Anabolic Androgenic Steroids in the Treatment of Acquired Aplastic Anemia

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PROGNOSIS in aplastic anemia has improved since the introduction of testosterone therapy.¹ This androgenic hormone has proved very useful in the treatment of children with congenital and acquired aplastic anemia,¹⁻⁵ but appears to be less effective in adults with the same disorder.⁶ Oxymetholone⁷⁻⁹ and other related steroids⁴⁻¹⁰⁻¹⁵ have recently been used in place of testosterone with good results in children and adults, as is shown in the present report of 14 children and 55 adults with acquired aplastic anemia treated with different anabolic androgenic compounds.

MATERIALS AND METHODS

Clinical material consisted of 69 cases of acquired aplastic anemia seen up to October 1966 in two hospitals.¹ All cases had normochromic anemia, thrombocytopenia, decreased or absent megakaryocytes in the bone marrow, clinically normal spleen and lymph nodes and absence of clinical or laboratory evidence of any infectious, neoplastic or deficiency states. In addition most cases had leukopenia and neutropenia. Bone marrow often showed increased numbers of fibroblasts and tissue basophils and was hypocellular in 3 out of 4 cases; in the remaining fourth, it was normocellular (15 cases) or hypercellular (4 cases) when first examined, but in further studies showed hypocellularity in many of them and necropsy examination demonstrated marked fatty replacement of the marrow in all but one of the cases dying in the hospital. The distribution of cases according to age, sex and etiologic, is given in Table 1. The magnitude of the cytopenias in each case is shown in Figure 4.

The duration of the illness to start of anabolic steroid therapy was 2 months or less in 25 cases; 2.1 to 6 months in 21; 6.1 to 12 months in 12 patients and 13 to 46 months in the others. Previous therapy had consisted of: prednisone (60 to 120 mg./day for more than two weeks) in 30 patients; splenectomy in 7; testosterone, 100 and 800 mg./week for 12 and 8 weeks respectively in two cases; and folic acid and vitamins B₉ and B₁₂ in others. In none of these cases was there any response to prior therapy.

The steroids used were: 17β-hydroxy-17α-methyl-2-hydroxymethylene-5α-androstan-3-one (oxymetholone) in 59 patients; 17β-hydroxy-1-methyl-5α-androst-1-en-3-one (methenolone) in 17 patients; 17β-hydroxy-2α-methyl-5α-androst-3-one (metholone or dromostanolone) in 5 patients; and 17β-hydroxy-17α-methylandrosta-1,4-dien-3-one (methandro-

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†Oxymetholone (Anadrol) and metholone or dromostanolone (Drolban) were kindly supplied by Syntex; methenolone (Primobolan), by Schering A.G., and methandrostenolone (Dianabol), by Ciba.
Fig. 1.—Time elapsed in the 33 cases responding to therapy from the initiation of anabolic administration to: 1) the last blood transfusion (column A); 2) when hemoglobin started to rise (column B); and 3) when hemoglobin reached 12 Gm./100 ml. in females and 13 Gm./100 ml. in males (column C).

Fig. 1 A.—Chemical configuration of anabolic androgenic steroids used. I=oxymetholone; II=methenolone; III=dromostanolone or metholone, and IV=methandrostenolone. A methyl in C17 position is observed in compounds I and IV.

Oxymetholone and methandrostenolone are C-17 alkylated compounds, both possess a methyl in the C17 position (Fig. 1A); the other two compounds are not C17 alkylated.

All compounds were given by mouth at doses ranging from 0.25 to 3.0 mg./Kg./day.
Fig. 2.—Changes in neutrophils in the 33 cases who responded to therapy. On the abscissas the number of mature neutrophils at the initiation of therapy was plotted, and on the ordinates the number attained when hemoglobin reached normal levels.

Twenty patients received less than 1.0 mg./Kg./day; 30 received 1.0 to 2.0 mg. and 19 received 2.1 to 3.0 mg. In two, the dose was increased to 5.0 mg./Kg./day after the patients failed to respond to lower doses. In addition to the androgenic steroids, 15 to 60 mg./day of prednisone or related corticosteroids were given to 40 patients. All statistical comparisons were done using Student's test.

RESULTS

I. Therapeutic Effects

On erythrocytes. A remission, as defined as a permanent rise in hemoglobin above 12 Gm. in females and 13 Gm. in males, occurred in 33 cases (47.9 per cent). However, if cases dying in the first 2 months and who presumably did not receive sufficient therapy are excluded, the remission rate rises to 70 per cent (33 out of 47 cases). Six of the 14 cases failing to respond to an adequate course of therapy received less than 1.0 mg./Kg./day of oxymetholone.

The remission was heralded by a rise in reticulocytes and stabilization of the hemoglobin concentration at a level (7 to 9 Gm.) at which blood transfusions were no longer necessary. In 4 cases, reticulocytes rose above 10 per cent (maximum 13.2 per cent); in the others, the reticulocyte rise was moderate and in half of the patients the highest figure was 5 per cent or less. These initial signs of improvement occurred after 0.5 to 6 months of therapy with a median of 2 months (Fig. 1).

On neutrophils and platelets. Less marked and slower improvement of the neutropenia and thrombocytopenia were frequently observed when the anemia remitted but not in the absence of red cell improvement (Figs. 2 and 3).
Clinical manifestations of bleeding in the cases responding to therapy began to diminish within 2 to 5 months after initiation of anabolic administration. No case had important bleeding manifestations after the red cell element had responded to therapy.

