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# NEWS AND VIEWS

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## BLOOD CLUB THIRD ANNUAL MEETING

### ACTH IN LEUKEMIA

The Blood Club held its third annual meeting at Haddon Hall Hotel, Atlantic City, New Jersey on Sunday evening, April 30, 1950 with about 300 participants. The program was devoted to a discussion of the effect of ACTH and cortisone on certain hematologic conditions, notably leukemia. Dr. Howard L. Alt, Chairman, introduced the principal speakers: Drs. George W. Thorn (Introduction), O. H. Pearson, M. M. Wintrobe, Sidney Farber, and J. M. Stickney. General discussion then took place. Abstracts of most of the remarks follow:

HEMATOLOGIC EFFECTS OF ACTH AND CORTISONE: INTRODUCTORY REMARKS. *George W. Thorn.* (From the Medical Service, Peter Bent Brigham Hospital, Boston, Mass.)

As an introduction to the interesting papers which are to follow, a review of the present status of our knowledge regarding some of the more important mechanisms of action believed attributable to ACTH and cortisone appears appropriate.

With the exception of minimal side-effects due to contamination with minute quantities of pitressin, the changes induced by ACTH are due to a stimulation of the adrenal cortex to increase the secretion of adrenal steroids, including cortisone and related compounds. ACTH, by stimulating the secretion of several adrenal steroids, is potentially capable of producing effects other than those obtained with administration of a single adrenal hormone such as cortisone.

The limiting factor in the degree of response to ACTH is the capacity of the adrenal cortex to react to stimulation. A hyperactive gland is likely to respond more readily and to a greater degree from a given dose of ACTH than is a relatively quiescent gland. Cortisone suppresses endogenous ACTH production of the pituitary. In patients with a high level of adrenal activity, it is conceivable that moderate quantities of cortisone (75-100 mg.) might result in an over-all decrease in 11,17-oxysteroids, rather than an increase, due to anterior pituitary suppression.

The over-all metabolic effects of the adrenal cortical hormones may be divided into three general groups: electrolyte-regulating effects; regulation of the rate of utilization of carbohydrate, protein and fat; and an androgenic effect. Following the administration of ACTH, a decreased urinary sodium, chloride, and potassium excretion may be observed. This is accompanied by an increase in plasma and extracellular fluid volume. The 11,17-oxysteroids, of which cortisone is an example, exhibit much less sodium-retaining effect and much more pronounced carbohydrate-regulating effects. They induce an increase in liver glycogen and blood glucose secondary to increased gluconeogenesis and reduced peripheral utilization of glucose. The increased conversion of protein to carbohydrate and the diversion of amino acids to pyruvic acid and glucose formation rather than to body protein probably account for the antianabolic effect observed with increased urinary nitrogen excretion and negative nitrogen balance. The androgenic effects of adrenal steroids are due to the secretion of steroids exhibiting effects similar to the testicular androgens. These consist in masculinization, accompanied by a retention of nitrogen, phosphorus, potassium, sodium and chloride.

An interesting and intriguing development relative to the adrenal cortical steroids has been their influence upon a variety of enzyme systems. The gastric secretion of pepsin may be increased with cortisone or ACTH but the degree of gastric acidity remains unaltered. Lysozyme activity in feces of patients with ulcerative colitis has been observed to be reduced with ACTH or cortisone. Blood glutathione levels are reduced with ACTH administration. Sulfhydryl systems, so important in the metabolic activ-

ity of several enzyme systems, may also be inactivated by adrenocortical hormones. The relationship between the oxidation of melanin and the inactivation of sulfhydryl systems strongly suggests a basis for the role of the adrenal cortex in abnormal skin pigmentation. Skin pigmentation, generally believed characteristic only of adrenal cortical insufficiency, has been observed with both ACTH and cortisone administration. An increase in kidney arginase and serum peptidase activity has been reported.

