1953

Use of ACTH and cortisone in the acute leukemias of children

Donald Edward Rice
University of Nebraska Medical Center

THE USE OF ACTH AND CORTISONE IN THE ACUTE LEUKEMIAS OF CHILDREN

Donald Edward Rice

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska

February 27, 1953

Omaha, Nebraska

TABLE OF CONTENTS

INTRODUCTION

As early as 1942, Heilman and Kendall (1) had observed temporary regression of a lymphoid tumor in mice with the administration of Cortisone (compound E). Publication of these observations was witheld until 1944, because extension of the experiments was not possible with the available supplies of Cortisone. Protection against transplanted leukemia in rats by the administration of adrenal cortical hormones and ACTH was reported by Murphy and Sturm (2), Dougherty and White (3) demonstrated the depressing effect of ACTH on the circulating lymphocytes in 1943. Hills, Forsham and Finch (4) showed that, in the human, the administration of ACTH resulted in an increase in the circulating neutrophils and a decrease in the circulating lymphocytes and eosinophils. Because of this background of experimental work indicating a relationship between the adrenal cortex and the lymphatic and hematopoietic systems, attention was focused on the possibilities of using ACTH and Cortisone in the treatment of leukemia. ACTH was first used by Pearson et. al. (5) and Farber et. al. (6) in 1949. Since the latter part of 1949, studies of the effectiveness of both ACTH and Cortisone in the treatment of leukemias and lymphomas have been

in progress in several centers. A number of reports have recently appeared which indicate that these hormones have a beneficial but temporary effect in diseases of this type in that they have caused some degree of abatement of the malignant process both in man and in experimental animals.

In this thesis I shall review the literature on the reported effects of ACTH and Cortisone on the acute leukemias. Next I shall report the effects of these hormones on humans who have no apparent disease process. In my discussion I shall attempt to explain the possible mechanism of action of these hormones which temporarily cause a regression of the neoplastic process in the acute leukemias in many cases.

THE EFFECTS OF ACTH AND CORTISONE ON THE ACUTE LEUKEMIAS

In five cases of acute leukemia of which four were granulocytic and one lymphocytic in type, Pearson et. al. (7) obtained remissions in all using ACTH in the daily dosage of 50 milligrams for children and 100 milligrams for adults for 24 to 30 days. Within a few days of the start of treatment, all five patients showed symptomatic improvement with an increase of appetite, rapid shrinkage of enlarged lymph nodes,

spleen and liver, and cessation of hemorrhage. The first indication of improvement in the peripheral blood was an increase in the numbers of reticulocytes and platelets. The bone marrow showed improvement first in erythropoietic activity and later in maturity of the granulocytic series. In none of the pationts, however, was there complete disappearance of abnormal cells from the bone marrow or the peripheral blood. When the initial white counts were raised prior to treatment with therapy, prompt fall to subnormal levels was followed by a slow rise to normal, whereas when the initial counts were low there was a gradual rise to normal levels. In one case, a relapse occurred three weeks after the end of ACTH therapy, symptomatic improvement again followed treatment with this hormone. The periods of observation in the remaining four cases were too short to be significant. No response was obtained in patients who had previously received treatment with folic acid antagonists. Cortisone was used in two cases. In one of these a remission was obtained but in the other, the patient died within 48 hours.

Dameshek et. al. (8) in 1950 used ACTH in eight cases of acute or subacute leukemia of which six were lymphocytic and two were myelocytic. Complete or

incomplete remissions followed in five patients, all of whom were children with the leukopenic type of lymphocytic leukemia. No response was noted in the remaining three cases of which two were granulocytic and one lymphocytic leukemia. The ACTH was given in the daily dosage of 20 to 40 milligrams in children and 80 milligrams in adults for two weeks, after which the dosage was reduced to half, followed by a small maintenance dose. Five of the patients had previously been treated with folic acid antagonists, to which they had become refractory. The general improvement and the reversion of the leukemic processes were accompanied by an increase in numbers of reticulocytes, red cells, and platelets, with evidence of increased bone marrow activity on the part of the precursors of red cells and platelets.

