The Use of Adrenocorticotropic Hormone and Cortisone in the Treatment of Leukemia and Leukosarcoma

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During the past eighteen months, interest in the clinical use of adrenocorticotropic hormone (ACTH) and cortisone has become quite general. For some time, the limited supply of these hormones, together with a lack of knowledge as to their ultimate effects on the organism, necessitated their use as investigational tools only. As knowledge of their action was gained and the supply increased, clinicians in many fields were quick to seize upon these hormones as possible therapeutic agents in the treatment of diseases which had hitherto been unresponsive to most methods of treatment. The beneficial results obtained in certain cases has, in some measure, justified this hope although the rationale for use of the hormones has not always been clear.

The work of Dougherty and White focused attention anew on the reciprocal relationship between the adrenal cortex and lymphoid tissue. Their observations on the morphologic changes which occurred in lymphoid tissue and lymphocytes following adrenal cortical stimulation suggested that the adrenal glands might have an effect on leukemic proliferation. At their suggestion, one of usa treated 2 cases of chronic lymphocytic leukemia in 1943 with crude pituitary adrenotropic hormone extract daily for two weeks but since negative results were obtained, further studies were not carried out.

In 1944, Murphy and Sturm gave intraperitoneal injections of leukemic cells followed “some hours later” by injections of a hormonal preparation to rats of a strain highly susceptible to transmitted lymphocytic leukemia. When crude pituitary adrenotropic hormone was used, the survival rate was increased from the control rate of 5 to 10 per cent to more than 40 per cent. With adrenal cortical extracts, the survival rate was 20 to 60 per cent. In the same year, these authors showed that adrenalectomy greatly increased the susceptibility of rats to transplantable lymphocytic leukemia.b

In 1947, Nordenson reported little or no effect on the blood picture of 2 patients with chronic lymphocytic leukemia following the administration of a single injection of 150 mg. ACTH to one patient, and 212.5 mg. over a fifteen day period to the other.

Hellman in 1949, stated that little change occurred in humans with chronic
lymphocytic leukemia given single small doses of purified ACTH. More recently, Pearson et al.\textsuperscript{7} reported "dramatic and progressive" decrease in the size of the lymph nodes and spleen of patients with lymphoid tumors during treatment with ACTH or cortisone. The 4 patients with chronic lymphocytic leukemia at first showed a marked rise in total white blood cell count during hormone therapy; later, the count dropped below the initial level.

In April 1950 we reported our experiences with the use of ACTH in 8 cases of acute and subacute leukemia.\textsuperscript{8} The immediate results were often strikingly beneficial and in 5 of the 8 cases outspoken remissions with subjective, objective, hematologic and marrow responses occurred. The temporary nature of these remissions was recognized, and indeed the further course of these cases, all in children, has been far from satisfactory. It is the purpose of the present report to relate the further course of these patients, and in addition to report upon an additional group of 34 cases of leukemia and leukosarcoma\textsuperscript{*} treated with ACTH. These cases include acute, subacute and chronic leukemia; lymphosarcoma; Hodgkin's disease; multiple myeloma; and lymphosarcoma with symptomatic hemolytic anemia. On the basis of this experience with 42 cases, we believe that ACTH and cortisone have a distinct but limited and temporary value in certain selected cases of leukocytic proliferations.

**MATERIALS AND METHODS**

The details of procedure have been stated previously.\textsuperscript{9} Diagnosis was made by appropriate studies of cell morphology of peripheral blood and bone marrow. Lymph node biopsies were performed when indicated. In the overall series, there were 27 patients with some form of leukemia, 5 with multiple myeloma, 5 with Hodgkin's disease and 5 with lymphosarcoma. All of the patients with multiple myeloma (aleukemic plasmocytic leukemia) showed occasional plasma cells in the peripheral blood on careful search. One of the cases of lymphosarcoma was in the leukemic phase of this disease when treatment was begun. All the patients were hospitalized during the initial weeks of therapy and those who improved sufficiently were followed on an ambulatory basis while therapy was continued at home. Transfusions were withheld as far as possible after hormonal therapy was begun although in some cases this was not feasible. Antibiotics were given if complicating infection was present, and as a prophylactic measure if extreme peripheral granulocytopenia developed.

The first group of patients was treated with ACTH supplied us by Dr. E. B. Astwood and associates.\textsuperscript{11} Later cases received either Corticotropin (ACTH, Wilson) or Armour, ACTH. When the former was used, our dosage schedule in adults was 15 or 20 mg. subcutaneously every eight hours. The Armour product was usually given in doses of 20 mg. every six hours and smaller doses were used in children. There was considerable latitude in the dosage from patient to patient as well as at different intervals in the course of any one patient. Patients on ambulatory therapy were maintained on lower dosages (20 to 40 mg. /day). More recently, cortisone\textsuperscript{t} has been used frequently, particularly for maintenance therapy; this has been particularly true with the introduction of the oral preparation. The dosage of cortisone employed ranged from 100 to 150 mg. daily either intramuscularly or orally.

Detailed studies of electrolytes were not ordinarily made. Pre-treatment determinations of serum proteins, sodium, potassium and chlorides as well as of blood sugar and nonprotein nitrogen were always made and subsequent determinations were made according to the indications present in a given case. In the cases of multiple myeloma frequent determi-

\textsuperscript{*} The term leukosarcoma is used for a more or less localized leukocytic neoplasm such as lymphosarcoma, reticulum cell sarcoma and the like.

\textsuperscript{t} Generously supplied through the courtesy of Drs. James Carlisle and Augustus Gibson, Merck Chemical Company, Rahway, N. J.
nations of serum proteins and of the sedimentation rate were made. Originally, the attempt was made to control salt and water retention by omission of table salt from the diet. Since in several cases this measure was inadequate, the policy was then adopted of placing all patients on specially prepared 0.5 Gm. low salt diets as soon as the ACTH treatment was begun. The use of supplementary potassium did not become necessary in any of the cases but mercurial diuresis was required to relieve edema in a few instances.

