The Present Status of Treatment of Autoimmune Hemolytic Anemia with ACTH and Cortisone

By William Dameshek and Zacharias D. Komninios*

With the technical assistance of Louise Désy

MORE than five years have elapsed since the favorable effects of adrenocorticotropic hormone on the course of acquired autoimmune hemolytic anemia were first recorded.1,2 Since then numerous reports have appeared encompassing series of cases or individual case reports, all in general attesting to the usefulness of this form of therapy.3-22 The relatively large series of cases treated by this method in our clinic with subsequent extended follow-up studies now permit some estimation of the immediate remission rate, the rate of relapse, the feasibility of maintenance therapy, as well as some statement of our present impression regarding the role of splenectomy in this disorder. This paper is concerned with a study of 43 consecutive cases of autoimmune hemolytic anemia in which the initial form of therapy was the use of ACTH or one of the steroid hormones.

METHODS AND MATERIALS

The general criteria for the diagnosis of autoimmune hemolytic anemia and our methods of study have been reported previously.4 In all, forty-three patients were treated with either ACTH, ACTH-gel, Compound E (Cortisone), or Compound F to July, 1954. Twenty-one cases were “idiopathic,” the remaining twenty-two being associated with some underlying disorder such as chronic lymphocytic leukemia (18 cases), disseminated lupus erythematosus (2 cases), periarteritis nodosa (1 case), and cirrhosis of the liver (1 case). Table 1 lists the preparations used, together with sample dosage schedules for intensive initial therapy as well as maintenance therapy. During the early phases of therapy, ACTH was used, not only while the patient was in the hospital, but also for maintenance therapy at home, since at that time, this was the sole preparation available. When cortisone became available for oral administration, it became the drug of choice for maintenance therapy and was used more and more as the initial form of therapy.† Blood transfusions were given as indicated.

RESULTS

Initial response to hormonal therapy: (Table 2). Of the forty-three patients treated with full doses of one or the other above preparations, three showed no

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* This work was performed during the tenure of a Damon Runyon Clinical Research Fellowship.

† Since these cases were analyzed, we have used Prednisone (Meticorten, Schering) in most of our cases.

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TABLE 1.—Preparations of Steroids Used and Sample Dosage Schedule in Autoimmune Hemolytic Anemia

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Route</th>
<th>Dosage</th>
<th>Full therapy</th>
<th>Maintenance therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin* (Wilson)</td>
<td>Intramuscular</td>
<td>150-300 USP units daily</td>
<td>20-40 USP units daily</td>
<td></td>
</tr>
<tr>
<td>Corticotropin† Gel (Wilson)</td>
<td>Intramuscular</td>
<td>150-250 USP units daily</td>
<td>20 USP units daily</td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>Oral</td>
<td>200-400 mg. daily</td>
<td>25-100 mg. daily</td>
<td></td>
</tr>
<tr>
<td>Compound F. (Hydrocortisone)</td>
<td>Oral</td>
<td>150-200 mg. daily</td>
<td>20-40 mg. daily</td>
<td></td>
</tr>
<tr>
<td>Prednisone (Metacort, Schering)</td>
<td>Oral</td>
<td>40-80 mg. daily</td>
<td>5-15 mg. daily</td>
<td></td>
</tr>
</tbody>
</table>

* Each cc. contains 40 USP units.
† Each cc. contains 80 USP units.

TABLE 2.—Initial Response to Hormonal Therapy of Autoimmune Hemolytic Anemia

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) No response</td>
<td>3 cases</td>
</tr>
<tr>
<td>2) Favorable response</td>
<td></td>
</tr>
<tr>
<td>a) Limited</td>
<td>12 cases</td>
</tr>
<tr>
<td>b) Full</td>
<td>28 cases</td>
</tr>
<tr>
<td>Total</td>
<td>43 cases</td>
</tr>
</tbody>
</table>

response whatever, either clinically or hematologically. Forty patients were unequivocally improved as evidenced by a rise in the red cell count and hemoglobin level, decrease in reticulocytes, decrease in serum bilirubin levels and either abolition or drastic curtailment in the need for transfusions. However, in twelve cases the persistence of some degree of anemia and reticulocytosis indicated that the response was not complete. Twenty-eight patients underwent full clinical and hematologic remissions on continued therapy. The blood and bile pigment values, including the reticulocytes and the fecal urobilinogen output, returned to normal. In all cases, except for those few showing no response whatever to steroid therapy, the initial effects attending the use of one or the other of the steroids were very striking, particularly when sufficient (usually large) doses were given. The patient, previously very ill, often febrile and wasted, very pale and somewhat icteric, was transformed almost overnight into a happy, hungry individual with an unusual sense of well-being. Coincidentally, striking improvement in all such laboratory abnormalities as bilirubinemia, extreme reticulocytosis and spherocytosis, and anemia took place. The predictable transformation of patients with severe acquired autoimmune hemolytic anemia to a condition of almost complete normality within a few weeks was always a source of wonder and naturally of much gratification.