Spies et. al. (9) reports on five cases of acute leukemia, four of which were lymphocytic in type and one of which was granulocytic in type, in which ACTH was used. No effect was noted in one case, the patient dying on the fourth day. In the granulocytic leukemia, a partial remission was obtained, but the ACTH therapy had to be discontinued because of the development of severe mental side effects, and the patient died after

three months. Remissions were obtained in the remaining three cases. One patient relapsed five months after receiving 1400 milligrams of ACTH, but again responded to the second course, the effect of which persisted for six months. The patient showed good clinical and hematological response and was able to discontinue blood transfusions, which previously were necessary to maintain a normal number of red blood cells. A boy aged seven years, with the fulminating form of leukemia ahowed a dramatic response to ACTH in 15 days, but promptly relapsed when it was discontinued for 48 hours. With further ACTH therapy another prompt clinical and hematological remission ensued which persisted for a month after 1150 milligrams of ACTH had been given in 28 days. A third course of ACTH again induced a remission.

Kinsel et. al. (10) in 1950 reported a definite clinical remission which was complete in a patient with acute monocytic leukemia. The patient was treated with ACTH, 25 milligrams every six hours.

Stickney et.al(11) using Cortisone in 12 cases of acute lymphatic leukemia, noted a complete temporary remission in two, a partial remission in one and no improvement in nine cases.

Rosenthal (12) gives an excellant review in 1951 of 15 cases of acute and subacute leukemia in which

three died during therapy, two after only a few days and one after adequate therapy had been administered. Of the remaining 12 patients nine developed remissions of varying degree and duration, whereas three showed no response. On the patients in which therapy was begun at normal or only a slight increase in the leukocyte levels, they showed an initial fall in the total white count usually associated with disappearance of lymphoblasts. Later a secondary rise in the total white count occurs. In favorable responses to therapy, a gradual disappearance of primative leukocytes with a reversion of the differential formula to normal occurs. The rise of reticulocytes, platelets, red blood cells, and granulocytes ordinarily occurs in quick succession. Serial bone marrow observations showed parallel changes. There is a decrease in lymphoblasts and lymphocytes and a concomitant increase in the granulocytes, erythrocytes and megakaryocytes prior to detectable remission in the peripheral blood. This pancytosis probably indicated a total stimulation of the marrow. The duration of the remissions were brief, from one to ten weeks. This duration is very little influenced by maintenance therapy. When a relapse occurred there was an increase of lymphoblasts, severe anemia and thrombocytopenia. Retreatment

has caused from two to four remissions in some of the patients. Eventually a state of refractoriness occurred and the patients died. There were five cases of acute granulocytic leukemia. Two patients were uninfluenced by treatment. One patient had slight to moderate improvement with a decrease in white blood cells, immature forms, reticulocytosis, and distinct thrombocytosis, but relapsed in six weeks. Two patients were apparently made worse by therapy and there was intensification of the leukemic process and an increase in toxicity. In the two cases of acute monocytic leukemia, both were critically ill and succumbed after two and three days respectfully, with an increase in the white blood cells, a decrease in platelets and wide spread hemorrhagic phenomena. Another probable manifestation of an alteration in serum protein was a decrease in the blood sedimentation rate. The non specific effects which occurred with the treatment of leukemia with ACTH and Cortisone were the increase in appetite, decrease in pain, night sweats, fever, and decrease in skin findings and symptoms.

Bell (13) reports treating five patients, two of which were acute lymphocytic, one monocytic and two undifferentiated forms of leukemia, with Cortisone. The

response to treatment varied greatly. One patient with acute lymphatic leukemia had a dramatic temporary remission. The other patient showed no significant change other than a decrease in the lymphatic tissue. In the patient with acute monocytic leukemia, combined treatment with Cortisone and aminopterin was administered and the response was negligble. The two patients with the undifferentiated forms of leukemia responded poorly to Cortisone. Failure of 17-keto steroid excretion to rise with large doses of Cortisone was observed in one case.

Farber (14), in 1951, summarized his experience concerning the administration of ACTH or Cortisone as part of the total care given 113 children with various types of disseminated cancer. Rapid temporary improvement characterized by shrinkage in the size of tumor masses was observed in children with lymphosarcoma and with Hodgkin's disease. Administration of ACTH to 32 children with acute leukemia showed hematologic improvement in 43.8 per cent and clinical improvement in 66.3 per cent. The administration of Cortisone to 42 children with acute leukemia was followed by hematological improvement in 52.4 per cent and clinical improvement in 69 per cent. There was no effect on the course of

disease in children with chronic leukemia. The duration of remissions obtained with the use of ACTH or Cortisone was short. Improvement to a significant degree varied from two to thirty six weeks. In all children who experienced complete remissions, the duration varied from two to ten weeks; in four they averaged eleven to fifteen weeks; in three patients, sixteen to twenty weeks; and somewhat more than twenty one weeks in two patients. The average duration and rapid production of remissions by ACTH or Cortisone are reminiscent of spontaneous remissions. More than one remission may be obtained with ACTH or Cortisone after relapse, but in general these are of brief duration.