RESULTS (table 1: see note, page 823)

1. Acute and Subacute Lymphocytic Leukemia

Fifteen cases in this category were treated. Three died during therapy; 1 after an adequate course of therapy and 2 after only a few days. Of the remaining 12, 9 developed remissions of varying degree and duration; 3 showed no response. Remissions in most cases were heralded by the development of a marked reticulocytosis with peak values occurring from the eighth to the twenty-seventh day of therapy. The reticulocyte response was usually followed within one to several days by a marked increase in platelets. A well-defined rise in red cell count and hemoglobin then took place. The response in the total white count was variable. In general two patterns were noted: those patients who were leukopenic, whether intrinsically or secondary to previous therapy showed a rise in leukocyte count to normal or slightly leukocytic levels. On the other hand, patients in whom therapy was begun at normal or slightly elevated leukocyte levels showed an initial fall in the total white count. This was usually associated with a disappearance of lymphocytes and lymphoblasts and was followed by a secondary rise.

Those cases responding favorably to therapy showed a gradual disappearance of primitive leukocytes with a reversion of the differential formula to normal. Serial bone marrow observations showed parallel changes.

The duration of remissions was brief, ranging from one to ten weeks and seemingly little influenced by maintenance therapy. Relapse was heralded by the reappearance of considerable numbers of lymphoblasts, recurrence of severe anemia and thrombocytopenia. In 2 cases showing relapse (Cases 5 and 6) a curious phenomenon was noted, namely, the development of extreme leukocytosis and eosinophilia. In one of these cases, this was so striking as to have been suggestive of chronic granulocytic leukemia had the patient’s previous history not been known. Retreatment in relapse was often capable of inducing remission a second, third or even a fourth time. However, eventual refractoriness finally developed in every case, and was associated with the development of the striking “side effects” of this type of hormonal therapy.

Remissions occurred very consistently in children but developed in only one of the six adults, a physician age 34.

CASE REPORTS


This 5 year old female child was first admitted to the Boston Floating Hospital on January 4, 1950 because of anemia, fever, vomiting, occasional left-sided abdominal pain and lymphadenopathy of approximately three months’ duration. Positive findings on admission were (1) pallor of skin and mucous membrane, (2) enlarged, nontender, inguinal, cervical and left axillary lymph nodes and (3) hepatomegaly. Blood counts done on admission revealed a moderate anemia (R. B. C. 2.71 M; hemoglobin 6.9 Gm.), leukopenia
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(W. B. C. 3,200), thrombocytopenia (platelets 27,800), lymphocytosis (80 per cent) and lymphoblasts in the peripheral blood. Bone marrow studies showed a hypocellular marrow in which the predominating cells were lymphoblasts (46.5 per cent) and lymphocytes (47 per cent). During the first four hospital days three blood transfusions of 250 cc. each were given. On the tenth hospital day, ACTH therapy begun in a dosage of 40 mg. daily for eleven days and 30 to 20 mg. daily for seven days. There was marked clinical and hematologic improvement (table 1) and the bone marrow became essentially normal except for slight increase in mature lymphocytes (27 per cent). An attempt to maintain remission with 20 mg. of ACTH weekly was unsuccessful. Three clinical and hematologic relapses took place with successive remissions induced by ACTH therapy from April to August 1950. ACTH was usually started at a dosage level of 40 mg. daily and tapered off to 30 mg., 20 mg. and 10 mg. daily when signs of remission became evident. Signs of relapse reappeared soon after the dose was reduced to 20 mg. or less. Remissions were of shorter duration with each successive course of treatment, the latest one lasting only about two weeks.

ACTH therapy resulted in various physical changes such as considerable increase in weight, a round face, mild elevation of blood pressure, hirsutism and acne.

Case 9; Reed G.; B.F.H. 14634; age, 4; sex, male. This 4 year old white male child was first admitted to the Boston Floating Hospital on February 10, 1949 following the appearance of generalized ecchymoses of ten days' duration, easy fatigability of three months' duration and progressive pallor of four to five months' duration. Positive physical findings on admission were: petechiae of head, trunk, extremities, and oral mucous membrane, cervical, axillary, inguinal and epitrochlear lymphadenopathy, hepatomegaly, and splenomegaly. Blood counts were as follows: R.B.C. 3.18 M., hemoglobin 11 Gm., platelets 59,250, W.B.C. 34,100 with a differential count of 11 per cent polys., 60 per cent lymphocytes, 1 per cent myelocytes and 38 per cent lymphoblasts. Bone marrow aspiration revealed a "pure culture" of lymphoblasts. The patient was treated with aminopterin with the induction of a complete remission.

With the exception of minor relapses, the patient did well for approximately eight months after discharge, but about one month later, he was readmitted to the hospital because of purpuric areas over the entire body, bilateral subconjunctival hemorrhages, and low grade fever of about one week's duration. Physical examination revealed pallor and lethargy, bilateral subconjunctival hemorrhages, multiple ecchymoses over the lower extremities, hepatomegaly, and splenomegaly. Blood counts on admission were as follows: R.B.C. 2.91 M., hemoglobin 8.7 Gm., platelets 52,380, W.B.C. 21,000 with a differential count of 4 per cent polys., 60 per cent lymphocytes, 1 per cent myelocytes and 38 per cent lymphoblasts. Bone marrow aspiration revealed a normocellular marrow with 93 per cent lymphoblasts and 7 per cent lymphocytes; megakaryocytes and nucleated red cells were conspicuously reduced.

On the third hospital day, ACTH therapy was begun in the following doses: 40 mg. daily for nine days; 20 mg. daily for nineteen days, and 10 mg. daily for ten days. A striking clinical and hematologic remission (table 1) was obtained and the bone marrow reverted to an almost normal picture with 3.6 per cent lymphoblasts and 28 per cent lymphocytes.