On bone marrow. Bone marrow cellularity increased in remission in all cases in which the marrow was hypocellular prior to therapy. In 25 per cent of the cases, the bone marrow pattern returned completely to normal and megakaryocytes became plentiful; in the others megakaryocytopenia, ranging from slight to marked, persisted at the time of the last bone marrow examination.

Follow-up. In 22 cases, the remission induced was permanent; in 21, it has persisted for one to five years after stopping therapy (3 years or more in 16 patients). One patient relapsed after 18 months of unmaintained remission when he was reexposed to the offending agent (benzol). This new episode of aplastic anemia also responded successfully to the anabolic steroid therapy. Another patient (No. 15), as described in our previous article,7 relapsed after a heavy reexposure to the offending agent and died. No follow-up information could be obtained in two further individuals who had responded to anabolic steroids.

Eight cases relapsed after discontinuing therapy. The first evidence of relapse was observed 1 to 4 months (usually 2 months) after steroid withdrawal. Therapy was resumed in all, and in 7 a new remission was induced; the eighth was lost to follow-up. In four, the second remission has continued.
Table 1.—Effect of Several Factors on the Response to Anabolic Steroids

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of cases</th>
<th>Total</th>
<th>in remission</th>
<th>Remission rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>31</td>
<td>12</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>38</td>
<td>21</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 year or less*</td>
<td>14</td>
<td>6</td>
<td>42.8</td>
<td></td>
</tr>
<tr>
<td>16 to 30 years</td>
<td>22</td>
<td>10</td>
<td>45.4</td>
<td></td>
</tr>
<tr>
<td>31 to 87 years</td>
<td>33</td>
<td>17</td>
<td>51.5</td>
<td></td>
</tr>
<tr>
<td>Etiology:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>18</td>
<td>7</td>
<td>38.9</td>
<td></td>
</tr>
<tr>
<td>Insecticides</td>
<td>21</td>
<td>11</td>
<td>52.3</td>
<td></td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>11</td>
<td>7</td>
<td>63.6</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>11</td>
<td>4</td>
<td>36.3</td>
<td></td>
</tr>
<tr>
<td>Benzol</td>
<td>10</td>
<td>5</td>
<td>50.0</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow cellularity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercellular</td>
<td>4</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normocellular</td>
<td>15</td>
<td>7</td>
<td>46.6</td>
<td></td>
</tr>
<tr>
<td>Hypocellular</td>
<td>50</td>
<td>24</td>
<td>48.0</td>
<td></td>
</tr>
</tbody>
</table>

Males vs females $p = .2$
Idiopathic vs secondary $p = .3$ to .4

* 2 Cases were younger than 5 years.

for 6, 15, 16, and 40 months respectively, without maintenance treatment; 3 others have relapsed whenever anabolic steroids have been stopped.

Prognostic factors. Our data do not clearly indicate any influence of age, sex, bone marrow cellularity or etiology on the response to therapy (Table 1). A moderately higher rate of remission was observed in females than in males, but the difference was not significant ($p = .2$). Similarly, a higher remission rate was observed in the group of patients with aplastic anemia secondary to drugs or chemical agents (26 out of 51 cases, or 50.9 per cent) and particularly to phenylbutazone, as compared with those considered as idiopathic. The difference between these remission rates, however, was not significant ($p = .3$ to .4). Only the initial reticulocyte per cent value and the extreme neutropenia showed some relationship with the effect of therapy (Fig. 4). A remission occurred in 18 out of 23 patients (78.2 per cent) with a relative reticulocyte count greater than 1.0 per cent whereas such a favorable response was observed in only 12 out of 38 patients (31.6 per cent) with 0.5 per cent or less reticulocytes ($p$ less than 0.001). The presence of extreme leukopenia was ominous; all the eight patients with 250 neutrophils per cmm. or less died within two months. Above this level, the number of neutrophils did not seem to have any prognostic significance. The degree of anemia or that of thrombocytopenia did not correlate well with response to therapy. Only two cases out of five with 100,000 platelets per cmm. or more went into remission and similarly a remission rate of 48 per cent was obtained in the patients with less than 30,000 platelets per cmm.

Activity of different steroids. Results of the sequential use of oxymetholone, methenolone and dromostanolone in patients requiring continuous therapy or having relapsed on steroid withdrawal suggest that the three compounds have comparable therapeutic activity.
Fig. 4.—Relationships between the pretreatment number of neutrophils (left column), platelets (center column), and per cent reticulocytes (right column) versus response to anabolic steroid therapy.

One of the two patients treated previously with testosterone died within the first month of anabolic therapy; the other did not respond to 0.6 mg./Kg./day of oxymetholone given for four months. Four patients who did not respond to a prolonged administration of oxymetholone or methenolone failed also to respond to 1 to 3 mg./Kg./day of testosterone enantate given for 2.5 to 4 months. Finally, one patient who relapsed after oxymetholone withdrawal responded to testosterone.