Darte et. al. (15), in 1951, reports a series of 27 children with leukemia who were treated with either ACTH or Cortisone. Each course of treatment lasted 15 to 35 days and the amount of hormone given varied from case to case. Encouraging results were obtained in that 19 children had complete remissions lasting 14 to 243 days; four had incomplete remissions; three patients failed to respond to therapy; and one patient was worse after treatment. However improvement noted was always temporary and all patients eventually become refractory to hormone therapy. The average duration of the disease

in the 19 patients which had complets remissions was 247 days; in the 18 patients with no complets remission was 118 days. The average duration of the disease in patients with partial remissions did not differ appreciably from that in 152 cases of leukemia who had no specific therapy.

Franklin (16), in 1952, reported on the use of ACTH and Cortisone in treatment of 44 cases, from 6 months to 14 years of age. Twelve cases had received no previous treatment, but the response was similiar to the remaining 32 cases who had been treated and had become resistant to various folic acid antagonists. Dosage varied between 20 to 100 milligrams of ACTH per day and 50 to 200 milligrams of Cortisone per day, depending on the age of the patient and the response to therapy. Twenty four cases showed remissions. Fifteen of the 25 cases treated with Cortisone had remissions and 9 of the 19 cases treated with ACTH had remissions. There were 16 good remissions lasting from a minimum of 16 days to a maximum of 135 days, with an average of 48.5 days. The number of days of treatment in the remissions varied from 8 to 86 days with an average of 26.9 days. The average dose of ACTH was 61.7 milligrams per day, while the average dose of Cortisone was 130.2 milligrams per day. There were eight

partial remissions lasting from 6 to 21 days in duration. The average daily dosages were slightly higher than those reported in the good remissions. Of the 20 failures eleven patients were adequately treated with either Cortisone or ACTH. In 18 cases who were treated two or more times seven developed another remission. The average length of these remissions were 33.3 days. Higher dosages and longer periods of treatment were required to produce these additional remissions. From the above results this author concluded that ACTH was apparently more rapid acting, but that Cortisone was more effective in the treatment of acute leukemias.

EFFECT OF ACTH AND CORTISONE ON THE NORMAL HEMATOPOETIC SYSTEM

Hills, Forsham and Finch (17) report that pituitary adrenocorticotrophic hormone (ACTH), when administered in a single intramuscular dose of 25 milligrams to human subjects with apparently normal adrenal function results in a characteristic alteration of the leukocytic pattern. This consists of an increase of circulating neutrophils and a decrease of circulating lymphocytes and eosinophiles. The decrease in circulating lymphocytes and eosinophiles is contingent upon the stimulation of a functionally competent adrenal cortex, and does

not occur in its absence. The neutrophilic response is present but somewhat decreased in adrenal insufficiency. The entire patterns of leukocytic alteration found in normal subjects after administration of ACTH can be induced in patients with Addison's disease by 17-hydroxycorticosterone (20 milligrams), but not with desoxycorticosterone glucoside (30 milligrams). Prolonged adrenal stimulation by ACTH given over a four day period in a dose of 10 milligrams every six hours results in a sustained and striking elevation of the neutrophils and a decrease of the eosinophiles; the lymphocytes after an initial depression lasting not more than 24 hours, may increase above their initial levels in spite of the continued increased secretion of adrenal hormones.

Dougherty and White (18) have reported that adrenal stimulation by adrenocorticotrophic hormone (ACTH) in mice or rats causes an increase in tissue lympholysis, resulting in a decrease in the circulating lymphocytes, and an increase in the circulating neutrophils.

Lewis (19) reports that when adrenalectomized rats and dogs were well maintained by appropriate therapy, the blood picture was essentially normal regardless of the type of treatment. There was hemodilution in some

cases treated with desoxycorticosterone, slight hyperplasia of bone marrow and hemoconcentration in cats with mild symptoms of adrenal insufficiency and usually marked hypoplasia of bone marrow in terminal stages of adrenal insufficiency.