One month after discharge, the patient was readmitted because of fever, cough, anorexia, thrombocytopenia, leukocytosis and numerous lymphoblasts in the peripheral blood. Physical examination again revealed generalized lymphadenopathy, hepatosplenomegaly and petechiae and ecchymoses throughout the entire body. The blood counts at this admission were as follows: R.B.C. 4.15 M., hemoglobin 13.3 Gm., platelets 54,900, W.B.C. 21,000 with a differential count of 4 per cent polys., 36 per cent lymphocytes, and 60 per cent lymphoblasts. ACTH therapy was again given for fifty-five consecutive days but no improvement was evident either clinically or hematologically. The marked physical changes of prolonged ACTH therapy became evident.

2. Acute Granulocytic Leukemia

Five cases, all adults, were treated. Two patients were uninfluenced; 1 patient showed a slight to moderate improvement, but 2 were apparently made worse by therapy, 1 of these dying while on therapy. In the latter 2 cases, features
suggesting intensification of the leukemic process were increasing "toxicity," a rapidly rising white cell count and a falling platelet count. The single patient who showed a favorable response displayed distinct subjective improvement, disappearance of "toxicity," decrease in organ enlargement, some decrease in total white cell count and immature forms, reticulocytosis, and distinct thrombocytosis. However, relapse soon occurred and the patient died six weeks after leaving the hospital.

Case 20; Mary P., N.E.C.H. 50-210. A 55 year old married woman was admitted to the hospital on January 22, 1950 with the complaint of weakness. The diagnosis of subacute leukemia had been established in May 1949 following a five month history of fatigue, easy bruising, and swollen gums. Aminopterin was given at that time with a striking remission. In October 1949 the patient was rehospitalized because of relapse. Aminopterin was again administered this time with only partial response.

The patient remained relatively well until the end of December at which time she developed a severe respiratory infection. Cough, fever, pleuritic pain and cervical adenopathy were present. Although these symptoms subsided the patient lost weight and subsequently the fever returned. She was hospitalized for further therapy.

On admission the patient showed slight cervical lymphadenopathy, enlargement of the spleen and liver which were felt a handbreadth beneath their respective costal margins, bilateral pretibial edema and slight gingival hypertrophy.

Blood examination showed: R.B.C. 2.19 M., hemoglobin 9.3 Gm., reticulocytes 1.2 per cent, platelets 333,000, leukocytes 22,600 with polys. 19 per cent, lymphocytes 19 per cent, monocytes 6 per cent, eosinophiles 1 per cent, promyelocytes 6 per cent and 47 per cent blast forms. Bone marrow aspiration revealed an extremely hypercellular marrow compatible with the diagnosis of subacute granulocytic leukemia.

The use of ACTH was followed by marked subjective improvement and improvement in appetite. However, the white blood cell count rose from an initial level of 22,600 to a high of 197,000 within twelve days. There was no essential change in the differential count nor
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Fig. 2.—Morphologic changes in blood and bone marrow of acute leukemia on ACTH therapy.
A. Peripheral blood before therapy. Blasts predominate and few platelets are present.
B. Peripheral blood at height of remission. No blasts are present, and adult leukocytes and platelets are now seen.
C. Bone marrow before therapy. The marrow is replaced by a uniform, primitive cell.
D. Bone marrow at the height of remission. The normal cellular constituents have returned with only a few blasts cells remaining.

in reticulocytes or platelets. The patient then developed a febrile course and despite transfusions and antibiotics became progressively worse. The quick intensification of the leukemic process appeared to be due at least in part to the administration of ACTH.
3. Acute Monocytic Leukemia

Two cases of acute monocytic leukemia treated with ACTH were both in critical condition at the time of administration and succumbed after two and three days respectively. These patients, like those with granulocytic leukemia treated with ACTH, showed a strikingly rapid rise in white blood count and a fall in platelets with widespread hemorrhagic phenomena.

4. Chronic Lymphocytic Leukemia

A total of 5 cases were treated. These cases although few in number are best discussed in three separate categories. Two were middle-aged males with long standing leukemia whose disease had reached a terminal accelerated phase with anemia and refractoriness to x-ray therapy. The first of these showed slight improvement with a rise in hemoglobin values from 8.3 to 9.8 Gm. and a tran-

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Note: (a) Drop in R.B.C. and hemoglobin between August 1949 and April 1950. (b) Failure of 2000 cc. transfused blood to raise R.B.C. significantly. (c) Rise in reticulocytes after 18 days of ACTH followed by return of R.B.C. to high level. (d) Per cent lymphocytes failed to respond to ACTH. (e) Gradual rise in white count. (f) Gradual rise in platelets.

Concomitantly, the white blood cell count rose from 65,000 to 315,000. The overall clinical picture was not improved. The second of these patients (Case 24, following) showed a remarkable response.

Case 24, Kopland M., N.E.C.H., 49-024. A 53 year old male physician was admitted to the hospital on March 31, 1950 with the diagnosis of chronic lymphocytic leukemia. The diagnosis had been made in mid 1949 and x-ray therapy was given with an excellent response, the white count dropping to normal levels. In December 1949 the white count was 12,000 and the red cell count five million. The patient remained well until the middle of March 1950 when he noted tachycardia and exertional dyspnea.

Physical examination on admission revealed slight pallor, and slight generalized lymph node enlargement. There was no splenomegaly.

The laboratory data: hemoglobin 6.2 Gm., R.B.C. 2.1 M., reticulocytes 0.6 per cent, platelets 199,000, white count 19,800, polys. 28 per cent, lymphocytes 18 per cent, monocytes 3 per cent and young lymphocytes 51 per cent. The urine showed a very slight trace of albumin with many red blood cells per high power field. Bone marrow aspiration revealed
a hypocellular marrow grossly infiltrated with lymphocytes and showing scanty erythropoiesis.

The patient was started on ACTH on the seventh hospital day. Administration was complicated by a tendency to excessive fluid retention with incipient left ventricular failure. This responded readily to decreased dosage and mercurial diuretics.

Almost at once the patient showed marked subjective improvement. His appetite became voracious and he exhibited marked euphoria. The adenopathy receded until only a small right supraclavicular node was palpable.