Cessation of Therapy: (Table 3). In the attempt to evaluate the possible permanence of any beneficial effects, therapy was discontinued in twenty-three patients who had shown a good initial response. In fifteen of these cases, clinical and hematologic relapse ensued. Eight patients retained their remission after complete cessation of therapy, but in three of these, therapy was successfully
AUTOIMMUNE HEMOLYTIC ANEMIA TREATMENT

TABLE 3.—Results of Discontinuing Hormone Therapy in Autoimmune Hemolytic Anemia

<table>
<thead>
<tr>
<th></th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full relapse</td>
<td>15 cases</td>
</tr>
<tr>
<td>Sustained remissions</td>
<td>8 cases*</td>
</tr>
</tbody>
</table>

* In three cases the treatment could be successfully discontinued only after a long period of maintenance therapy.

TABLE 4.—Results of Continued Maintenance Hormone Therapy in Autoimmune Hemolytic Anemia

<table>
<thead>
<tr>
<th></th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited response</td>
<td>8 cases*</td>
</tr>
<tr>
<td>Full response</td>
<td>15 cases</td>
</tr>
</tbody>
</table>

* Four of these were later subjected to splenectomy.

discontinued only after a long period of maintenance therapy with small doses of cortisone. This tendency to relapse usually required the reinstitution of therapy with some form of steroid on a maintenance basis in order to retain the maximum benefit derived from the initial course. The data regarding these cases are discussed below.

Maintenance Therapy: (Table 4). Patients were considered to be on maintenance therapy if (1) intensive treatment produced a favorable response initially and (2) this remission could be sustained over long periods in dosages considerably lower than those necessary to produce the remission. Twenty-three patients were kept on some form of daily maintenance therapy. Eight patients who had shown a limited response to the initial intensive treatment continued to show a similar limited effect on maintenance therapy; of these, four were later subjected to splenectomy. Fifteen patients were maintained in a full clinical and hematologic remission on small doses of the drug.

Splenectomy: (Tables 5 and 6). In the present series of 43 patients, only nine were subjected to splenectomy. For almost three years, no splenectomies were performed, the better to evaluate the effects of steroid therapy. At the end of this time, a certain “residue” of cases was present, including (1) incomplete response to hormonal treatment (2 cases), (2) hypertension (1 case), (3) excessive water retention (2 cases), (4) old tuberculous infection of the hip joint (1 case),

TABLE 5.—Reasons for Splenectomy in Autoimmune Hemolytic Anemia

<table>
<thead>
<tr>
<th>Reason</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Incomplete response to hormonal therapy</td>
<td>2</td>
</tr>
<tr>
<td>2. Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>3. Excessive water retention</td>
<td>2</td>
</tr>
<tr>
<td>4. Old tuberculous infection</td>
<td>1*</td>
</tr>
<tr>
<td>5. Development of Cushing's syndrome</td>
<td>1</td>
</tr>
<tr>
<td>6. Rounding of the face</td>
<td>1†</td>
</tr>
<tr>
<td>7. Coexistence of thrombocytopenia</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
</tr>
</tbody>
</table>

* Developed a strongly positive L.E. phenomenon a few months after splenectomy.
† Developed typical L.E. rash after splenectomy.
WILLIAM DAMESHEK AND ZACHARIAS D. KOMNINOS

TABLE 6.—Results of Splenectomy in Autoimmune Hemolytic Anemia

<table>
<thead>
<tr>
<th>Results</th>
<th>No. of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full remission without maintenance hormone therapy</td>
<td>6*</td>
</tr>
<tr>
<td>Full remission with maintenance hormone therapy</td>
<td>2†</td>
</tr>
<tr>
<td>Partial response even with maintenance hormone therapy</td>
<td>1</td>
</tr>
</tbody>
</table>

* In all cases the Coombs test remained positive.
† One case could not be completely controlled with cortisone before splenectomy; now she is in full remission. In the second case, the follow-up is insufficient.