The immunologic effects of adrenal steroids have provided some of the most exciting and thought-provoking research of this new era. These observations stemmed from the studies of Dougherty and White, who described an involution of lymphoid tissue by adrenal steroids and an attendant release of antibodies from within these cells. Although these earlier observations have not been confirmed with the use of more accurate and more refined technics, they have served to focus attention on certain relationships of adrenal steroids to the antigen-antibody complex. In lupus erythematosus with an initially high serum gamma globulin and low serum complement titer, ACTH has produced a fall in the former with an associated elevation in the latter. Thus far, ACTH has produced no demonstrable effect on the level of circulating antibodies and reopens the question of whether adrenal steroids do effect antibody formation in man. The manifestations of reaction to antigen may be significantly altered by either ACTH or cortisone but this need not imply an effect on the antibody mechanism. Intradermal skin reactions to tuberculin are inhibited by ACTH or cortisone but the prevention of anaphylactoid reactions in certain species of animals is not prevented. The results are contradictory. Of interest is the fact that adrenal steroids inhibit histamine formation and accelerate its breakdown, thereby altering the allergic tissue reaction that follows the union of antigen and antibody. The ability to react to histamine itself, however, remains intact.

To the group assembled here tonight, it is necessary only to recall briefly some of the widely known hematologic effects of the adrenal steroids, particularly the 11, 17-oxysteroids. The polycythemia of hyperadrenocorticism, the lysis of fixed lymphoid tissue by adrenal steroids, the transitory decrease in circulating lymphocytes and the neutrophilia have been frequently observed. A more permanent and definite effect has been observed on circulating eosinophils, which almost completely disappear from the blood during periods of increased secretion of these steroids. Relative to the eosinopenia induced by cortisone or ACTH, recent work points to an explanation for this phenomenon on the basis of an initial increased tendency for agglutination of these cells and then their subsequent destruction by the reticulo-endothelial system. In this same regard there is a tendency of the so-called "allergic" eosinophils to be more resistant to the eosinopenic activity of a given level of adrenal steroid, but this may be readily overcome by prolonged administration of ACTH. Of particular interest has been the observation that ACTH induces a transitory reticulocytosis in patients with a variety of diseases, including pernicious anemia but not aplastic anemia.

In multiple myeloma, plasmablasts have been observed to be reduced in number and finally to disappear with the administration of ACTH. By x-ray, there is a decreased infiltrative reaction in the bone which confirms a lysing effect of these steroids on the myeloma cell.

ACTH has been observed to increase macrophage activity. Cortisone in cultures of spleen and lymph nodes has been observed to increase the growth of macrophages and inhibit fibroblasts and lymphocytes.

The precise role of the adrenal steroid in several of these actions described has thus far not been clearly defined. However, it does suggest even in these preliminary observations a multiplicity of diverse action which may eventually be shown to depend upon a common denominator. A failure or delay in delineating this need not discourage further investigation into these mechanisms or even into more unrelated pathways of research. For it is only by such progressive although often unrewarding exploring for further mechanisms of action that an explanation for the great diversity of influences of the adrenal cortical hormones is likely to result.

THE USE OF ACTH AND CORTISONE IN ACUTE LEUKEMIA.\* *O. H. Pearson, L. P. Eliel, T. R. Talbot, Jr., J. R. Burchenal, A. T. Petro, J. W. Poppell and L. F. Graver.* (From the Memorial Center for Cancer and Allied Diseases, New York City.)

We have previously reported (Bull. N. Y. Acad. Med. 26: 235, 1950) the results of studies with the use

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of ACTH and cortisone in 9 patients with acute granulocytic or lymphocytic leukemia. In 6 patients (4 children and 2 adults) a temporary clinical and hematologic remission was obtained. Remissions lasted from three weeks to two months. The 2 adults failed to show a second response to treatment and both have died. The 4 children are still living. Three have shown a second response to treatment, and the fourth is at present undergoing a second period of therapy but without improvement after two weeks. In one child, the second remission appeared to occur as readily as with the first course of treatment, whereas in the other 2 children, dosage had to be increased and continued for a longer period before a second response was obtained.

To the present time, 30 patients (10 adults and 20 children) with acute leukemia have received ACTH or cortisone. Of this group, 13 (9 children and 4 adults) have shown a good clinical and hematologic remission, 9 have shown objective clinical or hematologic improvement or both, and 8 have shown no response. Of the 8 patients who showed no response, 3 died within three days of starting treatment; 2 died with complicating hemorrhage after one and two weeks of therapy, respectively; and 3 had monocytic or myelomonocytic leukemia and died after three days, twenty days, and twenty-seven days of treatment, respectively, showing no beneficial effects.