There was a slight increase in reticulocytes to 4.6 per cent, followed by a progressive increase in red cell count and hemoglobin. The white count showed a tendency to seek higher levels while the platelet count remained unchanged. Bone marrow aspiration revealed no essential alteration in the basic picture despite the hematologic improvement. Following discharge on April 30, 20 mg. of ACTH were given twice daily. After two weeks of this therapy, polyuria and glycosuria were noted with a blood sugar of 500 mg. per cent. ACTH was discontinued and in four days the fasting blood sugar was 143 mg. per cent. Insulin tolerance test showed a 50 per cent reduction of the blood sugar level within thirty minutes indicating ready sensitivity to insulin. It was decided to maintain the patient henceforth on ACTH 10 mg. twice daily.

On continued administration the patient developed some cutaneous pigmentation and rounding of the face. Neither fluid retention nor diabetes constituted any problem. He felt quite well and the red count and hemoglobin were well maintained without resort to transfusions. The platelets rose gradually until they reached normal levels. The white count continued to show a progressive rise.

Two cases were treated in which the chief manifestation of leukemia was a marked degree of skin infiltration with the picture of erythroderma and exfoliative dermatitis. Neither case showed any significant change in hematologic findings while on therapy, but in each instance, subjective and objective improvement in the dermatologic findings took place within twenty-four hours reaching its peak in one week. There was diminution of pruritus, desquamation, erythema, induration and edema. Both patients required high dosage maintenance therapy to remain in remission and both relapsed after three to five weeks of continuous therapy. It is noteworthy that skin biopsies performed during therapy showed no essential change in histologic appearance.

One patient with chronic lymphocytic leukemia associated with symptomatic hemolytic anemia has been reported in detail elsewhere. This complication responded well to ACTH therapy with the complete disappearance of all evidences of hemolysis.

5. Lymphosarcoma

Five cases of lymphosarcoma were treated. Three cases with marked organ enlargement (liver, spleen, nodes, abdominal masses) showed dramatic regression of infiltrates. Two of these cases had in addition hemolytic anemia which was strikingly benefited. One case showed a moderate recession in adenopathy together with a rise in red cell count, while another case showed a decrease in “toxicity” and recession of adenopathy. In 3 of the 5 cases, the leukopenia which had been present prior to therapy disappeared during ACTH administration. In every case the remissions, although at first striking, were of only temporary nature and persisted at most three to four months with continued maintenance therapy.
6. Hodgkin’s Disease

Five cases of terminal Hodgkin’s disease were treated mainly with cortisone. All patients had previously received therapy with x-ray, nitrogen mustard, and triethylene melamine during the course of the disease and had become “refractory” to these agents at the time of cortisone or ACTH treatment. One patient derived no benefit from cortisone therapy while another patient developed signs of hypertension, azotemia, proteinuria and fluid retention which necessitated cessation of the drug. The remaining 3 patients displayed some improvement on cortisone therapy ranging from a simple increase in well being and appetite with no objective changes to a dramatic and complete remission. This last patient, who was apparently rapidly entering a terminal phase of his disease with severe bone pain, remitting fever, night sweats, anorexia, cachexia, splenomegaly, adenopathy and extraosseous masses of Hodgkin’s tissue showed a prompt response with a progressive gain in weight, vigor and freedom from pain. Splenomegaly receded as did the lymphadenopathy and extraosseous masses. This remission has been partially sustained for four months with continued cortisone therapy in a dosage of 50 mg./day.

7. Multiple Myeloma

This disorder was treated in five instances. Only 1 case, a man in whom urethane therapy was completely ineffective, showed a definitely favorable response to therapy with a well defined reduction in the plasma cell proliferation of the
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marrow, a striking reduction in the serum globulins, and in the urinary proteins together with marked increases in the red cell count and the blood platelets.

Four of the 5 patients showed the characteristic hyperglobulinemia associated with this disorder and 2 of the patients displayed Bence-Jones proteinuria. The hyperglobulinemia became decreased in every instance to a variable extent (1.5 to 5.8 Gm.) while Bence-Jones proteinuria disappeared in the 2 cases showing this abnormality. Associated with the fall in serum globulins there was a fall in the blood sedimentation rate.

All of these metabolic changes were most marked in the patient showing the favorable clinical response. No effect on bone pain was noted in the 2 cases in which this was present.

Fig. 4.—Hematologic and protein alterations in multiple myeloma treated with ACTH.

Case 33, Henry G., N.E.C. H. 47–235. The illness in this 57 year old white married man was characterized chiefly by the development of severe anemia, requiring frequent blood transfusions. He had received ten transfusions in the six months prior to admission. He had never complained of bone pain or tenderness. Three months before the present admission he had been given a trial of urethane therapy with little or no effect. Examination revealed marked pallor of the skin and mucous membranes, just palpable liver edge and the splenic edge palpable 3 cm. below the left costal margin.

Laboratory Data: urine: twenty-four hour protein excretion 7.8 Gm.; Bence-Jones protein present; specific gravity 1.027; 1 to 2 W.B.C. and 4 to 6 granular casts per high power field. Total serum protein 13.4 Gm. per 100 ml., 2.4 Gm. albumin and 11.0 Gm. of globulin (82 per cent of the total protein). Erythrocyte sedimentation rate 154 mm./hour (Westergren). Blood counts: R.B.C. 1.6 M., hemoglobin 6.2 Gm. (40 per cent), reticulocytes 5.8 per cent, platelets 83,200, W.B.C. 3.600; differential count: poly, 52 per cent, lymphocytes 24 per cent, monocytes 19 per cent, eosinophiles 4 per cent, myelocytes 1 per cent. Bone marrow examination revealed a hypercellular picture with diffuse sheet-like over-
growth of the marrow by myeloma cells of immature type amounting to over 90 per cent of
cells observed. Granulocytic, erythropoietic and megakaryocytic elements were markedly
decreased.