II. Side Effects

A. Virilization: Mild to moderate hoarseness was observed in all children and in all but 2 females treated for over one month; no adult male developed this symptom. Hirsutism developed in all children and in two-thirds of the adult females; this symptom was more marked in patients who were also taking corticosteroids. Acne was observed in all patients taking both glucocorticoids and androgenic steroids simultaneously, but in only two of those treated only with the latter. All females in menstruating age had amenorrhea throughout the course of therapy. Moderate enlargement of the clitoris in 2
females and mild increase in libido in one adult male were also observed. No difference in the virilizing activity of oxymetholone and methenolone was noticed; dromostanolone, methandrosterone and testosterone appeared to be associated with a relatively greater virilizing activity.

The virilizing phenomena induced by the anabolic steroids diminished when the dose was reduced; amenorrhea, however, persisted even with maintenance doses of 5 to 10 mg. daily of oxymetholone. After therapy was withdrawn, acne regressed quickly; hirsutism and hoarsening did so more slowly. In children, pubic hair persisted almost unchanged.

B. Hepatotoxic action: The appearance of manifestations of liver damage was followed clinically and by serial determinations of various liver function tests. In nine patients jaundice was noticed during anabolic therapy (Table 2). In four cases (Cases 13, 52, 55, and 66), moderate jaundice (1.4 to 2.6 mg./100 ml. of serum direct bilirubin) appeared after 20 to 180 days of therapy with 1.6 to 2.2 mg./Kg./day of anabolic steroids, which were of the 17-alkylated type in three instances. The liver lesion was probably secondary to the anabolic hormone as it regressed completely soon after therapy was stopped.

The other five patients died 1 to 21 days after clinical jaundice appeared. In three of them (Cases 43, 46, and 63), the liver lesion was clinically and histopathologically unrelated to the hormone therapy, as it was due to viral hepatitis in one (Case 63), and to septicemia and acute colonic process in the other two (necrotic amebic colitis, and phlegmonous colitis, respectively). One of them (Case 46) received nonalkylated steroids at a low dose (0.22 mg./Kg./day); the other 2 had been treated for only 9 and 13 days when jaundice appeared. In another case (No. 58) the liver alteration did not appear to be secondary to the anabolic agent as definite liver abnormalities were present before its administration. In this patient, the post-mortem anatomic changes were of the type seen in toxic hepatitis associated with thiazides which the patient was taking, and different from those usually observed after androgens. The fifth patient, who became icteric before death (No. 57) also had some liver alterations before the administration of anabolic steroids. In this patient, the jaundice progressed after the anabolic agent was stopped and he died 21 days after steroid withdrawal. Permission for post-mortem examination was denied and no definite conclusion on the etiology of the liver lesion could be reached.

Other patients showed milder nonprogressive alterations in liver function consisting of the appearance of elevated BSP retention values of 10 to 27 per cent (normal up to 5 per cent). These alterations became clinically evident from one to five months after therapy was instituted, and did not progress even though therapy was continued. Mild to marked alterations in liver function were observed in 80 per cent of the patients during therapy with oxymetholone, a 17-alkylated steroid, and in 26 per cent of those treated with metholone and methenolone, both nonalkylated forms. The lesser hepatotoxic effect of the latter two was particularly evident in 4 cases in whom alterations in liver function observed while receiving oxymetholone completely regressed when they were switched to metholone or methenolone. In 2 other
### Table 2.—Liver Data in the Patients who Became Jaundiced During Therapy

<table>
<thead>
<tr>
<th>Case</th>
<th>Steroid*</th>
<th>Dose†</th>
<th>Days‡</th>
<th>D.B.I</th>
<th>S.B.P.</th>
<th>G.P.T.</th>
<th>A.P.</th>
<th>Outcome and Histopathologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>MD</td>
<td>1.9</td>
<td>29</td>
<td>0 - 2.6</td>
<td>2 - 35</td>
<td>30 - 415</td>
<td>3.2 - 2.7</td>
<td>Recovered</td>
</tr>
<tr>
<td>52</td>
<td>ML</td>
<td>2.2</td>
<td>180</td>
<td>? - 1.5</td>
<td>? - 41</td>
<td>? - 650</td>
<td>? - 17.6</td>
<td>Recovered</td>
</tr>
<tr>
<td>55</td>
<td>OX</td>
<td>1.6</td>
<td>20</td>
<td>0.3 - 1.4</td>
<td>? - 27</td>
<td>265 - 305</td>
<td>-----</td>
<td>Recovered</td>
</tr>
<tr>
<td>43</td>
<td>ML</td>
<td>3.0</td>
<td>13</td>
<td>0 - 8.4</td>
<td>6 - 23</td>
<td>8 - ?</td>
<td>6.1 - ?</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2</td>
<td>8</td>
<td>? - 1.4</td>
<td>? - 33</td>
<td>? - 500</td>
<td>? - 5.9</td>
<td>-----</td>
</tr>
<tr>
<td>57</td>
<td>OX</td>
<td>1.9</td>
<td>25</td>
<td>0.4 - 14.4</td>
<td>? - 66</td>
<td>? - 2950</td>
<td>-----</td>
<td>Died: no postmortem studies</td>
</tr>
<tr>
<td>58</td>
<td>OX</td>
<td>2.3</td>
<td>12</td>
<td>0.8 - 4.4</td>
<td>? - 24</td>
<td>55 - 135</td>
<td>? - 5.9</td>
<td>Died: Bronchoneumonia. Marked hemosiderosis. Chronic cholangitis and pericholangitis.</td>
</tr>
<tr>
<td>63</td>
<td>MT</td>
<td>2.1</td>
<td>7</td>
<td>0.4 - 4.5</td>
<td>22 - 51</td>
<td>120 - ?</td>
<td>-----</td>
<td>Died: Cerebral hemorrhage. Phlegmonous colitis. Passive chronic congestion of the liver.</td>
</tr>
</tbody>
</table>