(5) development of full-blown Cushing's syndrome (1 case), (6) coexistence of thrombocytopenia (1 case), and (7) rounding of the face under hormonal therapy. Splenectomy was performed in these nine cases. After splenectomy, six of the nine patients developed a full remission without any further need for maintenance steroid therapy. One patient developed a full remission after splenectomy but required small maintenance doses of cortisone to maintain it. The patient with the coexistent thrombocytopenia developed a complete remission. Finally, one patient in whom splenectomy was performed could not be completely controlled even with hormonal therapy.

Serologic Investigations: (Tables 7 and 8). The direct Coombs test was strongly positive in all 43 cases studied. In 24 cases in which a well-defined clinical and hematologic improvement took place and enough follow-up studies were present to permit evaluation, a significant diminution in both the titer and the degree of agglutination with the Coombs antiglobulin sera took place in 16. Of three others the Coombs test became negative but in two of these it again became

TABLE 7.—Serologic Investigations before Treatment

<table>
<thead>
<tr>
<th>Test</th>
<th>Number of Cases Tested</th>
<th>Pos.</th>
<th>Neg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Coombs test</td>
<td>43</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Free antibodies in serum*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm</td>
<td>35</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Cold†</td>
<td>35</td>
<td>34†</td>
<td>1</td>
</tr>
</tbody>
</table>

* The sera were tested against normal erythrocytes in albumin medium or against trypsinized normal red cells. In most cases they were tested by both methods.
† Technic for detection of cold hemagglutinin: Blood from patient defibrinated at 37 C. immediately after collection. Centrifuged at room temperature, serum removed. Two-fold serial dilutions of the serum made with normal saline and 20 per cent bovine albumin (Armour), and placed in the icebox at 4 C. Cells from a normal O, Rh negative individual are washed three times in saline, and 2 per cent suspensions are prepared either in albumin or trypsinized in saline. The red cell suspensions are kept at icebox temperature until cold before being added to the serum dilutions, following which the serum-cell mixtures are kept at 4 C. for 4 hours and observed for agglutination.
† The titer of cold hemagglutinin in albumin was 1:16 or less in 25 of the 35 cases; and between 1:32–1:256 in 9 of the 35 cases; one case showed a very high concentration of cold hemagglutinin: 1:16,400. The significance of the co-existence of a probably nonspecific cold hemagglutinin in almost every instance in which warm hemagglutinin was found is obscure. Of course, many normal individuals show a small concentration of cold hemagglutinin, which may indicate an immunologic response to viral infection.
TABLE 8.—Serologic Investigations While the Patient Was in Remission

<table>
<thead>
<tr>
<th>Test</th>
<th>No. of Cases in Which There Was Adequate Follow-Up</th>
<th>Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Same</td>
</tr>
<tr>
<td>Direct Coombs test</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Free antibodies in sera</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Cold</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

* In two of these cases the test again became positive later.

positive at a later date. Although different Coombs sera were used during the period of study, the diminution in both titer and strength of agglutination was such as to be significant. In 5 cases, despite well-defined clinical and hematologic remissions, the strength and the titer of the Coombs test remained the same.

The sera of 35 of the 43 cases in this series were examined for free antibodies by our usual technics using saline, albumin and trypsin at temperatures of 37, 22 and 3°C. In 19 cases, "warm" agglutinins were detected at 37°C in albumin media or by the use of trypsinated normal erythrocytes. In 8 of these cases, all responding to therapy, the warm agglutinins disappeared either completely or almost completely, and in the rest there was distinct diminution in titer as the patient improved. In two cases warm hemolysins against trypsinated normal erythrocytes were present; in both, the hemolysin disappeared with treatment. In a third case an hemolysin against trypsinated erythrocytes was demonstrated at room temperature. We have no information as to what happened to this hemolysin under treatment, and the patient died of numerous complications shortly after the institution of therapy. Cold hemagglutinins in small titer were found in almost every instance. (Cf. table 7.)