ACTH therapy was begun in a dosage of 15 mg. three times daily. Two blood trans-
fusions totaling 1,000 cc. were given. The laboratory data all showed gradual and pro-
gressive improvement with most values returning to normal or near normal levels. The red
cell, platelet and granulocytic counts approached normality. At discharge after thirty-
five days of treatment, the following counts were obtained: R.C.B. 2.9 M., hemoglobin 9.8
Gm. (53 per cent), reticulocytes 3 per cent, platelets 250,000, W.B.C. 5,550, with a differ-
cental count of polys. 90 per cent (12 per cent hands), lymphocytes 3 per cent, monocytes
6 per cent and eosinophils 1 per cent. Serial bone marrow examination showed a progressive
decrease in the percentage of myeloma cells although they never completely disappeared.
Megakaryocytes became numerous and thrombocytopoiesis active. There was a striking
increase in the cells of the granulopoietic and erythropoietic series, with a slight shift t o the
left in both series (fig. 3). The sedimentation rate fell to 13 mm./hour. Total serum
protein was 7.8 Gm. per 100 ml., with 2.6 Gm. albumin and 5.2 Gm. globulin. The Bence-
Jones proteinuria disappeared and the urinary total protein was reduced to 1.3 Gm./twenty-
four hours. The patient was discharged on a "maintenance" dose of ACTH of 20 mg. per
day. With this decreased dosage a gradual increase in sedimentation rate and in globuli-
nemia occurred although the erythrocyte count and hemoglobin values were maintained
without the need for further transfusions. The patient resumed active full time work as a
lathe operator, but after five months of continued remission, there was a gradual relapse.
Further transfusions and an increased dosage of ACTH were ineffective and the patient
died seven months after the beginning of ACTH therapy.

This patient with multiple myeloma, unresponsive to urethane therapy, and
requiring numerous blood transfusions showed marked improvement in all find-
ings both hematologic and those referable to disturbed protein metabolism, on
ACTH therapy. He remained well and required no further blood transfusions
for a period of five months following which gradual and steady relapse occurred.

**DISCUSSION**

Irrespective of the type of leukocytic proliferative disease treated with ACTH
certain features were common to many of the cases which showed improvement.

**A. Specific Hematologic Effects**

Reticulocytosis, often of striking degree, was one of the earliest indications of
improvement and heralded remission in many cases. This has previously been
commented upon by us and by Pearson et al.8, 10 It was noted in 19 of the 42
cases in the present series and reached levels as high as 26 per cent in one instance.
In some patients the reticulocytosis was followed by an improvement in the
total red cell count and hemoglobin of such degree as to obviate the need for
transfusions. (Cases 1–4, 7, 9, 24, 28, 29, 31, 33, 36). In other cases despite
reticulocytosis of 9.8 per cent (Case 17) and 12 per cent (Case 30) transfusions
were necessary to maintain adequate hemoglobin levels.

The second prominent hematologic feature of the ACTH response was a
marked increase in platelets. Seventeen of 23 patients who showed signs of
clinical improvement of a variable extent displayed a significant rise in platelet
counts (Cases 1–7, 15, 17, 23, 24, 27–29, 31, 33, 42). On the other hand, 3
cases (Cases 16, 36, 41) without clinical improvement nevertheless developed
an increased platelet count.
Thus 20 of 42 treated patients developed a distinct thrombocytosis with ACTH or cortisone therapy. This was a welcome phenomenon since hemorrhagic manifestations represent a distinct problem in many cases of leukemia and lymphosarcomatosis. Most of the patients of this series had severe ecchymoses, but in some cases, there was, in addition, severe epistaxis, hematuria, massive gastro-intestinal bleeding and cerebral hemorrhage. The latter was the most frequent single cause of death in this series. Elevation of the platelet count early in the development of remission in these cases was usually followed by cessation of bleeding.

The response of the total white cell count appeared to depend on several factors, i.e. the initial level, the predominant cell type at the onset (i.e., the underlying disease) and previous therapy. It represented, furthermore, a composite of the individual responses of the several cell types, which can best be discussed separately. A distinct increase in granulocytes was evident in acute or subacute lymphocytic leukemia (Cases 1-7, 9) acute granulocytic leukemia (Cases 16, 19, 20), lymphosarcoma (Cases 29-32). Hodgkin's disease (Cases 38, 41, 42) and in multiple myeloma (Cases 33, 36, 37). This rise in granulocytes was of distinct benefit in those patients who displayed relative or absolute granulocytopenia whether due to overwhelming lymphocytic proliferation or induced by therapy. Thus, reductions in granulocytes brought about by x-ray therapy (Case 32), aminopterin (Cases 2-4, 9), nitrogen mustard (Case 38), triethylene melamine (Cases 31, 42), Fowler's solution (Case 30) and urethane (Cases 33, 36, 37) tended to be overcome by ACTH administration. On the other hand, this tendency toward stimulation of the granulocytic series was of no value and probably deleterious to those patients already suffering from a surfeit of these cells, i.e., granulocytic leukemia.

The rise in reticulocytes, platelets, red cells and granulocytes ordinarily occurred in quick succession; this “pancytosis” probably indicated a total stimulation of the marrow.

Nothing definitive can be said of the response of the monocytes in acute monocytic leukemia as only 2 cases were treated, both succumbing early. However, a trend toward a sharply rising white count was noted, the increase being in the monocytes.

The behavior of the lymphocytes, perhaps because of their peculiar relationship to the adrenal corticosteroids was most complex. This might be the result of two opposing tendencies: (1) the growth impetus of the basic lymphocytic neoplasm, (2) the process of lymphocytolysis. In those acute and subacute lymphocytic leukemias which responded favorably, there was a drop in lymphocytes and of lymphoblasts in the peripheral blood.

In some instances (Cases 2, 9, 12, 14) in which this drop occurred unaccompanied by or preceding a granulocytic response, the total white cell count fell to 0 to 700 cells/cu. mm. In the cases of chronic lymphocytic leukemia, the lymphocytolytic effect, at least as reflected by the peripheral white count was not observed, as the white count tended to rise due to an initial marked increase in mature lymphocytes (Cases 23 to 27). The mechanism of the differing reactions in the peripheral blood is obscure. In the acute cases in which the proliferation is composed largely of lymphoblasts, it is possible that the corticoids caused an
actual regression or cytolysis of lymphoblast proliferation. In the chronic cases, on the other hand, where the great bulk of the cellular proliferation is composed of mature lymphocytes, this effect would be minimal. There is furthermore the possibility that the reduction in swelling of the lymphoid masses in the chronic cases might result in an increased delivery of small lymphocytes into the peripheral blood thus accounting for the initial leukocytosis and lymphocytosis.