Of the 9 patients who showed some response to treatment, 2 are still under observation and 7 have died. Three patients showed objective clinical and hematologic improvement, but relapsed and died of hemorrhagic manifestations while on treatment. One child who showed clinical improvement and rapid shrinkage of lymph nodes, liver and spleen died from a hemorrhagic diathesis after one week of treatment. One child, who manifested a fairly satisfactory hematologic response, died of hemopericardium during a pericardial tap. One adult, who showed clinical improvement and regression of leukemia cutis, died suddenly after fourteen days of treatment. Autopsy failed to reveal an adequate cause for sudden death. One child, whose hematologic picture was improving, died of bronchopneumonia during therapy.

Of the 13 patients who obtained a good response, 5 have died. Three patients relapsed after four to six weeks and failed to respond to a second course of therapy. One adult committed suicide during a remission. One child developed septicemia and died of multiple abscesses during treatment and with leukemia in remission.

In this group of 30 patients, 8 children had previously been treated with folic acid antagonists and had become resistant to this type of therapy. Four of these patients had a good response to ACTH or cortisone, one showed some response, and three manifested no response.

Twenty-one patients received ACTH initially and 9 had cortisone. It would appear that responses are equally good with either ACTH or cortisone, although usually the response occurs sooner with ACTH than with cortisone.

It may be concluded from these observations that ACTH and cortisone can induce temporary remissions in patients with acute granulocytic and acute lymphocytic leukemia. Monocytic or myelomonocytic leukemia does not appear to be responsive to these agents. Remissions are of short duration. Although second responses have been obtained in a few children, it would appear that resistance to this type of therapy develops rapidly.

**ACTH AND CORTISONE IN THE TREATMENT OF LEUKEMIA AND ALLIED DISORDERS IN CHILDHOOD.** *Sidney Farber, Virginia Downing, B. Hughes Kennedy III, Harry Shwachman, Rudolf Toth (with the assistance of Ruth Appleton and Felix Heald).* (From the Children's Medical Center, The Children's Cancer Research Foundation, and The Department of Pathology, Harvard Medical School.)

The employment of ACTH and cortisone in the treatment of children with acute leukemia, lymphosarcoma, and allied disorders was suggested by evidence thoroughly established in the literature by others at the time these compounds became available in the summer of 1949 (Clinical ACTH, J. Mote, Blakiston Co., 1949). In October, 1949 the treatment of a boy  $5\frac{3}{4}$  years of age suffering from acute leukemia with ACTH for ten days was followed by the production of a typical remission (*Ibid.*, pages 328, 330). This summary is an extension of the initial observation.

*ACTH:* In the period from August, 1949 to the end of April, 1950, 17 children suffering from acute leukemia were treated with ACTH. Of these, 7 showed no improvement either hematologically or clinically; 5 showed definite clinical improvement but no changes hematologically, and 5 responded with complete hematologic remissions. One of the 5 showing complete remission had an associated bacteremia. The essential data concerning these patients are summarized in the three tables.

The limits of ACTH therapy are indicated by our experience with Patient D. V., a boy of  $5\frac{3}{4}$  years, the first part of whose story (until the end of December, at which time he was clinically well) is summarized in our first report of a remission in acute leukemia produced by ACTH. Approximately two weeks later his bone marrow showed 95.6 per cent blasts and relapse was definite. A second course of ACTH started at that time was followed by no improvement and anti-folic therapy was begun once more.

TABLE 1.—*Acute Leukemia Treated with ACTH. Duration of Disease and Preceding Therapy (Farber et al.)*

Duration of disease before ACTH therapy	Result of preceding PGA antagonist therapy	ACTH Therapy		
		Remission	Improvement	Failure
<i>months</i>				
1-2	No therapy 2	1		1
	No response 1			1
3-4	No response 2		1	1
5-6	Remission 2		1	1
	No response 3	1	2	
7-9	No response 1	1		
10-14	Remission 4	2	1	1
15-19	Remission 2			2
	Total no therapy 2	1		1
	Total remissions 8	2	2	4
	Total no response 7	2	3	2

TABLE 2.—*Acute Leukemia Treated with ACTH. Range of Therapy (Farber et al.)*

Age	Days	Amount (mg.)
1-3	14-25	622.0-1110.5
4-6	9-23	400.0-1177.0
7-13	14-20	622.5-1200.0
14-23	12-23	880.0-1505.0