Money et. al. (20) reports that the effects of ACTH and various steroids on the adrenal gland, thymus and lymph node weights of rats were studied and ACTH causes an increase in the weight of the adrenals. Cortisone and 11-dehydrocorticosterone cause a decrease in the weights of lymph nodes. Testosterone, estrogens and Reichstein's Compound L cause an increase in the weights of lymph nodes of rats. Cortisone and 11-dehydrocorticosterone have been shown to produce degeneration of lymphocytes in tissue cultures of lymph nodes.

Palmer et. al. (21) reports that in intact rats the administration of ACTH resulted in impared growth, transient neutrophilia, lymphocytopenia and eosinopenia. The administration of Cortisone was followed by lymphocytopenia, eosinopenia, but not neutrophilia. Neutrophilia produced by ACTH occurred in the absence of the adrenals, even though the animals were maintained on adequate doses of Cortisone. It is suggested that the neutrophilia may have been produced by a substance

or substances in the pituitary preperation which does not act through the adrenal. However this response could have also been due to adrenal rests.

Gauvreau (22) reported that in humans, ACTH and Cortisone causes slight stimulation of the bone marrow, about three per cent reticulosis, a slight stimulation of red blood cells, decreased cell fragility, eosinopenia, lymphopenia neutrophilia, and some shrinkage of lymphoid tissue.

DISCUSSION

Southam et. al. (23) reported that the average duration of acute leukemia in 85 infants and children from 0 to 14 years of age was 20.0 weeks for males and 18.6 weeks for females. The average survival time for both sexes was 19.3 weeks. These cases are a heterogenous group comprising of patients from 1926 through 1948, and include the period from onset of symptoms to death. Practically all of them received blood transfusions, more recent ones receiving more frequent transfusions and antibiotics.

Leiken (24) reported that in 27 patients the average survival time from onset of symptoms was 23.7 weeks. Seventeen patients receiving folic acid antagonists plus ACTH and/or Cortisone lived an average of 36.2

weeks after onset of symptoms. After a patient with acute leukemia has become resistant to therapy with the folic acid antagonists, remissions may again be produced with ACTH and Cortisone therapy. Thus therapy with these hormones does tend to prolong life in the patient with an acute leukemic process. The mode of action of ACTH and Cortisone must differ from that of the folic acid antagonists in that remissions are produced in patients resistant to folic acid antagonists.

The most important feature of this review is the fact that remissions of an important degree can be induced in the acute leukemias of children and to a lesser degree in adults by the administration of ACTH or Cortisone. In almost every case some abatement of the malignant process was evident. In a significant number of patients the improvement was so dramatic that at the fastigium of the remission there was no clinical or laboratory evidence of the leukemic process.

In general the lymphocytic type of acute leukemia, which is the most common form of acute leukemia in children responds best to ACTH and Cortisone therapy. The response is variable in the acute granulocytic leukemia with remissions of varying duration in some and an apparent intensification of the leukemic process in others. Remissions occur very seldom in acute mono-

cytic leukemia and generally there is an intensification of the leukemic process. However, in no case was permanent benefit obtained. An interesting observation, apparently more related to the fundamental nature of individual case of leukemia than either the intensity or duration of the treatment, is the variation in the length of the induced relapse.

The impression is that the lymphocytic leukemias with the low peripheral counts responded better than the so-called leukemic types.

Following the initial relapse apparently the majority of the cases that have been retreated have shown a more sluggish response or have been almost entirely refractory to further hormonal treatment, although a few have had a second, third or even a fourth remission.

What is the fundamental nature of the leukemias? Are they primarily malignant diseases or are they due to a lack of some factor necessary for the proper development and maturation of the various white blood cells? It is generally considered that leukemia is a neoplastic process, peculiarly modified by the type of tissue involved. Most therapeutic agents hitherto employed in the treatment of leukemias have been noxious agents

particularly lethal to cells in the process of multiplication. Their use has been directed toward the destruction of the leukemia cells in the hope that a sufficient differential effect will be maintained so that the toxic action of these agents on the abnormal cell will be lethal and any deleterious effect on normal tissue will be minimal. In the rationale behind all such forms of treatment there is a tacit assumption that the process is neoplastic.

With ACTH and Cortisone for the first time remissions in leukemia can be produced by steroids which are apparently normal products of the complex pattern of adrenal cortical activity. Although the administration of these hormones in the acute leukemias of children results in side effects which are evidence of either a distortion or over-activity of their normal physiologic function; in their action on the hemopoietic and lymphoid tissue, temporarily at least, they appear to supply or mediate the production of a substance necessary for normal activity.