COURSE AND END-RESULTS OF THERAPY

Splenectomy was performed only when steroid therapy was not sufficiently effective or because of complications which had ensued. Except for the initial beneficial response to large doses of steroids, the later course in these cases was notable for its great variation. In some there was a complete and sustained response, in others only a slight and barely effective result. These variations were probably due largely to variations both in the severity of the cases and in the degree of antibody production, those cases having the highest concentration of antibody being the most difficult to control. In the "idiopathic" cases, deaths were decidedly infrequent, whereas these were almost the rule in the cases associated with chronic lymphocytic leukemia and lymphosarcoma. In the latter, too, considerable variation occurred, depending largely upon the type and relative benignity of the leukemic process. In those cases with relatively slight leukocytosis and but little tendency to progress, the hemolytic process was rather easy to control. However, in those cases in which very high leukocyte counts were present and the leukemic process was "aggressive," the hemolytic process was difficult if not impossible to control. The course of the "idiopathic" cases was rendered even more unpredictable by the development of disseminated
lupus in two of the 9 splenectomized individuals. That so-called “idiopathic” cases may actually be at the surface of the “iceberg” of some more fundamental disturbance has become by now well-established.23

COMMENT

1. Results of Therapy

The present study of 43 cases of autoimmune hemolytic anemia indicates that with the use of adrenocorticotropic hormones or Compounds E or F, an immediate favorable response may be obtained in about 90 per cent of the cases. In about 65 per cent of the cases a complete clinical remission will probably be obtained whereas about 25 per cent of the cases will show a definite although not as spectacular degree of benefit. Complete failure may be expected in less than 10 per cent of the cases, particularly in those having very severe underlying disease or other complications. Contrasting with the highly favorable immediate remission rate is the high relapse rate when therapy is discontinued. Thus, approximately two-thirds of the patients may be expected to relapse upon complete withdrawal of hormonal therapy, with one-third continuing in remission. Fortunately the results with maintenance therapy are such that the favorable effects achieved by intensive initial treatment may be sustained for long periods with small doses of cortisone given over prolonged periods of time. In about 20 per cent of the cases, splenectomy may ultimately be required for various reasons. After splenectomy, hormonal therapy can be discontinued in most cases, although in some maintenance therapy may still be required. In two of our patients, however, although splenectomy was of benefit as far as the hemolytic anemia was concerned, overt disseminated lupus developed after the operation, indicating a possible “protective” effect of the spleen in this disease.

2. Program of Therapy: Advantages and Disadvantages of Steroid Therapy

Our program of therapy, as it has evolved, features four distinct phases: (1) initial treatment with high doses of steroids until a remission has been obtained, (2) withdrawal of therapy for assessment of permanency of initial results, (3) reinstitution of therapy if relapse occurs, then stabilization at a low dosage maintenance level, and (4) final appraisal as to whether or not steroid therapy will be sufficient to control the situation or whether splenectomy must be instituted. The entire period during which this regimen is carried out may require 6–18 months. Except for the expense (and expense) involved in the long period of trial and error, together with the numerous laboratory procedures required, the patient’s interests have appeared to be well served. During this lengthy period, the initial violence of the hemolytic process often diminishes as antibody concentration becomes distinctly lessened. Splenectomy, if needed, is thus carried out under far more favorable circumstances than when the patient was first seen.

We have found that it is absolutely essential to give sufficient steroid therapy initially. What is enough for one patient is by no means a good dose for another. The correct dose may well be that amount which is required and may vary all the way (in adults) from 100 to 400 units of ACTH subcutaneously and 100 to 400 mg. of cortisone daily. Much smaller doses of ACTH may be given by intra-
venous drip, although our experience with this method has been scant. Beginning remissions are indicated by a reduction in reticulocytes, a failure of the red cell count to drop, a reduction in icterus and bilirubinemia, and by an improvement in the clinical status of the patient. Following the initial beneficial response, the dose of steroid hormone is gradually reduced to the smallest amount compatible with sustained good hemoglobin and erythrocyte values. With an optimal maintenance therapy of no more than 50 mg. daily, impending relapse is indicated by a slight fall in the red cell count or hemoglobin together with a rising reticulocyte count. A persistently positive Coombs test without other manifestations of hemolytic disease may have but little significance and may indeed be simply a “landmark” of previous disease. Splenectomy remains available as a possible final form of therapy should steroids prove ineffective or their further use become unjustified because of various complications.

Both forms of therapy, the use of steroids and splenectomy, have their advantages and disadvantages. The phenomenal ability of ACTH or cortisone to induce immediate beneficial results in such a high percentage of cases is somewhat offset by the need in many cases for some form of maintenance therapy and by the development of so-called side-effects and later complications. These may be particularly important in the older age group, where water retention and osteoporosis are important features. On the other hand, splenectomy, although by itself incapable of producing the high immediate remission rate of the steroid hormones, has the advantage, if successful, of requiring no further treatment in many cases. It must be remembered, however, that this is an operative procedure and therefore subject to the usually variable degrees of surgical skill.