TABLE 3.—*Acute Leukemia Treated with ACTH. Complete Remissions (Farber et al.)*

Case	Age	Sex	Days	Therapy Amount	Duration	Present Status
D. O.	11	F	17	1200	<i>weeks</i> 10	Remission
D. V.	$5\frac{6}{12}$	M	10	487.5	8	Relapse
R. K.	$3\frac{7}{12}$	M	21	750	7*	Relapse
F. C.	3	M	20	927.5	4	Relapse
E. A. B.	$4\frac{10}{12}$	F	13	560.0	3	Relapse

\* Septicemia.

*The Effect of ACTH on Lymphosarcoma:* Five children with lymphosarcoma were treated with ACTH. One showed marked improvement on two separate occasions. In one more child, temporary improvement was noted. In three other patients with lymphosarcoma, no improvement was noted. In the one child who responded on two occasions, the changes produced in the mediastinal mass and in the mass in the abdomen were more striking than we have observed with any other form of therapy in such a short period of time—from twenty-four to forty-eight hours—after onset of treatment.

*Cortisone:* Three children with acute leukemia were treated with cortisone in doses of 100 mg. a day for

fourteen days. Two were clinically improved to an important degree and one responded with a complete remission.

*Discussion:* The remissions produced in ACTH and cortisone have been of short duration. In 3 children treated with ACTH a second time after relapse following initial remissions it was impossible to produce a second remission. Remissions have been produced in patients previously treated with anti-folic preparations or resistant to such therapy and in patients who had received no treatment of any kind prior to the use of ACTH. The longest remission produced when ACTH was employed was in Patient D.O., to whom amethopterin was administered as soon as ACTH therapy was discontinued. Subsequent experience has shown that the combination of anti-folic therapy and ACTH or cortisone given simultaneously or after cessation of ACTH or cortisone therapy has given much better results than when ACTH or cortisone were employed alone.

The present opinion of our group is that insufficient experience has been accumulated to permit accurate evaluation of ACTH or cortisone in the treatment of acute leukemia, lymphosarcoma, and allied disorders. The anti-folic acid compounds, such as aminopterin, amethopterin, amino-teropterin, and others, are responsible for remissions which last far longer than those produced by ACTH or cortisone. The anti-folic acid compounds remain the most effective therapeutic agents in the treatment of acute leukemia in children. The demonstration, however, that hormones such as ACTH and cortisone have a carcinolytic action is of great importance, not only because new agents have been proved to have carcinolytic power but also because these hormones act apparently through a mechanism quite different from that operative in folic acid antagonists.

The continuation of observations such as those reported here concerning the action of ACTH or cortisone on children with acute leukemia and related disorders in combination with or in sequence to folic acid antagonists and other substances known to effect lymphoid tumors, such as nitrogen mustards, should make for further advances in the control of the disease, if not the cure, in patients suffering from this type of presently incurable cancer. Until such studies are made and our understanding of the mechanism of action of these hormones clarified, a discussion of the value of ACTH or cortisone must remain within the realms of clinical investigation.

THE EFFECTS OF ACTH ON THE HEMATOPOIETIC SYSTEM. *M. M. Winthrope, G. E. Cartwright, W. J. Kubns, J. G. Palmer, and M. E. Labey.* (From the Department of Medicine, University of Utah College of Medicine and the Salt Lake General Hospital, Salt Lake City, Utah.)

The effects of the administration of ACTH were studied in 24 patients. Of 8 cases of acute leukemia, no benefit whatever was observed in 3. In one of these, a case of acute monocytic leukemia, a rise in the eosinophil count occurred in spite of a sharp increase in the urinary excretion of 17-ketosteroids. In another patient, in whom there was no benefit, the simultaneous administration of small doses of aminopterin was associated with a sharp fall in the leukocyte count but no significant clinical improvement took place.