* MD = methandrostenolone; ML = methenolone; OX = oxymetholone; MT = metholone or dromostanolone.
† Dose in mg./Kg./day. Days from start of therapy to clinical jaundice.
‡ D. B. = Serum direct bilirubin; S.B.P. = sulfobromophthalein retention in percent 30 minutes after the injection of 2mg./Kg.; G.P.T. = glutamic pyruvic transaminase (Karmen units); A.P. = alkaline phosphatase (Bodansky units). The first value is the result obtained before starting anabolic therapy; the second one is the most abnormal obtained during the jaundice episode.
patients, treated first with methenolone and later with oxymetholone, abnormalities in the liver function appeared only during therapy with the 17-alkylated compound. (See case J.C. in the appendix).

Post-mortem examinations in 15 patients treated for 1 to 10 months with no clinical jaundice at the time of their death failed to show any sign of liver cell damage or cholestasis.

C. Others: Moderate edema and cushingoid facies were frequently seen in patients treated with corticosteroids and anabolic agents simultaneously; when the latter were given alone, edema was observed in only one instance.

Body weight increased in all children after one month of therapy. However, as they were growing it is difficult to estimate what proportion of the weight increase can be ascribed to the anabolic agents. This difficulty was documented in a previous publication showing height and growth curves of patient No. 14, who in 4 years of cyclic therapy gained 24 Kgs. and 25 cm. In two-thirds of the adults a weight gain of 1 to 13 Kgs. occurred; in most cases, this ranged from 3 to 4 Kgs. No weight gain was observed in the other third.

No growth retardation nor radiologic evidence of any bone maturing effect of the anabolic steroids was observed.

Discussion

Diagnosis

Clinical material of the present report fulfilled all the requirements for the diagnosis of aplastic anemia except for the lack of bone marrow hypocellularity in some cases. However, although bone marrow hypocellularity is essential for diagnosis, the existence of cases lacking such a feature has long been recognized; these cases are otherwise identical with the typical ones in clinical and laboratory picture, etiology and prognosis. In addition, bone marrow cellularity in cases almost invariably becomes greatly reduced. The term “refractory anemia” suggested for these cases has not received general acceptance and they are usually considered as aplastic anemia.

The Effect of Anabolic Androgenic Steroids in Aplastic Anemia

The results reported here confirm our previous observation on the usefulness of oxymetholone in the treatment of acquired aplastic anemia. In addition, they show that other anabolic-androgenic steroids, methenolone, and dromostanolone, share the therapeutic activity of oxymetholone. The remission rate, 48 per cent for all cases and 70 per cent for those treated for a sufficient length of time (2 months or more), is similar to that of our initial series. Dameshek, Romero and Rosales, and Allen et al. have confirmed the beneficial effect of oxymetholone in the treatment of aplastic anemia. Other anabolic agents such as methenolone, stanozolol, methandrostenolone, and norethandrolone have also been found to induce a remission in about 50 per cent of patients with aplastic anemia.

The results obtained with anabolic androgenic steroids contrast with the general experience in aplastic anemia treated otherwise. Thus, we observed
only 6 remissions (11.7 per cent) in 51 cases treated with corticosteroids and 4 (23.5 per cent) in 17 treated with splenectomy. Prior to the use of anabolics, all patients with aplastic anemia secondary to insecticides and phenylbutazone seen by us died. Larger series of patients have been reported with even poorer results. In Wolff's series of 334 patients treated by different means, including splenectomy in 35, only 11 “were considered cured” and 7.7 per cent survived for more than 5 years, and in the most recent series reported by Najean et al., over 50 per cent of 116 cases died within one year, and only 12 achieved remission.

Sequence and Quality of the Remissions

Response to anabolic therapy is usually delayed (2 to 3 months), though in a few cases it starts earlier (15 to 30 days) or later (5 to 6 months). The initial signs of improvement have consisted of reticulocytosis, usually of moderate degree, stabilization of hemoglobin at a low level, 7 to 9 Gm./100 ml., and in many cases, marked diminution of abnormal bleeding. The hemoglobin level begins to rise slowly about one month after the onset of reticulocytosis (Fig. 1).

In all cases responding to therapy, hemoglobin rose to normal levels; in 2 out of 5 cases neutrophils increased to or above 2,500 per cmm. and in one-third of the cases, platelets became normal in number (above 180,000/cmm). In most of the others, there was some rise in neutrophils and platelets though in some the rise in platelets was almost negligible. Summing up our cases with those of Shahidi and Diamond and Najean et al., the neutrophils became normal in 24 and platelets in 18 out of 67 cases with acquired aplastic anemia who responded to therapy.

It is worth mentioning that in all cases developing a red cell remission, including those with little or no improvement in neutrophils and platelets, the clinical manifestations of the neutropenia and thrombocytopenia disappeared and even the menstrual bleeding became normal. Najean et al. and Allen et al. have reported similar observations.

