 patients were given ACTH and 6 received cortisone. The daily dose of drug administered to each patient remained constant in most instances, but in a few cases it was increased or decreased by 10 to 20 mg. a day during therapy.

The patients with rheumatoid arthritis were hospitalized for periods of from a week to several months before treatment was initiated. All had severe active joint disease associated with fever and elevated sedimentation rates. Many had been completely refractory to other protracted forms of therapy. The patients with scleroderma and periarteritis nodosa were also in very active phases of their diseases.

Observations

1. Clinical Response to Therapy

The total therapeutic response to ACTH and cortisone, although about equal was poorly correlated either with the degree of depression of the peripheral eosinophils or rise in 17-ketosteroid excretion. ACTH appeared to act more rapidly, but disturbing side effects were more common (table 1). In general, therapy resulted in marked decrease in joint pain, redness, swelling and tenderness during the first week with an associated fall in temperature and sedimentation rate. The beneficial effects were well maintained or bettered with continuation of hormone administration, but with cessation of therapy most patients relapsed within two weeks. There were only 2 poor clinical responses (A.Z. and N.H.) observed during the period of intensive hematologic study. Increases in weight and appetite, and moderate to marked euphoria were frequently observed, and 1 patient (A. N.) developed a marked but temporary psychic disorder while on ACTH. The details of these clinical responses are to be reported elsewhere.12

2. Reticulocyte Response

Reticulocytosis of significant degree occurred in every patient, although its magnitude was not closely correlated with the severity of the initial anemia (table 2).* The peak was reached at about the ninth day in patients receiving

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* Tables 2, 3, and 4 have been deposited with the American Documentation Institute, 1719 N. St., N. W., Washington 6, D. C. For copies of these tables order document number 3357 directly from the American Documentation Institute, remitting $1.00 for microfilm or photoprints, specifying which is desired.
### Table 1.—Clinical and Hematocrit Response to ACTH and Cortisone Therapy

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J. D.  
- **Rheumatoid arthritis**  
- Good clinical response to cortisone followed by severe relapse.  
- Good remission while on therapy followed by prompt relapse.  
- Response as before, but with slower relapse.  
- Good response to drug followed by slight relapse.

N. H.  
- **Rheumatoid arthritis**  
- Poor clinical response to cortisone.  
- No clinical response.  
- No clinical response to therapy with further drop in htc. to 33.8 one month later.
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ACTH, while the average peak did not occur until the thirteenth day with those receiving cortisone (fig. 1).

Fig. 1.—Reticulocyte change with ACTH and cortisone. The curves represent the average changes in reticulocytes of the cortisone and ACTH treated patients during and after twenty-one days of therapy.

Fig. 2.—Hematocrit change with ACTH and cortisone. The curves represent average hematocrit values of all patients treated with either ACTH or cortisone for twenty-one days.

3. Erythropoietic Response

In patients with anemia, hematocrit, hemoglobin and red cell levels rose toward normal concomitantly with the clinical response (tables 1 and 3, fig. 2).
Two adult patients (H. C., A. N.), who had no anemia in spite of active disease, failed to demonstrate any increase in hematocrit or red cell mass under therapy, even though a good clinical response was obtained. It was also noted that the anemic patients (N. H., E. A., A. Z.) who had poor clinical responses to therapy failed to show significant improvement in their hematocrits. Initially and throughout the period of therapy erythrocyte indexes remained normocytic and normochromic. Blood volume determinations performed on anemic subjects demonstrated an absolute increase in red cell mass in response to therapy, an increase which averaged 18 per cent (fig. 3). Although 2 of the children (R. R., A. S.) developed high normal hematocrits, polycytemic levels did not occur in any patient even though second or third courses of therapy were given to many patients. After discontinuation of therapy, if the underlying disease state relapsed there was invariably a recurrence of anemia.

4. Leukocyte Response

A polymorphonuclear leukocytosis of variable magnitude occurred in all patients, and was generally most marked in the younger subjects (A. S., N. T., D. P., J. D.) (table 4). The type and degree of response followed no uniform pattern, but was slightly different to ACTH and cortisone (fig. 4). Although most patients showed some initial drop in circulating lymphocytes, lymphopenia was not consistently observed and was not sustained (table 4, fig. 5); however, eosinophils remained depressed throughout therapy in most instances. ACTH appeared to exert a more profound effect in depressing lymphocytes and eosinophils than did cortisone. It was of considerable interest that there was often a poor correlation between the degree of depression of eosinophils and either the extent of clinical or erythropoietic response.
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Fig. 4.—Per cent polymorphonuclear change with ACTH and cortisone. The curves represent average per cent change from pretreatment polymorphonuclear leukocyte levels during twenty-one days' therapy with ACTH and cortisone. The absolute values are included in table 4.