In 5 cases of acute leukemia, improvement associated with ACTH administration ranged from slight to dramatic, but even in the last mentioned case relapse took place within two to three days on cessation of therapy, and treatment with ACTH and cortisone failed to interrupt the steady progress of the disease. When ACTH therapy was associated with improvement, fever disappeared, enlarged lymph nodes and splenomegaly became reduced or disappeared, immature white cells were no longer found in the blood and were greatly reduced in the bone marrow, anemia decreased and even disappeared and the platelet count rose to normal. It cannot be stated from these observations that acute lymphoblastic leukemia is more responsive to ACTH than the myeloblastic form.

In 2 cases of pernicious anemia, the administration of ACTH was associated with an irregular, plateau-type of reticulocytosis but, in marked contrast to the effects of vitamin B<sub>12</sub>, this was not accompanied by a decrease of anemia or clinical improvement. In a case of myelophthisic anemia, a great number of normoblasts appeared in the circulating blood but the anemia was relieved to only a slight degree. In a case of idiopathic thrombocytopenic purpura, the platelet count rose, bleeding time was reduced to normal and clot retraction improved, but the changes which followed subsequent splenectomy were much more marked. Other cases studied included one case of aplastic anemia, one of undiagnosed anemia, one multiple myeloma, 4 patients with rheumatoid arthritis and anemia, 2 with disseminated lupus erythematosus and one case each of acute nephritis, chronic pyelonephritis and cirrhosis of the liver, all with anemia.

With the exception of the cases of rheumatoid arthritis and disseminated lupus, no clinical benefit took place in these cases. However, an irregular rise in the percentage of reticulocytes was observed in 8 of the 16 cases and a slight reduction in the degree of anemia in 2. Slight, moderate or even pronounced increases in the leukocyte count took place in 13 cases. This was due to an increase in the quantity of polymorphonuclear leukocytes.

In 7 of the 24 patients, wide facial contour and edema developed. A significant rise in blood pressure was noted in 4 and pigmentation in 3. Acne, hirsutism and striae were observed in only one case. A rise in the urinary excretion of 17-ketosteroids was noted in 5 of the 7 patients with acute leukemia in whom measurements were made and in 9 of the 10 remaining patients for whom data are available so far.

Experimental studies are being conducted in animals with the object of gaining some insight concerning the influence of ACTH, cortisone and other hormones on the hemopoietic system.

THE EFFECT OF CORTISONE AND ACTH ON DISEASES OF THE BLOOD. *J. Minott Strickney, Frank J. Heck, and Charles H. Watkins.* (From the Division of Medicine, Mayo Clinic, Rochester, Minn.)

Cortisone acetate and ACTH have been given to patients suffering from various diseases of the blood. The initial daily dose for adults has been 200 to 300 mg. of cortisone or 200 mg. of ACTH. For children, about three-quarters of these amounts have been used. When possible, the administration has been continued twenty to thirty days. The physiologic effects have been similar to those noted in patients with other diseases who have received cortisone or ACTH. Rapid gain in weight with edema and cardiac enlargement, severe leukopenia and hypopotassemia have made necessary modification of the dosage schedule. Acne and rounding of the face were frequently observed. No unusual euphoria or mental depression was encountered. One instance of an easily controlled steroid diabetes occurred. When ACTH was used, the increased amounts of the 17-ketosteroids and corticosteroids in the urine indicated satisfactory adrenal stimulation in all cases. Cortisone usually produced a decrease in the 17-ketosteroids and an increase in the corticosteroids.

Eleven patients with acute leukemia received cortisone. Only one had a response which could be considered a complete remission. It was induced by 5 Gm. of cortisone. The blood and bone marrow became so nearly normal that a diagnosis of leukemia was no longer possible. The complete remission lasted five weeks. Although the patient has remained well, the bone marrow has reverted to a leukemic state. A course of 5 Gm. of cortisone did not bring on a second remission. The blood and marrow of one other patient improved, but there was no clinical remission. Nine patients were not favorably affected. We have not detected any significant improvement when thrombocytopenia with bleeding tendency has been present.

Five patients with acute leukemia have received ACTH. One responded with a complete remission after five days of treatment during which he received 1 Gm. in a course of 2.9 Gm. This remission has lasted thirteen weeks. One patient made a satisfactory hematologic response but suddenly became comatose and died. This death has not been explained, since the electrolyte pattern of the plasma was normal and at necropsy there was not the usual histologic evidence of leukemia except in the kidneys and liver. The other 3 patients made no response.