Course After Discontinuation of Therapy

Androgen-induced remissions may be permanent in acquired aplastic anemia, and after stopping therapy the improvement persists and may indeed increase. This has occurred in over two thirds of our cases and in 58 out of 76 cases reported in four large series (2, 13, 16 and present report). Other patients have relapsed one to four months after therapy was stopped. Second remissions have been induced with renewal of therapy. In several cases, these second remissions have been permanent. Thus, relapse after the first therapeutic trial does not mean that the patient will constantly require maintenance therapy.

The Concomitant Administration of Corticosteroids

The concomitant administration of corticosteroids with anabolic steroids is not necessary in the treatment of acquired aplastic anemia. In no case of our series has the hematologic course been significantly modified by the addition
of corticosteroids. The remission rate in our patients treated only with anabolic agents (14 remissions in 29 cases) is comparable to that attained in those who received in addition prednisone (19 remissions in 40 cases). In patients requiring maintenance therapy or who have had relapses, the response to the androgenic hormones has not been improved by the simultaneous administration of glucocorticoids. Furthermore, in young patients no bone maturation effect of oxymetholone and methenolone has been detected. On the contrary, prednisone greatly increases the side effects of androgens and its use in aplastic anemia may be dangerous, particularly when neutropenia is severe.

The Useful Doses of Anabolic Steroids

It is not possible, from the present data, to delineate the optimal dose of these anabolic steroids. This is probably due to two reasons: a) the small size of the groups, and b) the therapeutic activity of even small doses. The latter point is confirmed by the responses observed by Romero with 0.25 to 0.91 mg./Kg./day of oxymetholone and by Pavlovsky and Bergna with 10 mg./day of stanozolol. We believe, however, that large doses, such as 2 mg./Kg./day should be used, since a) a relationship between amount of steroid and magnitude of the response has been observed in 2 of our patients permanently requiring maintenance therapy, 2 mg./Kg./day having been necessary to obtain the highest response; b) two cases showing no response after 12 and 3 months of therapy with 0.5 and 0.25 mg./Kg./day of oxymetholone, respectively, entered in remission when the dose was increased to 1 mg./Kg./day; c) low doses of anabolic steroids have been found useless by some authors; and d) a longer period for the remission seems to be required when low doses are given. In the series of Romero the average duration of treatment to the start of improvement was about 11 months. The importance of the rapidity with which the response to therapy occurs in a condition with a high mortality risk does not need to be emphasized.

Prognostic Factors

Our observations together with those of others indicate that the response of aplastic anemia to therapy is unpredictable. Age, sex, etiology of the anemia, duration or severity of the disease, degree of the anemia or of the thrombocytopenia, and cellularity of the bone marrow do not seem to be relevant factors in determining the response to therapy. In our as well as in others experience only the presence of extreme degrees of neutropenia and reticulocytopenia appear to have some prognostic significance.

Testosterone and the Anabolic Steroids

Certain anabolic androgenic compounds appear to be more active bone marrow stimulators than testosterone. We have reported that oxymetholone, dromostanolone and methenolone have greater erythropoietic effect on rats and mice that does testosterone. It has also been observed that adults with aplastic anemia respond poorly to testosterone. This was particularly evident in the report of Seligman consisting of a survey among clinical investigators.
from North and South America, Europe and Japan: 13 out of 17 scientists consulted reported that testosterone had been of little or no value in the treatment of adults with aplastic anemia, and only two of them had observed a sizable number of remissions: 25 per cent (Storti) and 49 per cent (Bierman). In contrast are the results of the use of oxymetholone and similar agents. In the report of Seligman, one of the investigators (Dameshek) was quoted as follows: "he contrasts the almost nil results obtained with massive doses of testosterone with the very encouraging results he has recently observed with 100 to 300 mg. of oxymetholone daily per os; in 50 per cent of the cases, he has noticed a striking effect on hemoglobin values after 2 to 4 months of treatment." Furuhielm and Ekiund have reported that 0.1 mg./Kg./day of ethylestrenol was sufficient as maintenance dose in children with Fanconi's aplastic anemia whereas 10 mg. or more of methyltestosterone daily are required for the same purpose.

Comparison of the therapeutic effect of testosterone and anabolic agents in limited numbers of cases of aplastic anemia have failed to show clear superiority of any agent. Most interesting is the observation of Allen et al. of 2 children with aplastic anemia, refractory to testosterone (2 mg./Kg./day for 7 months in one, and 4 mg./Kg./day for 8 mos in the other), who responded to oxymetholone. However, more cases treated with both androgens are necessary to elucidate whether oxymetholone and other similar steroids are therapeutically more effective than testosterone. Patients requiring constant maintenance therapy, such as those with congenital aplastic anemia, appear to be best for this purpose.