It has been suggested that the immediate beneficial effects of hormonal therapy are of greatest value in preparing patients for splenectomy. Utilization of these agents in such fashion undoubtedly aids materially in assuring the surgeon of a patient in optimal condition. However, the remission rate of such a procedure, combining first hormonal therapy and then splenectomy, probably depends ultimately upon the response to splenectomy; at least there is no evidence to the contrary. The relatively disappointing results with splenectomy as the sole therapeutic procedure led us to attempt reduction of antibody production by such measures as nitrogen mustard and later ACTH and cortisone. At present, we depend primarily upon prolonged hormonal therapy and restrict the use of splenectomy for special situations. This willingness to use long term and repeated maintenance courses has been conditioned by the ready availability of technical facilities for following the patient and the recognition that autoimmune hemolytic anemia is subject to “spontaneous” variations in activity. It should be realized that once an autoimmune mechanism has developed in an individual, it is usually self-perpetuating and may even persist permanently. Thus the disease is unpredictable and may show relapse after years of clinical inactivity. The original hope that the hormones might “burn out” the hemolytic process has only occasionally been fulfilled, although this in no way impairs the usefulness of these agents. It is of considerable interest that in our youngest case, in whom therapy was begun at the age of 1, a final complete recovery with negative Coombs test took place only after three years of continued and at first massive steroid therapy.
Splenectomy is no longer urgent nor does it represent the only form of therapy, as in the days before steroid therapy. In a previous study of 63 cases of autoimmune hemolytic anemia, comprising both "idiopathic" and "symptomatic" cases, the recovery rate after splenectomy, done as the initial procedure, was approximately 40 per cent. This relatively disappointing rate appears to be considerably improved by initial therapy with steroids, since in the present series of cases, the overall complete remission rate, as induced either by steroids or by steroids and splenectomy was 62 per cent. If a full remission can be maintained by the use of small doses of cortisone (25–50 mg. daily) and the individual is relatively young, there seems little reason to urge splenectomy. Indeed, by continued postponement in this rather unpredictable disease, it is possible that the autoimmune process may eventually become "burnt out." To use steroids merely for a brief period preparatory to splenectomy may not allow full opportunity to develop a complete remission. We have therefore not been in a hurry to perform splenectomy in our cases, but have reserved the operation for those cases with either an incomplete response or requiring relatively large doses of steroid to maintain remission. Our present method of therapy is therefore to use steroids in every case initially, to use them consistently for as long a time as seems feasible, and to remove the spleen only when it seems essential to do so. In the cases showing only a partial response to steroid therapy, removal of the spleen is often highly beneficial. Thus, with two therapeutic methods: steroids and splenectomy, the outlook for autoimmune hemolytic anemia, at least of the "idiopathic" type, is far better than it was before ACTH was introduced.

Individualization in handling the patient has constituted the keystone of therapy. Although sample dosage schedules have been presented, they have by no means been rigidly adhered to. Thus, the responsiveness of patients hemolyzing at approximately equal rates to similar doses may differ greatly. Some patients may require very large daily doses, productive of many side-effects, while in others an excellent response may be obtained with amounts not much above ordinary maintenance levels. In addition, although every preparation used in this study produced full remissions in some patients, they could not be used interchangeably in equivalent doses. Thus, hydrocortisone was only about two-thirds as effective as cortisone, whereas recent experience with Prednisone (Meticorten) indicates that it is 3–4 times as effective, mg. for mg. In occasional cases, cortisone was ineffective, whereas Prednisone proved remarkably effective. Thus, failure to respond to one preparation could not be construed as a real failure in therapy unless other preparations and possibly other routes of administration had been tried with a similar lack of success; Cortisone, hydrocortisone, and Prednisone were always given by mouth, and ACTH by intramuscular route, using either the regular or the long-acting variety. Intravenous ACTH was used for brief periods in only two cases.

Blood transfusions are of great value in the management of patients with autoimmune hemolytic anemia, particularly in tiding the patient over the initial critical period. However, in none of our cases were transfusions of more than temporary value. This is readily understood when it is realized that an extrinsic (autoimmune) mechanism is present, destroying not only the patient's cells but transfused normal cells as well. In all patients with very low hemoglobin and red cell values, two to four transfusions were given during the first period of obser-
AUTOIMMUNE HEMOLYTIC ANEMIA TREATMENT

IRVING D. 63, 70444 "IDIOPATHIC"
AUTO-IMMUNE HEMOLYTIC ANEMIA

BILIRUBIN
mg./100cc.