Where marked organ enlargement or infiltration occurred referable to lymphocytic proliferation (spleen, liver, nodes, marrow, skin) the decrease in size of these tissues under therapy was at times dramatic. Whether this was due to (1) lymphocytolysis; (2) a redistribution of lymphocytes (from organ to peripheral blood) or (3) to a decrease in an inflammatory response about the lymphocytic infiltrates cannot be stated. There is a certain amount of evidence that each of these factors was operative.

Changes in the bone marrow were at times difficult to evaluate. In the cases of acute leukemia, the degree of improvement in the peripheral blood was usually a direct reflection of a distinct improvement and frequently a complete reversal to normal in the bone marrow picture. The serial studies of the marrow in Cases B. T., C. C. and R. G. (3, 6, 9) revealed decreasing numbers of lymphocytes and lymphoblasts in the marrow and a concomitant increase in granulocytes, erythrocytes and megakaryocytes prior to a detectable remission in the peripheral blood.

On the other hand, in the cases of chronic lymphocytic leukemia showing improvement, K. M., and V. G. (Cases 24 and 25) no such improvement in the marrow could be detected despite excellent clinical and hematologic improvement.

In the one case of multiple myeloma showing clinical and hematologic improvement successive aspirations showed a gradual and striking reduction in plasma cells from an initial value of over 90 per cent to 12 per cent after sixty-five days of therapy (fig. 4). Concomitantly a decrease in serum globulins and urinary proteins took place.

Those hematologic disorders associated with either an elevation of total plasma globulin (multiple myeloma) or an abnormal globulin (acquired hemolytic anemia with circulating antibody) demonstrated the effectiveness of ACTH in reduction of globulin. As mentioned previously all of the myeloma cases displaying hyperglobulinemia showed a decrease in protein on therapy although clinical and hematologic improvement might be slight. The site of globulin production has been variously ascribed as being in the lymphoid tissue or in the system of plasma cells. Several observers\textsuperscript{15,16} including Fagraeus\textsuperscript{16} have stated that the plasma cell may be a major source of serum globulin inasmuch as these cells are known to be increased in certain conditions in which a high serum globulin is present. Our data did not permit us to make any definite correlations in this regard.

The efficacy of ACTH in diminishing the abnormal hemagglutinin associated with the hemolytic anemia of certain acquired cases of this disorder including those symptomatic of malignant white cell proliferations has been detailed elsewhere.\textsuperscript{12} In 9 of 10 cases thus far treated, striking remissions took place. In these, there was a disappearance of icterus, restoration of the red cell count and
hemoglobin to near normal, complete suppression of the activity of the hemagglutinin in vitro, eventual disappearance (in 3 cases) of a positive Coombs test and return to normal fecal urobilinogen excretion. Here again, we cannot state whether the diminution in the hemagglutinin, presumably a gamma globulin, occurred as the result of a plasma cell curtailment or whether it was a consequence of suppression of the lymphoid apparatus. However, the parallel drop in (1) leukocytes, lymphocytes, abnormal lymphoid cells in blood cells and (2) abnormal antibody in a case of lymphosarcoma with leukemia is strong presumptive evidence that lymphoid tissue regression resulted in reduction in antibody.

Another probable manifestation of an alteration in the serum protein was the diminution in the blood sedimentation rate. This occurred during the therapy of a variety of hematologic disorders but in many instances did not reflect the true status of the fundamental clinical abnormality.

B. Nonspecific Effects

An important factor in the ACTH response was the presence of certain effects which may be called nonspecific. These effects should be discriminated from those that are apparently specific and usually hematologic. As with various other disorders treated with ACTH, the hematologic disorders also showed the striking “tonic” effects induced by that hormone. Thus, patients critically ill, and in an apparently terminal phase of their condition, volunteered after only a few or several injections that they felt subjectively better than for months or years. Striking improvement took place quickly in the appetite, in various pains and in night sweats and fever. The usual accompaniments of an inflammatory reaction became greatly diminished. This was demonstrated graphically in the cases of leukemic cutis in which there was marked improvement of the skin. Despite subjective and objective amelioration, a comparison of skin biopsies prior to and during the favorable response showed little if any change in lymphocytic infiltration. The reactivity of the dermis to the lymphocytes had evidently been altered leading to a decrease in erythema, edema, desquamation and fissuring although the fundamental process had not been influenced. These effects are of definite therapeutic value in selected cases, i.e., leukemia cutis, but it should be emphasized that they are of transitory nature and that cessation of therapy is followed by a quick recurrence of those signs and symptoms which had been suppressed by this masking effect. This is in contrast to the more gradual relapse seen when an actual fundamental alteration has been produced, as for example, in acute lymphocytic leukemia.

C. Undesirable Reactions

Undesirable reactions to ACTH therapy, as seen in the hematologic disorders differed in no respect from those seen in other conditions. Mild psychoses were seen in 3 cases (28, 36, 37). Two of these occurred in emotionally labile individuals and hence presumably rather poor subjects for ACTH administration. One patient developed a fixed obsession of pregnancy related to the presence of an abdominal lymphomatous mass. This idea was retained despite the discontinuance of ACTH. One patient developed a state of agitated depression. Al-
though this was not extreme, it was of sufficient severity to warrant cessation of therapy. The remaining patient showed inappropriate emotional responses which subsided in a few days after withdrawal of ACTH. Excessive fluid retention occurred in 5 cases (1, 24, 27, 29, 42) and responded to lowered dosage and mercurial diuretics. Hypertension occurred in only 2 cases (1, 42), one being a child who also developed convulsions. Both of these side effects appeared to be related to the rapid fluid retention which occurred. Diabetes mellitus appeared in one adult patient (K. M., 24). The blood sugar rose to 500 mg. per cent and was associated with moderately severe glycosuria. No ketonuria was present. Lowering of the ACTH dosage as well as a moderate restriction in carbohydrate intake, brought about ready control of the diabetes without the use of insulin. Nitrogen retention with development of azotemia was seen in 2 cases (36 and 42) one being a case of multiple myeloma with probable myeloma kidney and the other patient having a probable pre-existing nephritis.