Anabolic and Liver Damage

The problem of the hepatotoxicity of the anabolic-androgenic steroids, though decreased, has not been completely eliminated with the use of non-17-alkylated compounds. Alterations in liver function tests were observed in a fourth of the cases receiving metholone and methenolone. In most cases, they were very mild, with no clinical significance and if not specifically searched for might have been passed unnoticed. In animal experimentation it has been seen that even testosterone produces some morphologic abnormalities in the liver canaliculi. It seems likely that large doses of testosterone produce similar subclinical alterations in liver function in a small percentage of patients. Such abnormalities have probably been missed because they have not been adequately looked for. Mild rises in serum transaminases after a moderately large dose of testosterone enantate (500 mg. per week) have already been reported. Thus, it seems that all the androgenic-anabolic steroids exert some hepatic effect which is certainly greater in those compounds alkylated in the C17 position. Patients with aplastic anemia not treated with anabolic-androgenic agents have a high risk of liver dysfunction. In the series of Mohler and Leavell, 24 per cent of the patients showed definite abnormalities in liver function tests. Hemosiderosis, bacterial infections and serum viral hepatitis appear to be more important factors than steroids in the production of severe liver
alterations. Thus, in the present series, 4 of the 5 cases dying with jaundice, the former were the most likely responsible factors. Occasionally, (as in case J. C. in the appendix) marked liver impairment is produced by the administration of a 17-alkylated steroid forcing its withdrawal. In these cases, the substitution of the 17-alkylated compound by a non-alkylated one may permit continuation of therapy.

**SELECTED CASE REPORTS**

F.C., (Case 53), a 17 year old girl, was first seen in January 1965 with a past history of repeated exposures to DDT and several courses of chloromycetin. Two weeks prior to admission she began to complain of easy fatigue and purpura. Physical examination revealed only pallor and generalized petecchiae and ecchymoses.

Initial laboratory data: hemoglobin, 7 Gm./100 ml., hematocrit, 22 per cent; reticulocytes, 3.4 per cent; WBC, 7,250 with 25 per cent PMN and 72 per cent lymphocytes, platelets 10,000. Bone marrow: markedly hypocellular with no megakaryocytes.

Therapy with oral methenolone, 150 mg. (2.5 mg./kg./day), prednisone, 60 mg. daily, and blood transfusions was started. At the end of February she developed profuse melena for 15 days and a severe bronchopneumonia. The white blood cell count decreased progressively to 2,600 cmm. with 9 per cent PMN. A needle bone marrow biopsy taken in May showed severe hypoplasia. From March to May she continued to exhibit purpura and required 600 ml. of blood weekly. Thrombocytopenia and neutropenia persisted without change. From the middle of May to early August she was under Dr. William Dame shek's care. During these months she received daily 300 mg. of oxymetholone and 60 mg. of prednisone. On May 17 she underwent splenectomy. In June and July, phytohemagglutinin was added to her therapy and she was given 300 ml. of her father's bone marrow. In August she returned to Mexico and continued to receive oxymetholone, but prednisone was discontinued. From then on, blood cell values improved slowly and at the end of October, anabolic steroid therapy was stopped. The blood counts at that time included: hemoglobin, 12.6 Gm./100 ml.; hematocrit, 41 per cent; WBC, 5,000 with 42 per cent PMN, 108,000 platelets, and reticulocytes, 5.6 per cent.

She was off therapy for 4 months. During this time, her blood cell counts slowly deteriorated, the lowest values being: hemoglobin, 9.6 Gm./100 ml; hematocrit, 31 per cent, WBC, 4,000 with PMN 28 per cent, reticulocytes, 2.5 per cent; and platelets, 44,000. Oxymetholone was restarted, 100 mg. daily for 3 months, and lower doses, 6 to 12 mg., for 5 additional months. A second remission occurred: reticulocytes rose to 7 per cent (in 60 days), and immediately thereafter, all cell values improved: hemoglobin to 16 Gm.; hematocrit to 48 per cent; WBC to 7,700, PMN to 60 per cent, and platelets to 130,000. At present, 18 months after oxymetholone was stopped, she continues to have mild thrombocytopenia (160,000 per cmm.) but no anemia or neutropenia. The last bone marrow examination revealed hypercellularity with moderately decreased megakaryocytes and a moderate normoblastic reaction.

The patient developed moderate hirsutism, acne and cushingoid facies when taking both cortico- and anabolic steroids. These signs were not observed when therapy consisted only of oxymetholone. Moderate hoarsening was noticed whenever the dose of anabolic steroids was 50 mg. or greater, and disappeared within 3 months after its withdrawal or after reducing the dose to 12 mg. per day. Menses were absent during methenolone and oxymetholone administration, regardless of the dose, but reappeared at 1.5 and 1 months, respectively, after therapy was stopped. No clinical jaundice nor any alteration in liver function tests other than a rise of serum direct bilirubin to 0.3 mg./100 ml. were observed.

**Comment**

This patient with very severe aplastic anemia went into an excellent remission after a prolonged treatment with methenolone and oxymetholone. In addition, other therapies were
used and though it is possible that the latter might have contributed to the improvement, it seems more likely that the remission was due to the anabolic therapy as it occurred when the patient was taking only oxymetholone, a relapse followed its withdrawal and a second permanent remission followed oxymetholone readministration. This patient exemplifies several points: a) the beneficial effect of anabolic therapy in aplastic anemia may take over 6 months to occur; b) a relapse may occur when anabolic therapy is stopped, but this does not indicate that permanent maintenance therapy will be necessary; c) corticosteroids increase the side effects of anabolics and are not necessary for the effectiveness of the latter; d) small dose of oxymetholone are sufficient to produce amenorrhea; e) hoarsening and amenorrhea secondary to anabolic therapy are rapidly reversible; f) large doses of 17-alkylated anabolic steroids may be tolerated for several months without liver alterations.