1)

COOMBS TEST

ACHT
300
200
100
200

COUMBS SERA USED

TRANSFUSIONS

Fig. 1.—Irving D.—"Idiopathic." Good, but poorly sustained responses to steroids. Eventual "cure" following splenectomy and long-term maintenance steroid therapy.

A.G. 51, 73 241 "IDIOPATHIC"
AUTO-IMMUNE HEMOLYTIC ANEMIA, I.E.

BILIRUBIN
mg.

COOMBS TEST

ACHT

Fig. 2.—Albertina G.—"Idiopathic," but with old history of bone and pulmonary tuberculosis. Splenectomy performed after initial course of ACTH. Disseminated lupus developed about 4 months after splenectomy. Patient now controlled with small doses of steroids, with streptomycin and paraaminosalicylic acid as prophylactic agents.
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CBG, 1 yr. old "IDIOPATHIC"
AUTO-IMMUNE HEMOLYTIC ANEMIA

RBC RET
mil. %
1 10 20 30 40
A.B. TITER
37° ALBUMIN
10 - 20 -

Spleenectomy of no value. Massive steroid therapy at first combined with 2 doses of TEM was eventually successful in causing a complete remission.

ELWIN S. 66, 62 205 "IDIOPATHIC"
AUTO-IMMUNE HEMOLYTIC ANEMIA

RBC RET.
mil. %
1 10 20 30 40

A.B. TITER
37° ALBUMIN
10 - 20 -

Splenectomy was performed with excellent result.
Fig. 5.—Rebecca T.—A mild case of chronic lymphocytic leukemia and auto-immune hemolytic anemia controlled by small maintenance doses of TEM and cortisone.

Fig. 6.—Roland W.—Splenectomy in 1947 was of no value. ACTH therapy in 1950 was followed by complete clinical and hematologic response for five years. Coombs direct antiglobulin test has remained positive.
vation. At the same time hormonal therapy was begun. In cases with hemoglobin and erythrocyte values about one-half normal, transfusions were ordinarily withheld, and only steroids given. We have gained the impression in recent years that the fewer transfusions given, the better, not only on account of the possibility of reactions, but because the patients with autoimmune hemolytic anemia are good "antibody producers" and will thus develop antibodies against various specific blood group antigens. This may make successive transfusions difficult and result in hemolytic transfusion reactions to apparently compatible blood.

No serious transfusion reactions were encountered in this series of patients. If great difficulty was encountered in cross-matching the patient because of the presence of a potent cold pan-hemagglutinin, group O, Rh negative blood was given initially. Correct typing of the patients' blood cells under these conditions is often unreliable due to the fact that the strongly "coated" Coombs positive cells are readily agglutinated by the proteins in the typing sera. In a few cases, transfusions of carefully matched compatible blood were followed by severe nonhemolytic transfusion reactions, due probably to the development of hypersensitivity to a plasma factor in normal blood. Such cases were successfully transfused with the use of washed red cell transfusions.

The use of ACTH, cortisone, and related steroids in clinical medicine must be rated as among the striking therapeutic advances of the last decade. Although these hormones have been used in a wide variety of often unrelated conditions, their effects in autoimmune hemolytic anemia are among the most dramatic both from the standpoint of predictability and the degree of clinical and laboratory benefit. We were originally led to use these materials in this condition because of
Table 9.—Comments on Cases