Spontaneous remissions particularly following severe infections which have been noted in the past are probably the result of increased adrenal cortical function. Frequently in the first few days after a child with leukemia is admitted to the hospital there

is a change toward normal in the peripheral blood before any specific treatment is instituted, reports Snelling et. al. (25). As this is a period in which the child is adjusting to a new enviornment and when numerous therapeutic and diagnostic proceedures are employed, this temporary improvement might be explained on the basis of a stress reaction inducing some degree of increased adrenal cortical activity.

It may be postulated that, as a part of the effect of the increased physiologic activity of the adrenal cortical steroids induced or supplied by the hormone therapy, a milieu is produced which is so unfavorable to the leukemic cells that they are destroyed. There is considerable evidence to support this concept. There is no flooding into the peripheral circulation of maturing or adult white cells proportional to the disappearance of the leukemic forms from the peripheral circulation, or bone marrow, or in the size of the lymph nodes, spleen and liver. Repeated marrow aspirations prior to and during the administration of the hormones indicate that there is a marked decrease in the total nucleated cell population of the marrow coincident with a decrease in the proportion of blasts and subsequently there is a reappearance of normal marrow constituents and a rise in the total nucleated

count toward normal. Chemical studies by Pearson et. al. (26) find that the relative increase in excretion of uric acid and creatine appears to be proportional to the disappearance of leukemic cells and indicate a considerable breakdown of leukemic tissue. Whatever the mechanism may be, there is considerable evidence, particularly in the early stages of the hormone therapy, that there is a massive dissolution of leukemic tissue.

From a therapeutic aspect, the disappointing feature of ACTH and Cortisone therapy is the evanescent nature of the remission and the sluggish or refractory response to further treatment. This may indicate an antihormone effect. There is some clinical evidence to support this idea as the side effects of ACTH or Cortisone therapy do not appear to be so marked during periods of retreatment. Chase (27) and Gordon (28) have adduced experimental evidence that antihormones against purified adrenocorticaltropic hormone can be demonstrated in the mouse and rat following administration of the hormone. However, if leukemia is fundamentally a neoplastic process it may be that after a shorter or longer period of time the leukemic cells become adapted to the altered environment with progression of the disease to its ultimate termination.

A more optimistic concept, which to date has little evidence to support it, is that the leukemias are not neoplastic processes but rather they represent a defeciency or block at some stage in development or maturation of the white blood cells. In an attempt to compensate for the deficiency of normal mature white cells, there is an outpouring of abnormal immature forms. To fit in with this hypothesis, the action of ACTH and Cortisone may be explained by the assumption that at some stage of the complex metabolic change induced by the administration of these hormones, temporarily at least, a hypothetic maturation factor is supplied in sufficient quantities to initiate normal development of the white cells. Coincident with this there is an elimination and destruction of the unuseable and imperfect immature cells.

An observation impossible to explain is the wide variations from case to case in the reaction to the hormones, both in regard to side effects and hematologic response. Dosage in the individual case was in main based upon the eosinophile response. An attempt in many of the patients treated with these hormones, was made during treatment to adjust the dosage at a level which maintained the peripheral circulation free of eosino-

philes. In those children who initially showed only one or two eosinophiles per cubic millimeter, this criterion was obviously of little use.

The side effects in most children were in most cases, relatively unimportant, and were apparently tolerated well.

In the reaction following the first flush of enthusiasm, for this new method of approach to the leukemia problem, one is apt to minimize the advance that has been achieved. There is little doubt that in the leukemias of children, with the administration of ACTH or Cortisone, more complete hematologic and clinical remissions can be obtained in a higher percentage of patients, with less toxic effects than with any other therapeutic agents thus far employed. The relief of anemia, thrombocytopenia and leukopenia often brought about by ACTH and Cortisone therapy suggests that in contradistinction to other forms of therapy in white cell proliferation, the action is myelostimulatory rather than myelosuppressive. This is of considerable advantage in the treatment of cases displaying deficient bone marrows, whether due to primary disease or previous therapy. Although the temporary nature of the remission is disappointing, an invaluable tool has been added to the armamentarium of the investigator. Because of the

prompt clinical improvement which may occur in the patient with acute lymphocytic or granulocytic leukemia ACTH and Cortisone may be considered an important adjunct in the therapy of the above acute leukemias.