R.S.R., (Case 64), a 47 year old retail salesman, was admitted to the Hospital de Enfermedades de la Nutrición on May 26, 1966, with a 4 month history of progressive pallor and spontaneous ecchymoses. Prior to admission he had been treated with blood transfusions, folic acid, vitamin B₁₂, parenteral iron and prednisone 40 mg. daily for 25 days) without improvement. He denied exposure to toxic substances, including insecticides, and ingestion of drugs of any type. Three years before he had been icteric for 2 months, unaccompanied by any other symptoms.

Physical examination showed a pale, moderately obese man with a subconjunctival hemorrhage in the left eye and several ecchymoses on the legs. There was no lymphadenopathy, hepatosplenomegaly, or any other relevant abnormality.

Initial laboratory data: hemoglobin, 8.4 Gm./100 ml.; hematocrit, 25 per cent; reticulocytes, 1 per cent; WBC, 3,250 with 37 per cent PMN and 23,000 platelets. Bone marrow: markedly hypocellular with no megakaryocytes, 21 per cent normoblasts, 33 per cent lymphocytes, 3 per cent plasma cells and 42 per cent granulocytes. Hemoglobin F, 2.4 per cent. Serum direct bilirubin, 0.2 mg./100 ml., BSP retention 7.5 per cent (after 30 minutes), serum pyruvic transaminase, 2 K. units, alkaline phosphatase 1.4 B. units. Blood chemistry, urine, sero-latent reactions, acid hemolysis test and fecal parasitic examination gave normal or negative results.

On June 4, 1966, the patient was begun on oral methenolone, 150 mg./day (2 mg./Kg.). Over the next 2 months he received 2 transfusions of 500 ml. each, as the hemoglobin had fallen to 5.4 Gm./100 ml. In August, the reticulocytes rose to 4 per cent and the hemoglobin leveled off at about 8.5 Gm. From September on, he had no new ecchymoses and on November 24, the anabolic steroid therapy was withdrawn. At that time, he had: hemoglobin, 12 Gm./100 ml.; hematocrit, 37 per cent; reticulocytes, 6 per cent; WBC, 4,100 with 57 per cent PMN; platelets were observed diminished ++ in the smear. Hemoglobin and platelets continued to rise and since February, 1967 to the last examination (June, 1968), his hemoglobin has ranged from 14.4 to 15 Gm. and leukocytes and platelets have been normal. A bone marrow puncture in February, 1967 showed normal cellularity and megakaryocytes, 32 per cent normoblasts and 17 per cent lymphocytes. The patient did not show any side effect to the anabolic-androgenic steroid therapy.

Comment

This adult male with aplastic anemia, apparently idiopathic, promptly and completely responded to the administration of anabolic steroids. The response pattern was the usual one: the erythrocyte improvement was slow, it took about 2 months to start and 7 months to be complete. Improvement continued after therapy was withdrawn, and has continued without any maintenance therapy for over two years. This patient exemplifies that anabolic steroid therapy is effective in the idiopathic form of acquired aplastic anemia and in males in the active androgenic age. It also shows that the addition of corticosteroids is not necessary.

J.C., a 35 year old male started with symptoms of anemia, epistaxis and purpura in early 1964, shortly after having taken chloramphenicol. He was seen by a hematologist who made the diagnosis of aplastic anemia and started treatment with blood transfusions and daily oral oxymetholone, 150 mg. (2.2 mg./Kg.), and prednisone 30-40 mg. Around the
fiftieth day of oxymetholone therapy, jaundice was noticed and liver function tests showed:
serum direct bilirubin, 3.4 mg./100 ml. alkaline phosphatase 3.0 B. units, and serum pyruvic transaminase 2,275 units. Hematologic improvement had already been noted and continued for the next 4–5 months without oxymetholone. The hemoglobin rose to 14.2 Gm. and platelets to 110,000/cmm. (pretherapy value 20,000). Jaundice slowly regressed and disappeared completely 2.5 months after stopping oxymetholone. Serum pyruvic transaminase values took 7 months to become normal. When liver disfunction had regressed completely, the patient was in hematologic relapse: anemia and abnormal bleeding had reappeared and blood transfusions were again necessary. Oxymetholone, 150 mg. daily, was reintiated and was increased to 300 mg. one month later. After 2.5 months of anabolic therapy, jaundice reappeared and oxymetholone was discontinued. During this icteric episode, the serum direct bilirubin rose to 5.7 mg./100 ml. and pyruvic transaminase to 2,280 K. units. Alkaline phosphatase remained normal (1.95 and 3.6 B. units). At that time, improvement in all blood cells had been induced and persisted for 5 months, when a second hematologic relapse occurred. Prednisone, 80 mg. daily was given without benefit. A third course of oxymetholone was followed by both hematologic improvement and liver alterations. The latter regressed within 2 months and oxymetholone, 75 mg./day, was re-instituted and given for 4 months. As the serum direct bilirubin and pyruvic transaminase again rose (see below), oxymetholone was substituted by intramuscular metholone, 200 mg./day, and liver function tests regressed completely to normal.

Comment

This patient was seen by one of us (LSM) only occasionally and for that reason he was not included in the material analyzed for the present paper. However, his history is given above for the purpose of illustrating several unusual features: a) maintenance therapy may be occasionally needed in acquired toxic aplastic anemia and not only in the congenital type; b) profound alterations in liver function may be observed with the administration of 17-alkylated androgenic steroids; c) liver disfunction secondary to a 17-alkylated steriod often regresses completely when the latter is withdrawn or is substituted by a non-alkylated one; and d) the pattern of anabolic steroid induced liver alteration most often is not that of obstructive jaundice. In a number of our cases, along with the rise in direct bilirubin and in BSP retention, high serum pyruvic transaminase values were observed without any significant rise in alkaline phosphatase.