1. Idiopathic. Clinically and hematologically well after 3 yrs., with positive Coombs test as the only abnormality.
2. Idiopathic. Clinically and hematologically well. The Coombs test eventually became negative after a period of four years.
3. Idiopathic. Asymptomatic and idiopathic chronic autoimmune hemolytic anemia; no response whatever to hormone therapy.
4. Chronic lymphocytic leukemia. Excellent result with steroid therapy. Triethylene melamine (TEM) was administered in small doses on several occasions, but the effect of this drug on the hemolytic process could not be definitely evaluated. However, an excellent effect on the leukemic process followed TEM therapy.
5. Lymphosarcoma. The hemolytic process responded to steroid treatment but the patient eventually succumbed to the lymphocytic proliferation.
7. Idiopathic (?). The results of steroid therapy were excellent. Splenectomy was performed at the patient's own request because steroids caused undue rounding of the face. A few months after the operation, overt disseminated lupus erythematosus developed. The histology of the spleen at operation disclosed minimal changes consistent with lupus erythematosus. Patient now has discoid lupus, but is asymptomatic, hematologically well, and requires no cortisone.
8. Idiopathic. Limited initial response to steroid therapy. Attempts to discontinue the drug followed by full relapse. Following splenectomy, full remission developed but only with the use of small maintenance doses of hormones.
9. "Idiopathic"; later lupus erythematosus. Excellent initial response to steroid therapy. Because of an old tuberculous infection, continued steroid therapy was considered inadvisable. Splenectomy was performed; result excellent even without hormones. Later, severe overt disseminated lupus developed requiring cortisone. Streptomycin and PAS also used. Patient is now in excellent clinical and hematologic remission.
10. Lymphosarcoma. Good initial response but the lymphocytic proliferative process eventually proved fatal.
11. Chronic lymphocytic leukemia. The patient entered the hospital in a terminal state of his leukemic process. The concomitant hemolytic process failed to respond to steroid therapy, and the patient died of terminal bronchopneumonia in a few days.
12. "Evans Syndrome" ("Idiopathic" autoimmune hemolytic anemia with "Idiopathic" thrombocytopenic purpura). A striking response to steroid therapy in a case in which previous splenectomy had been of no value.
13. Chronic lymphocytic leukemia. Good temporary improvement of the hemolytic process with steroid therapy only. However, the patient died of severe leukemia and carcinoma of the lung.
14. Complex case. Carcinoma of the rectum, Gaucher's disease and lymphocytic leukemia all present simultaneously, together with the hemolytic anemia. The latter was un influenced by steroid therapy or splenectomy and the patient died after many transfusions.
15. Periarteritis nodosa. Initial splenectomy and relatively small doses of steroids of no value. Striking and life saving effect with large doses of ACTH. Periarteritis nodosa has been progressive but relatively mild. Continued positive Coombs test.
16. Chronic lymphocytic leukemia. The results of steroid therapy in this case were only fair even after splenectomy, due possibly to the underlying leukemic state.
17. Idiopathic. Steroid therapy was minimal and irregular with limited result. Subsequently died after developing thrombocytopenic purpura and probable thrombocytopenic purpura.
TABLE 9.—Continued


20. Idiopathic. Full initial response but response to maintenance therapy only fair. Full remission after splenectomy even after withdrawal of hormones.


23. Idiopathic. Excellent remission on maintenance steroid therapy but continued slight hemolysis persists, for which splenectomy has been advised but not as yet accepted.

24. Chronic lymphocytic leukemia. Excellent early response. Hemolysis and leukemic process both became worse later and eventually proved fatal.


26. Idiopathic. Fair result with maintenance steroid therapy.

27. Idiopathic. Excellent response.


30. Idiopathic. Good initial response to steroids. Because of resulting water retention, splenectomy performed with excellent response. No further cortisone required.

31. Chronic lymphocytic leukemia; benign type. Excellent response to maintenance steroid therapy.


33. Cirrhosis of liver. Limited response to steroid therapy. Full remission after splenectomy even after withdrawal of hormones.

34. Idiopathic. Excellent response to steroid therapy. Very weakly 1)ositive Coombs test still present.

35. Chronic lymphocytic leukemia. Excellent response to steroid therapy, but relapse eventually led to splenectomy. Finally died of leukemia.


37. Idiopathic. Initial splenectomy of no benefit. Excellent response after a very short course of steroid therapy, although Coombs test still strongly positive.

38. Idiopathic. Excellent and complete response to steroids. Coombs test now negative.

39. Chronic lymphocytic leukemia. Excellent response to steroid therapy; leukemic process held under partial check with TEM.

40. Idiopathic. Excellent response to steroid therapy.

41. "Evans Syndrome." Excellent response to steroid therapy and splenectomy.

42. Chronic lymphocytic leukemia. Excellent response to steroid therapy but splenectomy advised because of continued need for large doses of Cortisone. Splenectomy followed by extensive thrombophlebitis and death.