Fig. 5.—Per cent lymphocyte change with ACTH and cortisone. The curves represent average per cent change from pretreatment lymphocyte levels during twenty-one days of therapy with ACTH and cortisone. The absolute values are included in table 4.

5. Bone Marrow

Initial bone marrow studies usually revealed moderate depression of erythroid elements, but granulocytic precursors (including eosinophilic type cells) were
present in normal numbers. At the conclusion of therapy eosinophils and their precursors either remained normal or were slightly increased in spite of profound eosinopenia in the peripheral blood (fig. 6). The marrow showed no significant hyperplasia of granulocytic or erythroid elements, although the latter were more nearly normal during and following therapy than before. No morphologic or quantitative changes were noted in the megakaryocytes or blood platelets.

6. Blood Volume

The initial average total blood volumes of the male subjects were 96 per cent of predicted normal, while those of the females were only 79 per cent of predicted normal, as calculated from the relationship of height to blood volume. At the end of therapy there was little change in total blood volume in either the ACTH or the cortisone treated group. The nonanemic subjects showed no significant change in cell mass. In marked contrast, however, the anemic subjects in each group showed an average increase of red cell mass amounting to 18 per cent (fig. 3). This represented average increases of 19 per cent in the females and 12 per cent in the males studied.

7. Variation in Response

Certain striking differences in hematologic response to ACTH and cortisone were noted. The reticulocyte response to ACTH was earlier than it was with cortisone, but was less sustained. Similarly, the leukocytosis appeared slightly

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**Fig. 6.—Eosinophil response to ACTH and cortisone.** The top panel shows the relative number of eosinophilic type cells in the bone marrow per 1,000 granulocytes at the beginning and end of therapy. Peripheral total eosinophils per cu. mm. at corresponding times are shown in the lower panel.
earlier under ACTH than with cortisone. These differences closely parallel the differences in clinical response which were usually slower with cortisone. In general, there was much less marked depression of circulating eosinophils in the cortisone treated group.

Another profound variation in response was the difference in effect on body water. Thus, shortly after the initiation of ACTH therapy there was a transient drop in hematocrit; whereas following the cessation of therapy there was a sharp but unsustained hematocrit rise (table 1, fig. 2). The post-therapy hematocrit rise correlated well with the changes in fluid balance, body weight, and with the method of withdrawing effective adrenal cortical stimulation (fig. 7). These changes were absent or minimal with cortisone.

**DISCUSSION**

The most striking and probably the most significant hematologic effect of ACTH and cortisone which we have observed in this study was the acceleration of red blood cell formation and the increase in total circulating red cell mass. All of our anemic patients showed definite reticulocytosis with a subsequent rise in red cell, hemoglobin and hematocrit levels, often to normal. Blood volume determinations proved that these changes represent absolute increases in red cell mass and not hemoconcentration. The average increases in red cell mass amounted to 18 per cent in 21 days, or 0.86 per cent per day, a rate which, interestingly, is approximately the same as the rate of normal red blood cell replacement.14
What is the mechanism by which these hormones bring about the marked increase in circulating red cell mass? Several possibilities exist: (1) correction of a deficiency of erythrocyte “building substance”; (2) reduction in the rate of erythrocyte destruction; (3) a “specific marrow stimulation”; and (4) release of the marrow from an “inhibiting process.”

The anemia existing in patients with these diseases is not due to any deficiency in iron, vitamin B₁₂, folic acid, or other vitamins, and the administration of these preparations has no beneficial effect. Abnormalities in the function of the pituitary, adrenal and thyroid glands are associated with abnormalities in hematopoiesis,¹ ² and the relative depression of adrenal cortical function of some patients with active rheumatoid arthritis has been recognized.¹⁵ The possibility exists that the anemia of our patients may have been related to endocrine deficiency. Although 3 patients (H. A., E. A., R. G.) had abnormally low pretreatment 24 hour 17-ketosteroid excretions, the other patients were normal, and all had intact pituitary-adrenal axes as measured by the 4 hour epinephrine¹⁶ and ACTH¹⁷ tests. Since there was demonstrably normal pituitary and adrenal function present in our patients, it appears improbable that their anemia was attributable to a deficiency in these hormones, or that the improvement in red blood cell levels following administration of ACTH or cortisone was due to correction of a deficiency of these substances.

It is unlikely that a decrease in the rate of erythrocyte destruction explains the beneficial effects observed in our patients. Although ACTH therapy relieves certain types of acquired hemolytic anemia by reducing the rate of hemolysis,¹⁸ there is no evidence that it reduces the rate of red cell breakdown in normal subjects.