SUMMARY

Because of the experimental work by Heilman and Kendall (1), who had observed temporary regression of a lymphoid tumor in mice with administration of Cortisone, Murphy and Sturm (2) who reported protection against transplanted leukemia in rats by the administration of adrenal cortical hormones and ACTH, and Forsham and Finch (4), who showed that, in the human, the administration of ACTH resulted in an increase in the circulating neutrophils and a decrease in the circulating lymphocytes and eosinophils, attention was focused on the possibilities of using ACTH and Cortisone in the treatment of leukemia. ACTH was first used by Pearson et. al. (5) and Farber et. al. (6) in 1949.

The acute lymphocytic leukemias, which are by far the most common type in childhood, respond best to therapy by ACTH and Cortisone. Out of 178 cases of acute lymphocytic leukemia reported in this treatise, 104 or 58.4 per cent showed evidence of hematological remission. In only one case, which was reported by

Darte et. al. (15) was apparently worse after therapy with these hormones. The length of remissions varied considerably, but generally speaking, were brief. Farber (14) reports that in 30 of 39 patients who experienced complete remissions, the average duration was from two to ten weeks, while in the other nine patients the length of remission varied from ten to twenty one weeks in duration. Franklin's (16) results of 24 cases which showed remissions were similiar to those of Farber.

The response of acute granulocytic leukemia to therapy by ACTH and Cortisone is much more variable. Remissions occur less frequently and a more frequent number of patients are apparently made worse by therapy with these hormones.

The acute monocytic forms of leukemia are almost completely refractory to ACTH and Cortisone therapy, although there is one case reported in the literature by Kinsel (10), in which a clinical remission was complete. As in acute granulocytic leukemia, the disease process may be aggravated by therapy with these hormones.

Reversion of the leukemic processes are usually accompanied by increased bone marrow activity as evidenced by an increase in the numbers of granulocytes, reticulocytes, red cells and platelets in the peripheral

circulation. Usually the first indication in the peripheral blood is an increase in the reticulocytes and platelets. Clinical remissions occur more frequently than hematological remissions.

In general when the initial white count was raised in a leukemic patient, in favorable responses to treatment with these hormones, there was a prompt fall to subnormal and a gradual rise to normal levels, whereas when the initial white counts were low, there was a gradual rise to normal levels. Disappearance of most of the primitive forms of leukocytes usually occurs in those who have remissions of varying degrees, with reversion of the differential formula to normal. Parallel changes occur in serial bone marrow studies.

Previously treated patients and untreated patients usually respond about the same to treatment with ACTH or Cortisone. All other types of treatment against the acute leukemias tend to be myelosuppressive, whereas these hormones either tend to stimulate bone marrow activity, or tend to eliminate the supressive action of the leukemic cells on the bone marrow by destroying them.

The non specific effects which occurred with the treatment of acute leukemia with ACTH and Cortisone

were the increase in appetite, and a decrease in pain, night sweats, fever, skin findings and skin symptoms.

The effects of these hormones on the hematopoietic system in human with no disease process are a decrease in the circulating eosinophiles, a primary decrease in the lymphocytes which later under continued ACTH or Cortisone administration returns to pre-treatment base line levels, a distinct tendency for the polymorphonuclear count to rise 50 to 100 per cent above the base line level, a rise in the red blood count to normal levels if the count is low initially, with a reticulocytosis, and an increase in the platelet count if the platelet count is initially low. The most sensitive test of adrenal cortical stimulation is the eosinophil count in the peripheral blood. This decreases markedly when ACTH is administered and is a rough and ready guide of adequate ACTH stimulation. Generally, there is very little, if, any change in the clinical status of a patient if the dose is such that the eosinophil count does not drop.

The most important feature of this review is the fact that remissions of an important degree can be induced in the acute leukemias of children and adults by the administration of ACTH or Cortisone. With ACTH

and Cortisone for the first time remissions in leukemia can be produced by steroids which are apparently normal products of the complex pattern of adrenal cortical activity. Although the administration of these hormones in the acute leukemias of children results in side effects which are evidence of either a distortion or over-activity of their normal physiologic function, in their action on the hemopoietic and lymphoid tissue, temporarily at least, they appear to supply or mediate the production of a substance necessary for normal activity.