Cosmetic disfiguration occurred in several cases especially among the children given the material over a lengthy period of time. There was the development of a gross, porcine obesity, acne and hirsutes. The physical appearance of these children was altered in such a uniform way as to suggest a superficial resemblance among them. These features subsided somewhat as treatment was either discontinued or decreased in amount.

D. Mode of Action of ACTH and Cortisone

It is doubtful that our knowledge of the pathogenesis of leukemia is much greater today than it was several decades ago. Recent developments in the field of chemotherapeutic agents, vitamins, endocrinology, enzyme chemistry and
histochemistry, all give hope that as our knowledge increases a more basic understanding of the disease process will eventually develop.

The very fact that cases of acute and presumably rapidly fatal leukemia have been so altered by such radically different agents as aminopterin and ACTH suggests that these agents have probably influenced at some point, possibly at different points, a vital regulatory mechanism of the organism. To date, the locus and the exact nature of these therapeutic effects have eluded recognition. It is possible to speculate, however, that folic acid antagonists owe their activity to a direct effect on enzyme systems within the rapidly growing cells of the leukocytic series, notably the lymphoblasts and myeloblasts. In addition the folic acid antagonists affect the various normal elements of the marrow adversely and may thus be said to be myelosuppressive agents. In contrast, ACTH and cortisone stimulate the production of all the marrow cells, (nucleated red cells, granulocytes and megakaryocytes) and may thus be thought of as myelostimulatory. Conversely, lymphocytic tissues and to a lesser extent plasmocytic tissues appear to be influenced in a reciprocal fashion with the result that lymphocytic proliferation may be reduced. Based on these premises, one would expect the lymphocytic malignancies to regress following ACTH administration and the granulocytic proliferations to become aggravated. With possibly one exception this actually proved to be the case in the present series. On the other hand, Pearson et al. have reported beneficial effects in granulocytic leukemia.

E. Evaluation of Therapeutic Effects

In evaluating ACTH and cortisone as therapeutic agents, it is necessary to compare them with other forms of treatment. The most widely used agents in acute leukemia have been the folic acid antagonists. Thus, Farber reported approximately 50 per cent remissions in 60 cases of acute leukemia treated for three weeks or longer with these drugs. Dameshek obtained remissions in 10 out of 32 cases treated, most of whom were adults. Weber et al. observed "improvement" in 20 of 24 children with acute leukemia given aminopterin. The chief disadvantages of treatment with anti-folic acid drugs have been the high degree of toxicity of the drugs when given in effective doses, their myelosuppressive quality, as seen both initially and after continued therapy, and the often short duration of the remission or improvement obtained.

With ACTH our gross results in 15 cases of acute and subacute lymphocytic leukemia showed 9 cases clinically and hematologically improved. Inasmuch as 2 of these patients died before five days of treatment had been given it would seem reasonable to exclude them from consideration since ACTH probably requires at least one week to become noticeably effective in cases of acute leukemia. This leaves 9 remissions of 13 cases adequately treated or an immediate remission rate of approximately 70 per cent. This figure is considerably better than that obtained with aminopterin in our hands.

In children the immediate and overall remission rates are very much higher than that obtained with aminopterin. Two possible explanations suggest themselves. First, the dosage of ACTH used in the children was greater on a weight basis than that given adults. Secondly it is distinctly possible that the adrenal cortex of the young is capable of a greater degree of response and thus is produc-
tive of a greater degree of cytologic effect than is possible in adults. It is apparent from our observations in children previously treated with aminopterin, that an almost completely destroyed marrow may be stimulated to produce normal cells, presumably from latent precursors by the prolonged use of the hormone.

ACTH has in our hands proved to be of little value in acute granulocytic or monocytic leukemia. Indeed, it seemed to intensify the leukemic process in some of these cases. This is in line with previous thoughts as to the reciprocal or antagonistic relationships of lymphocytic and granulocytic tissues. Regression of lymphoid tissue might conceivably be associated with stimulation of myeloid tissue and vice versa.

Of the 5 cases of chronic lymphocytic leukemia, and the 5 of generalized lymphosarcoma, all showed improvement to a variable degree. In the most chronic forms of the disease, greater caution must be exercised in drawing conclusions from short term results. There is no question, however, that some of the cases which were unimproved and perhaps aggravated by x-ray and nitrogen mustard therapy were benefited by ACTH which in selected cases seemed to be superior to all other forms of therapy. For example, K. M. developed severe anemia during the course of chronic lymphocytic leukemia. This development usually heralds a terminal phase of the disease when radiotherapy is no longer of any value. In cases treated with radioactive phosphorus Lawrence et al.23 state that since anemia and thrombocytopenia may be produced by both the disease and by radiation therapy, the therapeutic problem becomes of major importance. A similar situation exists with all other therapeutic agents which may be said to be myelosuppressive (nitrogen mustard, urethane, triethylene melamine). It is thus gratifying to have available an agent the mechanism of whose action is myelostimulatory and which may in fact counteract the depressant effects of previous therapy. This suggests the possibility of combined use of ACTH or cortisol with the other therapeutic agents.

In the treatment of hemolytic anemia with circulating antibodies occurring as a secondary manifestation in the course of chronic lymphocytic leukemia and lymphosarcoma, splenectomy, x-ray therapy, urethane and nitrogen mustard have all been relatively ineffective in our hands. These cases represent a very difficult therapeutic problem which seems to be resolved to a major extent by the use of ACTH. The striking therapeutic effects in these cases represented the one outstanding bright spot in this series of cases.