43. Idiopathic. Excellent response to continued steroid therapy.

a possible effect on antibody production based on the known inhibitory or lytic effects of the steroids on lymphoid and plasmocytic tissues. All our clinical studies seem to bear out our original contention that the steroids act by diminishing antibody production by various tissues rather than through any other effect such as that of reducing the union of antibody with antigen, etc. The development of remission before any evidence of fall in antibody titer by the
ordinary in vitro technic does not invalidate this concept, as the titer of antibody in plasma may take some time to diminish, compared to that of antibody in the tissues. Although the experimental evidence for this view has been to some extent contradictory, there is now considerable evidence indicating an actual diminution in antibody production by the use of ACTH and the steroid hormones.

**Summary**

Forty-three patients with autoimmune hemolytic anemia (both "idiopathic" and "symptomatic") were treated with ACTH, Cortisone, or Compound F. In more recent cases not reported here, Prednisone (Meticorten) was used. Intensive and presumably adequate hormonal therapy resulted in sustained and complete clinical and hematologic responses in 65 per cent of the cases. Complete and sustained remissions were more commonly obtained in the "idiopathic" group (80 per cent remissions) than in the "symptomatic" variety. In 28 per cent of the cases, although the response was definite, it was not so striking. Complete failure was obtained in 3 cases (7 per cent) of this series. When therapy was discontinued, following a remission, some degree of relapse developed in approximately two-thirds of the cases. In the remaining one-third, full clinical and hematologic remission continued well after discontinuance of therapy, although the persistently positive Coombs test indicated the possibility of future recurrence. Splenectomy was performed as the final therapeutic maneuver in 9 of the 43 cases and resulted in complete remissions in 6 without the further use of steroid hormones. In two cases splenectomy was followed by the development of outspoken disseminated lupus, previously undiscovered and presumably latent.

It is apparent from these studies that the steroid hormones in adequate dosage represent a remarkably effective form of therapy for at least the initial control of most cases of autoimmune hemolytic anemia. Their use for a lengthy period is often followed by a lasting remission, and the end-results of continued steroid therapy, either used alone or in some cases combined with later splenectomy, are definitely better than with splenectomy alone. Thus, control of this rather unpredictable disease has become a distinct possibility in most cases, and its management simply a matter of varying the dosage of steroid hormone.

**Summario in Interlingua**

Quaranta-tres patients con autoimmun anemia hemolytic (o "idiopathic" o "symptomatic") esseva tractate con ACTH, Cortisone, o Composito F. In plus recente casos, que es non includite in le presente reporto, Prednisone (Meticorten) esseva usate. Intense e supponitemente adequate therapias hormonal resultava in persistente e complete responsas clinic e hematologic in 65 pro cento del casos. Complete e persistente remissions esseva obtenite plus generalmente in le gruppo "idiopathic" (80 pro cento de remissions) que in le gruppo "symptomatic." In 28 pro cento del casos le responsa—ben que definite—esseva minus frappante. Malsucesso complete resultava in 3 casos (7 pro cento) del presente serie. Quando le therapia esseva discontinue post que le remission esseva manifeste, un certe grado de recidiva se disveloppava in circa duo tertiis del casos. In le remanente tertio, le complete remission clinic e hematologic perdurava post le discontinuation del therapia, sed le persistente positivitate del
reaction de Coombs indicava le possibilitate de recurrentias futur. Splenectomia esseva execute como ultime mesura therapeutie in 9 del 43 casos. Le operation resultava in complete remissiones in 6 casos sin le uso subsequente de hormones steroide. In duo casos le splenectomia esseva sequite per le disveloppamento de pronunciate grados de lupus disseminate le qual habeva previamente essite indiscoperite e probablemente latente.

Il es apparente ab iste studios que le hormones steroide in doses adequate representa un remarcariblemente efficace forma de terapia pro al minus le controlo initial del majoritate de casos de autoimmune anemia hemolytic. Lor uso durante periodos prolongate es frequentemente sequite per remissiones de character durative, et le resuitatos final del continue terapia steroide – in uso exclusive o in certe casos in combination con subsequente splenectomia – es definitemente melhor que le resuitatos final de splenectomia per se. Assi le controlo de iste satis inpredicible morbo ha devenite in le majoritate del casos un clar possibilitate, et le manipulation del morbo es nunc simplemente un question de variar le doses de hormon steroide.

REFERENCES


AUTOIMMUNE HEMOLYTIC ANEMIA TREATMENT


The Present Status of Treatment of Autoimmune Hemolytic Anemia with ACTH and Cortisone

WILLIAM DAMESHEK, ZACHARIAS D. KOMNINOS and LOUISE DÉSY