In the pretreatment period none of our patients showed evidences of increased hemolysis (there was no bilirubinemia, reticulocytosis or erythroid hyperplasia). Furthermore, relief of hemolytic mechanisms would not account for the reticulocytosis observed in our patients in response to therapy.

The possible existence of bone marrow “stimulants” has been hypothesized repeatedly, but the physiologic mechanism of lowered oxygen tension remains the only unequivocally proven stimulant of erythropoiesis. Because of the profound hematologic effects seen in patients receiving ACTH and cortisone, it has been suggested¹⁹, ²⁰ that these hormones actually are marrow stimulants. Without entering into a discussion of the semantics of the concept of bone marrow “stimulants,” in our opinion the responses in our patients do not indicate responses to a “stimulant.” Although 2 children developed high normal hematocrits, none of our patients reached polycythemic blood levels even though some had little or no anemia prior to treatment, and several patients had protracted courses of therapy. Those patients with the most severe arthritis and anemia before treatment, in general, showed the better hematologic response although it would seem that patients who were the least ill and debilitated would have been capable of the best response to any true stimulant. The anemia improved in our patients only if they exhibited a good clinical response to therapy. Finally, the bone marrows of our patients did not show erythroid hyperplasia after twenty-one days of therapy, although such hyperplasia would have been expected if the marrow actually had been “stimulated.” It is possible that
with more intensive and more prolonged ACTH and cortisone administration the magnitude of the erythropoietic response might have been enhanced, but our observations make this appear improbable.

We believe that the most probable explanation of the erythropoietic action of ACTH and cortisone appears to be that by controlling the underlying inflammatory disease (rheumatoid arthritis, scleroderma, etc.) they release the bone marrow from the depressant effects of these diseases and allow a resumption of normal hematopoietic function. The mechanism by which inflammatory disease inhibits erythropoiesis is beyond the scope of this discussion, but that such an inhibitory effect is exerted is well established. Removal of the inflammatory process (e.g., excision of an abscess) allows blood regeneration to proceed normally. ACTH and cortisone therapy unequivocally suppress inflammatory disease and it appears probable that this suppression of inflammation in our patients acts in a fashion analogous to excision of a local abscess, and allows the marrow to resume normal function. This explanation is strongly supported by the fact that erythropoietic response occurred only in those patients who showed improvement in their underlying disease—if ACTH or cortisone therapy did not alleviate their arthritis there was no improvement in their anemia.

Therapy characteristically produced a neutrophilic polymorphonuclear leukocytosis, and an eosinopenia. In most patients there was a decrease in lymphocytes but this was not sustained, and there was no absolute lymphopenia in any patient at any time. Patients treated with cortisone usually showed less change in the leukocyte picture than did those treated with ACTH. Hills et al. obtained similar results, but Dougherty and White found a constant lymphopenia in animals given ACTH.

A significant observation was the persistence of eosinophilic leukocytes and their precursors in normal or increased numbers in the bone marrow of our patients while under therapy, even though there was marked eosinopenia in the peripheral blood. This observation suggests that the eosinopenia is due to increased destruction or peripheral sequestration of eosinophils. However, to our knowledge the in vitro destruction of eosinophils exposed to either cortisone or “stressed” plasma has not been demonstrated. The possibility exists that there is “failure of release of eosinophils” from the marrow, but it appears improbable in view of the observed normal maturation of the marrow eosinophils, and the increased rate of release of the other marrow elements (erythrocytes and neutrophilic leukocytes). If the eosinopenia were due only to “failure of marrow release,” the probability would exist that the life span of the eosinophil was 4 to 5 hours, since normally 70 to 100 per cent of them disappear from the peripheral blood within 4 hours following the administration of ACTH.

The rapid but transient decrease in hematocrit following the administration of ACTH is believed to be caused by hemodilution. Following the administration of ACTH the adrenal cortex is stimulated to release increased amounts of various adrenal cortical substances, including salt-retaining hormones. In response to this there is salt and water retention and consequent hemodilution. With the continuation of ACTH therapy pituitary function is depressed with consequent reduction of endogenous ACTH production so that when the exo-
genous supply is abruptly stopped, adrenal cortical stimulation is negligible. This state of relative hypoadrenalism may last for six to eight days before pituitary-adrenal function is again restored, and it is during this period of time that a marked diuresis occurs with an associated hemocoagulation. It is interesting that the average percentage increase in hematocrit was almost identical to the average decrease in body weight during this post-therapy phase (fig. 7). When ACTH therapy was gradually reduced there was a gradual return of pituitary-adrenal function to normal, and these marked changes in fluid balance and hematocrit did not occur (fig. 7). Cortisone therapy, on the other hand, produces no adrenal cortical stimulation and, therefore, had less capacity for producing these fluid shifts (fig. 7), in the dosages employed in this study.