SUMMARY

The results of the oral administration of high doses of anabolic hormones (oxymetholone, metholone or dromostanolone and methenolone) in the treat-
ment of 69 patients (14 children and 55 adults) with aplastic anemia are presented. Remission rates were 48 per cent for the whole group and 70 per cent for those treated for more than two months. Twenty-two cases have been in remission for 1 to 5 years without maintenance therapy. Eight others relapsed 2 to 4 months after stopping therapy, but responded to the reinition of medication. However, four of them have had several relapses and appear to require permanent therapy. In the other four, the second remission has continued for 6 to 40 months. Clinical response was first noted after 0.6 to 6 months of therapy and was characterized by a rise of hemoglobin to normal levels with a variable degree of improvement in the leukopenia and thrombocytopenia. The number of neutrophils and platelets rose to normal levels in over a third of the cases which responded. Response to therapy was not related

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*We are indebted to R. González, M.D. and E. Gutman, M.D. for their permission to report the clinical history of this case.
to age, sex, etiology, degree of pancytopenia or bone marrow cellularity. The three anabolic hormones seemed equally effective.

Nine patients became clinically jaundiced during therapy; four recovered and five died. Abnormalities in liver function existed before treatment in three of those who died. In four of these five cases, the liver lesion was due to an independent cause: viral hepatitis in one, gram negative septicemia and necrotic colitis in two and thiazide toxicity in the fourth. No autopsy was performed in the other case and the etiology of his liver damage could not be determined. Three of the fatal cases were taking a non-17-alkylated steroid. Other patients presented mild, subclinical and nonprogressive rises in serum direct bilirubin and in BSP retention. The frequency of liver function changes was greater (80 per cent) with oxymetholone than with the other two non-17-alkylated steroids (26 per cent). The changes induced with the former drug regressed completely when metholone or methenolone was substituted. Other side effects were amenorrhea and mild virilization; no growth retardation or changes in bone maturation were observed.

Our results suggest that some anabolic adrogenic steroids may be more useful than testosterone in the treatment of aplastic anemia.

SUMMARIO IN INTERLINGUA

Es presentate le resultatos del administration oral de alte doses de hormones anabolic (oxymetholona, metholona, e methonolona) in le tractamento de 69 patientes (14 juveniles e 55 adultos) con anemia aplastic. Le proportion de remissions esseva 48 pro cento pro le gruppo total e 70 pro cento pro le gruppo de subjectos tractate durante plus que duo menses. In 22 casos, le condition ha essite in remission durante inter 1 e 5 annos sin therapia de mantenentia. In 8 altere, recidiva occurreva 2 a 4 menses post le discontinuation del therapia, sed le condition respondeva al reinstitution del medication. Tamen, 4 del 8 patientes in iste gruppo habeva repetite recidivas e pare requirer un therapia permanente. In le alte 4, le secunde remission ha continuate durante 6 a 40 menses. Le responsa clinic esseva primo notate post 0,6 a 6 menses de therapia. Illo esseva characterisate per le ascension del nivello de hemoglobina a valores normal con grados variabile de melioration in le leucopenia e le thrombocytopenia. Le numero de neutrophilos e de placchetas montava a nivellos normal in plus que un terto del casos in que le responsa esseva positive. Le responsa al therapia non esseva correlationate con le etate o le sexo del patientes e non con le etiologia del condition o le grado de pancytopenia o de cellularitate del medulla ossee. Le tres hormones anabolic pareva esser equal in efficicatate.

Durante le therapia, 9 del patientes disveloppava grados clinic de jalnessa. Quatro de illes se restabliva, sed 5 moriva. In 3 del 5 casos de morte, le patientes esseva terminalmente sub tractamento con un sterile non-17-aloxylate. Altere patientes presentava leve, sub-clinic, e nonprogressive augmentos del valores seral de bilirubina directe e de retention de sulfobromophthaleina. Le frequentia de alterationes in le functiones hepatic esseva plus grande (80 pro cento) post oxymetholona que post le alte doui steroids non-17-aloxylate (26 pro cento). Le alterationes inducte con oxymetholona regredeva completely quando metholona o methenolona esseva substituite. Altere effectos lateral esseva amenor-rhea e leve e leve grado de virilisation. Esseva observate nulle retardo de crescentia e nulle alteration in le maturation del ossos.

Nostre resultatos suggestiona que certe anabolic steroides androgenic es possibilemente plus utile que testosterona in le tractamento de anemia aplastic.

REFERENCES
Testosterone-induced remission in aplastic
2. Shahidi, N. T., and Diamond, L. K.:
ANABOLIC ANDROGENIC STEROIDS


ADDENDUM

Recently the following three reports have been published confirming the favorable effect of oxymetholone in the treatment of aplastic anemia:


Anabolic Androgenic Steroids in the Treatment of Acquired Aplastic Anemia

L. SANCHEZ-MEDAL, A. GOMEZ-LEAL, LORENZO DUARTE and MARIA GUADALUPE RICO

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