In Hodgkin’s disease, x-ray, HN2 and triethylene melamine are effective for the greater part of the disease. In the later stages, these agents are apt to be less efficacious. The ability of ACTH and cortisol to reduce “toxicity” and thus to make the management of these terminal cases easier and in one case in this series even to restore the patient to a useful life is most gratifying.

In the treatment of multiple myeloma, urethane has not infrequently been of definite value. In a group of 15 cases treated with urethane for considerable periods 3 showed definite evidence of response. One of the cases showing no effect from urethane was remarkably benefited by ACTH indicating a different type of action. However, 4 other cases showed no definite response to ACTH, 3 of these having previously reached a state of refractoriness to urethane.

In evaluation of the general results, it is important to consider the status of
these patients who were under continuous therapy with the hormone. Whatever
the disease or its degree of severity, there was an almost constant and striking
increase in vitality and appetite. The adults became quite active and were able
to resume some activity. On the other hand, the children became quite altered
in appearance with prolonged therapy and even though they felt well and were
active, retained an unsightly obesity and hirsutism for some time after treat-
ment was discontinued. The duration of single remissions varied from one to ten
weeks and was seemingly but little influenced by maintenance therapy. The use
of multiple courses in the cases of acute leukemias responding to therapy defi-
nitely prolonged life. However, in the chronic cases, it was impossible to evaluate
the matter of an increase in the survival time. However, there can be no doubt
that the use of ACTH made management of these conditions somewhat easier.
In this group which comprises chronic lymphocytic leukemia, lymphosarcoma,
Hodgkin's disease, leukemia cutis, and acquired hemolytic anemia, home main-
tenance therapy proved to be both practical and beneficial. This has become
particularly true since tablets of cortisone for oral use have been introduced. To
summarize our discussion in general terms we can say:

1. ACTH and cortisone are active and highly interesting therapeutic agents.
2. Much of the clinical improvement with these hormones relates to their
   "nonspecific" effects.
3. In acute leukemia, real or objective improvement is transitory at best and
   may be said therefore to be of "pathetic benefit," since death always occurs
   although it is a little delayed.
4. In certain chronic situations, the results may be of distinct practical benefit.
5. Our most striking results were obtained in acquired hemolytic anemia, presum-
   ably because of a reduction and even disappearance of abnormal antibody.

SUMMARY

Forty-two patients with various diseases of leukocytic proliferation were
treated with one or more courses of adrenocorticotropic hormone or cortisone.

Of 13 patients with acute or subacute lymphocytic leukemia who received
adequate courses of treatment, 9 (69 per cent) developed objective and hemat-
ologic evidence of well defined remissions. Remissions were, however, brief, lasting
one to ten weeks. Retreatments produced further remissions but a state of re-
fractoriness was eventually reached.

Of 5 patients with acute granulocytic leukemia only 1 showed a slight clinical
improvement with therapy. An actual acceleration of the process occurred in 2
cases.

Two cases of monocytic leukemia showed no response and death seemed to be
haftened.

In 5 cases of chronic lymphocytic leukemia, distinct improvement occurred in
4, particularly in those showing terminal leukemia with anemia, exfoliative der-
matitis, or symptomatic hemolytic anemia.

All of 5 cases of lymphosarcoma showed some degree of improvement. Features
benefited were organ enlargement, symptomatic hemolytic anemia and anemia.

In 5 cases of Hodgkin's disease, 3 were notably benefited particularly with
respect to constitutional symptoms. There was, however, no fundamental alteration of the disease process.

Only 1 case of 5 with multiple myeloma showed a favorable response. Hyperglobulinemia decreased to a variable extent in all cases, as did Bence-Jones proteinuria. The characteristics of remission including reticulocytosis, thrombocytosis, white cell response and marrow picture are detailed. The effect of ACTH on the level of serum globulins, the activity of abnormal hemagglutinins, and sedimentation rate are likewise discussed. The nonspecific effects of adrenocorticotropic therapy are indicated.

Comment is made of the undesirable effects of ACTH therapy. These included psychoses, fluid retention, hypertension, convulsions, porcine, obesity, acne, hirsutes and diabetes mellitus.

The therapeutic effectiveness of ACTH is compared with the existing available methods of therapy in the hematologic conditions under discussion.

CONCLUSIONS

1. A high immediate remission rate using ACTH or cortisone may be obtained in cases of acute or subacute lymphocytic leukemia in children. The remissions are unfortunately only of short duration in most cases.

2. Retreatment may produce further remissions but an eventual state of refractoriness is reached. Treatment must be intensive and prolonged.

3. Certain cases of generalized lymphosarcoma and chronic lymphocytic leukemia may be strikingly improved by ACTH therapy. This seems particularly true of cases displaying large lymphoid masses, skin infiltration, symptomatic hemolytic anemia, and anemia and leukopenia, all of which may be resistant to or aggravated by x-ray therapy. Maintenance therapy in this group is beneficial and practicable.

4. The management of the very last stages of Hodgkin’s disease may be rendered more satisfactory through the use of ACTH or cortisone. In occasional instances, the patient may be restored to reasonably active life.

5. Certain cases of multiple myeloma which have not responded to urethane treatment may be improved by ACTH.

6. The relief of anemia, thrombocytopenia and leukopenia often brought about by ACTH therapy suggests that in contradistinction to other forms of therapy in white cell proliferations, the action is myelostimulatory rather than myelosuppressive. This is of considerable advantage in the treatment of cases displaying deficient bone marrows, whether due to the primary disease or previous therapy.

7. The final evaluation of the place of ACTH in the therapy of the various proliferative diseases of the white cell tissues remains to be established. In any event, the mere fact that continued administration of this hormone may cause regression of widespread neoplastic tissue is of unusual interest and poses numerous physiologic problems.

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**NOTE**

For supplementary material, incorporating tabular data dealing with specific clinical and hematologic details of all the cases treated, order Document 3348 from American Documentation Institute, 1719 N Street, N.W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $1.35 for photocopies (6 x 8 inches) readable without optical aid.
The Use of Adrenocorticotropic Hormone and Cortisone in the Treatment of Leukemia and Leukosarcoma

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