It may be postulated that, as a part of the effect of the increased physiologic activity of the adrenal cortical steroids induced or supplied by the hormone therapy, a situation is produced which is so unfavorable to the leukemic cells that they are destroyed. Chemical studies by Pearson et. al. (26) find that the relative increase in excretion of uric acid and creatine appears to be proportional to the disappearance of leukemic cells and indicate a considerable breakdown of leukemic tissue. Whatever the mechanism may be, there is considerable evidence, particularly in the early stages of the hormone therapy, that there is a massive dissolution of leukemic tissue.

From a therapeutic aspect, the disappointing feature of ACTH and Cortisone therapy is the evanescent nature of the remission and the sluggish or refractory response to further treatment. This may indicate an antihormone effect. However, if leukemia is fundamentally a neoplastic process it may be that after a shorter or longer period of time the leukemic cells become adapted to the altered environment with progress of the disease to its ultimate termination. A more optimistic concept, which to date has little evidence to support it, is that the leukemias are not neoplastic processes but rather they represent a defeciency or block at some stage in development or maturation of the white blood cells. In an attempt to compensate for the defeciency of normal mature white cells, there is an outpouring of abnormal immature forms. To fit in with this hypothesis, the action of ACTH and Cortisone may be explained by the assumption that at some stage of the complex metabolic change induced by the administration of these hormones, temporarily at least, a hypothetic maturation factor is supplied in sufficient quantities to initiate normal development of the white cells. Coincident with this there is an elimination and destruction of the unuseable and imperfect immature cells.

An observation impossible to explain is the wide variations from case to case in the reaction to the hormones, both in regard to side effects and hematologic response. The side effects in most children were relatively unimportant and were apparently tolerated well.

In the reaction following the first flush of enthusiasm for this new method of approach to the leukemia problem, one is apt to minimize the advance that has been achieved. There is little doubt that in the leukemias of children, with the administration of ACTH or Cortisone, more complete remissions can be obtained in a higher percentage of patients with less toxic effects than with and other therapeutic agents thus far employed. The relief of anemia, thrombocytopenia and leukopenia often brought about by ACTH and Cortisone therapy suggests that in contradistinction to other forms of therapy in white cell proliferation, the action is myelostimulatory rather than myelosuppressive. This is of considerable advantage in the treatment of cases displaying deficient bone marrows, whether due to primary disease or to previous therapy. Although the temporary nature of the remission is disappointing, an invaluable tool has been added to the armamentarium of investigator and physician.

CONCLUSIONS

1. In this treatise, I have reviewed the literature on the effects of ACTH and Cortisone on patients with acute leukemia.

2. Acute lymphocytic leukemias respond best to therapy with these hormones. The response of acute granulocytic is more variable, and in some cases there seems to be an apparent intensification of the leukemic process upon administration of these hormones. Acute monocytic leukemias respond very poorly to therapy.

3. The response of the normal hematopoietic system to administration of ACTH and Cortisone is discussed.

4. Two possible theories on the mechanism of action of these hormones on the leukemic process are discussed.

5. ACTH and Cortisone often relieves the anemia, thrombocytopenia and leukopenia which is brought about by either other therapy or the leukemic process, and therefore is an important adjunct in the therapy of the acute leukemias.

6. The life of the leukemic patient is prolonged and the patient is temporarily relieved of the distressing symptoms that occur with the acute leukemias, in the favorable responses to this hormonal therapy; however the patient eventually becomes resistant to therapy and dies.

BIBLIOGRAPHY

1. Heilman, F. R. and Kendall, E. C.: Influence of 11-dehydro-17-hydroxycorticosterone (compound E) On Growth of Malignant Tumor In Mouse. Endocrinology 34:416 1944.

2. Murphy, J. B., and Sturm, E.: Effect of Adrenal Cortical and Pituitary Adrenotropic Hormones On Transplanted Leukemia in Rats. Science 99:303 1944.

3. Dougherty, T. F., and White, A.: Influence of Hormones On Lymphoid Tissue Structure and Function: Role of Pituitary Adrenotropic Hormone in Regulation of Lymphocytes and Other Cellular Elements of Blood. Endocrinology 35:1 1944.

4. Hills, A. G.; Forsham, P. H., and Finch, C. A.: Changes in Circulating Leucocytes Induced by Administration of Pituitary Adrenocorticotropic Hormone Hormone (ACTH) in Man. Blood 3:755 1948.