Three patients with chronic lymphocytic leukemia were given one or more courses of cortisone. In one, leukemia cutis was kept under control for three months after a course of 2 Gm. In all, the spleen, liver, and lymph nodes became 40 to 60 per cent smaller without significant change in the blood or marrow. This effect lasted from ten to twenty days and a second course was effective for about the same period. In one patient, there was an unusual resistance to subsequent roentgen therapy.

Three patients with Hodgkin's disease received full courses of cortisone. The spleen and lymph nodes regressed in all, but in fifteen to thirty days all beneficial effects were gone. Second courses produced similar results. Subsequent roentgen therapy was more effective than cortisone. No significant changes occurred in the blood, and when biopsies, made before and after treatment with cortisone, were compared, no significant differences were seen.

Cortisone did not affect chronic granulocytic leukemia and multiple myeloma.

## ADDITIONAL DISCUSSION:

*Dr. J. G. Palmer* (University of Utah, Salt Lake City, Utah) reported the effects of ACTH and cortisone in normal rats and in rats with a number of acute disturbances of the blood. In normal rats, 8 mg. ACTH daily retarded growth. Prolonged administration of ACTH led to a sustained fall in lymphocytes, eosinophiles and an increase in polymorphonuclear leukocytes without change in total white cell count. None of these rats showed reticulocytosis or polycythemia.

ACTH and cortisone were both effective in suppressing the leukocytosis and the fall in hemoglobin in rats receiving small doses of anti-rat red cell rabbit serum. Similarly, ACTH and cortisone were effective in suppressing leukocytosis following injection of turpentine. ACTH given to folic acid-deficient pigs caused a neutrophilic leukocytosis, while cortisone was without effect. The white cell count returned to the previous leukopenic levels when the drug was discontinued. These animals responded to staphylococcal abscesses with a leukocytosis; the addition of folic acid to the diet resulted in only a slightly greater increase in white cell count.

In rats, the effect of aminopterin was exaggerated by ACTH administration, as was the effect of chronic folic acid deficiency. ACTH and cortisone given to splenectomized rats still produced lymphopenia and neutrophilia. In adrenalectomized rats, however, ACTH had no effect on the lymphocytes and produced a slight neutrophilia which may have been due to impurities in the ACTH.

*Dr. William Dameshek* (New England Centre Hospital, Boston, Mass.) related the discussion to the previous work of Dougherty and White on decrease in lymphoid tissue and modification of antibody production in rats receiving pituitary and adrenal extracts. Reference was also made to the work of Wiseman and Doan, showing a reciprocal relation of lymphoid and granulocytic tissue. The relationship of these two mechanisms to the "stress mechanism" of Selye was emphasized.

Dr. Dameshek reported his experience with ACTH in the treatment of 17 cases of acute leukemia, 7 in children and 10 in adults. In this group, better responses were noted in the lymphocytic malignancies; it was felt that the course of granulocytic malignancies was accelerated. No adults with acute leukemia showed improvement during therapy, but 5 of the 7 children had complete or almost complete, although temporary, remissions. All these remissions were in lymphocytic leukemia and were usually accompanied with a striking reticulocytosis and thrombocytosis. The course of one case of chronic granulocytic leukemia was accelerated, while one patient with chronic lymphocytic leukemia experienced a remission. Two cases of multiple myeloma were treated, one showing a striking fall in urinary and plasma proteins and an improvement in marrow and peripheral blood. Two patients with acquired hemolytic anemia associated with generalized lymphosarcoma demonstrated startling improvement on ACTH therapy with a fall in bilirubin and antibody content of the serum, an improvement in the lymphosarcomatous process, and marked hematologic improvement. Discontinuance of therapy led to relapse, which was again modified with maintenance therapy. Two patients with acquired hemolytic anemia of the "idiopathic" variety, with failure of response to splenectomy, showed a beneficial response with ACTH therapy. In all 4 cases, no further transfusions were required, although previously many transfusions had been necessary to maintain blood counts at fairly good levels. These results warrant further clinical and experimental studies.