How do our observations coincide with available information relating to the role of pituitary and adrenal cortical hormones in hematopoiesis? Moderate anemia, neutropenia, and lymphopenia have been described in experimental hypophysectomy,1 panhypopituitarism,2 26 and Addison’s disease.3 24 27 It has been suggested that these blood changes are a direct reflection of the hormonal deficiency on the bone marrow. Another possible explanation of some of these changes is that they may be secondary to the disordered metabolism produced by endocrine deficiency. Overproduction of adrenal cortical hormones, seen clinically in Cushing’s disease, may be associated with polycythaemia, neutropenia, lymphopenia25 and eosinopenia,29 observations suggesting specific effects of adrenal hormones on the blood or bone marrow.

Experimentally, prolonged stimulation of the adrenal cortex in animals may produce a rise in erythrocytes, hemoglobin, and neutrophils and a persistent lymphopenia.24 25 However, our observations, and those of others21 29 do not corroborate all of these findings, raising the question of species variability. It is well recognized that most of the effects of ACTH depend upon the presence of adrenal tissue capable of function. Similarly, our observations would tend to indicate that ACTH produces no direct erythropoietic effect on the bone marrow, since patients (N. H., E. A., A. Z.) who had either little adrenal cortical or clinical response also failed to show an improvement in their anemia.

Striking hematologic effects have been described in leukemic patients treated with ACTH1 19 30 31 and frequently there has been restoration of peripheral blood and bone marrow to an almost normal state. In several leukemic patients treated with ACTH by us when there was no beneficial effect on the leukemia there was no evidence of bone marrow “stimulation,” or improved red blood cell regeneration.18 Furthermore, in patients with “aplastic” or “hypoplastic” anemia we have observed no improvement in response to ACTH therapy.18 Finally, several patients with polycythaemia, secondary to bronchial asthma, showed a reduction in their red cell levels in response to ACTH therapy.19 These observations suggest that the hematologic effects of ACTH therapy in various disease states in large measure are dependent on the effect of the therapy on the underlying disease state itself, and that many of the blood changes are secondary to improvement in the underlying disease. What effects prolonged therapy with ACTH or cortisone may have on the blood and hematopoietic system of “normal” man still remains to be determined.
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SUMMARY AND CONCLUSIONS

1. Detailed hematologic observations, bone marrow aspirations and blood volume determinations were made on 20 patients with rheumatoid arthritis and allied disorders before, during and after the administration of either ACTH or cortisone.

2. Significant reticulocytosis occurred in every patient during therapy, but its magnitude was poorly correlated with either the initial degree of anemia or subsequent increase in circulating red cell mass.

3. There was an increase in hematocrit and total circulating red cell mass of all anemic patients who responded clinically to either ACTH or cortisone. There was little or no improvement of anemia when the clinical response was poor.

4. Polycythemia did not occur in any patient during prolonged therapy or with repeated courses of either ACTH or cortisone.

5. Hemodilution and hemoconcentration were much more profound during and after ACTH administration than they were with cortisone.

6. Bone marrow studies revealed moderate depression of the erythroid series before treatment. At the end of therapy erythroid elements were normal.

7. Significant polymorphonuclear leukocytosis occurred in all patients during therapy while lymphopenia was inconstant and unsustained. Circulating eosinophils were depressed more with ACTH than with cortisone treatment.

8. Before treatment eosinophils and their precursors were present in the bone marrow in normal or increased numbers. During therapy the number of these cells was unchanged in the marrow, even when there was profound peripheral eosinopenia.

9. The role of ACTH and cortisone in the physiologic mechanism of hematopoiesis is discussed.

10. The improvement in the anemia associated with inflammatory disease in response to ACTH or cortisone therapy probably is a reflection of the control of the underlying disease rather than a primary “stimulation” of the bone marrow.

ADDENDUM

The doses of ACTH and cortisone administered to the patients reported in this study were small, and the possibility should be considered that larger doses of these substances might result in different hematopoietic effects. Subsequent to the preparation of this manuscript we have observed a similar group of patients treated with 500 mg. of cortisone a day for periods of from two to four weeks. The hematopoietic responses were essentially the same as those observed in these patients. These observations will be reported subsequently.

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Hematologic Changes with ACTH and Cortisone Therapy of Rheumatoid Arthritis

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