5. Pearson, O. H.; Eliel, L. P., and Talbot, T. R. Jr.: The Use of ACTH and Cortisone in Neoplastic Disease. Bull. N. Y. Acad. Med. 26:235 1950.

6. Farber, S., and others: The Effect of ACTH in Acute Leukemia in Childhood, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, pp. 328-331.

7. Same as (5).

8. Dameshek, W.; Saunders R. N., and Zamnos, Leda: The Use of ACTH in the Treatment of Acute and Subacute Leukemia. Bull. N. England Med. Center 12:11-21 1950.

9. Spies, T. D.; Stone, R. E., and others: Response to Adrenocorticotropic Hormone and Cortisone in Persons with Carcinoma, Leukemia and Lymphosarcoma. Lancet 259:241 1950.

10. Kinsel, L. W., and others: Monocytic Leukemia Treated with Pituitary Adrenocorticotropic Hormone (ACTH). J. A. M. A. 114:617-618 1950.

11. Stickney, J. M., and others: Cortisone and ACTH in the Management of Leukemia and Lymphoblastoma. Proc. Mayo Clin. 25;488-489 1950.

12. Rosenthal, M. C.; Saunders, R. H.; Schwartz, L. I.; Zannos, L.; Perez, Santiago F., and Dameshek, W.: The Use of ACTH and Cortisone in Treatment of Leukemia and Lymphosarcoma. Blood 6:804-823 (Sept.) 1951.

13. Bell, R. E., and Thompson, R. K.: Treatment of Leukemia with Cortisone. Canad. Med. Ass. J. 64:43 (Abst. JAMA 145:1294 1951).

14. Farber, S.: The Effect of Therapy on the Life History and Biologic Behavior of Leukemia. Proc. Inst. M. Chicago 18:311-325 (15 May) 1951.

15. Darte, J. M.; Snelling, C. E., and others: ACTH and Cortisone in the Treatment of Leukemia in Children. Canad. Med. Ass. J. 65:560-564 1951.

16. Franklin, J. E.: Influence of Cortisone and ACTH on Leukemia. Ped. 9:339-341 (March) 1952.

17. Hills, A. G.; Forsham, P. H., and Finch, C. A.: Changes in Circulating Leukocytes Induced by the Administration of Pituitary Adrenocorticotropic Hormone (ACTH) in Man. Blood 37:755-763 (July) 1948.

18. Dougherty, T. F., and White, A.: An Evaluation of Alterations Produced in Lymphoid Tissue by Pituitary-adrenal Cortical Secretion. J. Lab. and Clin. M. 32:584-605 1947.

19. Lewis, L. A.: The Blood Picture of Adrenalectomized Animals Treated with Different Adrenal Fractions. Endocrinology 28:821-867 1941.

20. Money, W. L.; Fager, J., and Rawson, R. W.: The Comparative Effects of Various Steroids on Lymphoid Tissue of the Rat. Cancer Res. 12:206-210 (March) 1952.

21. Palmer, J. G.; Cartwright, G. E., and Wintrobe, M.: The Effects of ACTH and Cortisone on the Blood of Experimental Animals, in Mote, J. R.: Proceedings of the Second Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1951, Vol. 1, pp. 438-449.

22. Gavreau, N. O.: Review of Adrenal Physiology and Related New Drugs. J. Maine Med. Ass. 43: 73-75 (March) 1952.

24. Leikin, Sanford, and others: The Treatment of Leukemia in Children. J. Pediat. 41:40-46 (July) 1952.

23. Southam, C. M.; Craver, L. F.; Pargeon, W. H., and Burchenal, J. H.: A Study of the Natural History of Acute Leukemia with Special Reference to the Duration of the Disease and the Occurrence of Remissions. Cancer 4:38r 1951.

25. Snelling, C. E.; Donohue, W. L.; Laski, B., and Jackson, S. H.: ACTH and Cortisone Therapy in Leukemia and Lymphomas of Children. Pediatrics 8:22-25 (July) 1951.

26. Pearson, O. H., and Eliel, L. P.: Metabolic Effects of ACTH in Acute leukemia. J. Clin. Invest. 29:838-839 1950.

27. Chase, Jeanne H.: Serological Studies on Crystalline Adrenocorticotrophic Hormone: Production of Antiadrenocorticotrophin: Endocrinology 45:96 1949.

28. Gordon, G. L.: Development of Refractory State to Adrenocorticotrophic Hormone. Endocrinology 45:571 1949.