*Dr. Frank Gardner* (Peter Bent Brigham Hospital, Boston, Mass.) reported 3 cases of acquired hemolytic anemia treated with 60-100 mg. of ACTH per day. Two were treated in preparation for splenectomy and one after splenectomy. The first case was a 5 year old girl who, during treatment, showed a decrease of osmotic and mechanical fragility to normal and a fall in the Coombs titer, with transfusion therapy becoming unnecessary. Similar but less marked improvement was noted in the other 2 patients. Two of the patients responded to a second course of ACTH. The drug seemed to be temporarily effective in suppressing agglutinins and hemolysins active against the patients' own cells at an acid pH.

One case of multiple myeloma with immature plasma cells in the marrow responded temporarily to ACTH with a decrease in plasma protein and an increase in hematocrit. This was compared to the cases of multiple myeloma with more mature plasma cells which seemed to respond better to urethane.

One case of pernicious anemia responded to ACTH with a slight increase in reticulocytes and an increase in the polychromatophilia of the bone marrow megaloblasts.

*Dr. Joseph Burchenal* (Memorial Hospital, New York City) discussed the experience with 25 cases of acute leukemia treated with cortisone in a dosage of 150 mg. daily. Four of these were eliminated from the series because they had been treated for less than three weeks. Of the remaining 16 patients, 6 showed no response and 7 showed a complete return of marrow function with partial morphologic remission. Several patients had become resistant to the effect of folic acid analogues at the time of therapy with cortisone. Five of the 7 resistant patients responded well. The possibility that patients resistant to folic acid analogues can be "resensitized" with cortisone or ACTH was considered. One case resistant to ACTH and another resistant to cortisone were treated with folic acid analogues and seemed to be responding to this therapy.

*Dr. E. H. Reisner, Jr.* (Bellevue Hospital, New York City) reported results on the hormonal therapy of 15 cases of acute leukemia and 2 cases of chronic lymphatic leukemia, one of which was showing a change toward an acute course. Hematologic and clinical remissions occurred in 8 cases, lasting from a few weeks to three months. In one case there was a return to a normal bone marrow picture. In the remainder of the cases showing remission, a partial return of the marrow to normal occurred, but 6-18 per cent "blasts" persisted. Maximal improvement was noted while the patients were still undergoing therapy, but 2 patients relapsed during therapy. Eosinophils were frequently low before therapy and in some cases rose during the course of treatment.

Dr. Reisner did not agree that the lymphoblastic leukemias were the most susceptible to the effect of ACTH and commented on the difficulty of classification of acute leukemias. Cases responding to therapy showed an increase in reticulocytes with the onset of clinical improvement. During hormonal therapy the total red count in almost every case fell initially in spite of reticulocytosis. This was probably an effect of hemodilution. In 2 cases, reticulocytosis and normoblastosis were noted in the peripheral blood while the marrow was completely filled with "blast" cells. The origin of these new erythrocytes is in question, and the possibility that they may come from extramedullary sites was considered.

Three cases of monocytic leukemia showed no response, and 2 of these were made worse hematologically. One patient undergoing hormonal therapy developed a hemolytic *Staphylococcus aureus* abscess of the buttock, which on incision produced no frank pus. This may have been related to poor wound healing and low state of tissue defense during adrenal hormonal therapy. No correlation between remissions produced by adrenal hormonal therapy and folic acid antagonist therapy was noted.

*Dr. G. O. Brown* (St. Louis University, St. Louis, Mo.) commented on the known fact that desoxycorticosterone produces no effect on the circulating eosinophiles but that the simultaneous use of Doca and vitamin C has been reported effective in some cases of rheumatic disease. A series of patients with various lymphatic neoplasms treated with Doca, vitamin C and colchicine was reported. Two patients with Hodgkin's disease showed good response. The second of these patients also had rheumatoid arthritis which responded within forty-eight hours. A third case of Hodgkin's disease, resistant to x-ray and nitrogen mustard therapy, failed to respond. Three patients with lymphatic leukemia, one with lymphosarcoma and 3 with reticulum cell sarcoma failed to respond to this combined therapy.

*Dr. J. M. Stickney* (Mayo Clinic, Rochester, Minn.) stated that he had seen the fall in red count as well as the low initial eosinophil count which subsequently rose on therapy, referred to by Dr. Reisner.

*Dr. John Mote* (Armour Laboratories, Chicago, Ill.) suggested that it was probable that adrenal cortical hormones act on the leukemic process at a different level than do the folic acid antagonists. This suggests a rationale for the combined use of these drugs.