Steroid Hormone Metabolism in Chronic Myelogenous Leukemia

By T. F. Gallagher, Leon Hellman, Barnett Zumoff and Daniel G. Miller

EARLIER REPORTS from these laboratories have described abnormalities in the production and metabolism of adrenocortical hormones in patients with chronic lymphatic leukemia. In order to explore further the possible relationship of adrenocortical function to neoplastic disease of the hematopoietic tissues, similar studies have now been made of a group of patients with chronic myelogenous leukemia. The majority of these patients were in good general condition at the time of the study; a smaller group was acutely ill, and one subject was otherwise well but under treatment with a chemotherapeutic drug. These latter are included for comparison with the “well” patients in order to shed light on some possible factors which might influence adrenocortical function in this disease. The results of the present study differ significantly from the earlier findings in chronic lymphatic leukemia. There was no evidence of the prominent sex difference in steroid metabolism noted in lymphatic leukemia. The depressed output of corticoid metabolites seen in men and the low production of androgen metabolites seen in both sexes with lymphatic leukemia were likewise absent. However, the abnormal pattern of peripheral hydrocortisone metabolism previously observed in chronic lymphatic leukemia (i.e., more tetrahydrocortisol than tetrahydrocortisone) was also found in chronic myelogenous leukemia, if anything, to an even greater extent. The findings indicate that these two diseases, clinically so different, are also characterized by differences in endocrine function.

MATERIAL AND METHODS

Hormone Metabolites

Complete 24 hour urine collections, as judged from the constancy of creatinine excretion, were obtained on 3 consecutive days. These were combined and processed promptly by methods that have been described in detail. The individual compounds were isolated by quantitative chromatography on paper. Metabolites containing a dihydroxyacetone side chain were isolated from unfractionated neutral steroid extract obtained after treat-

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The following abbreviations and trivial names are employed: Hydrocortisone: 11β,17,21-trihydroxy-Δ4-pregnen-3,20-dione; Tetrahydrocortisol: THF: 3α,11β,17,21-tetrahydroxy-pregnane-20-one; Tetrahydrocortisone: THE: 3α,17,21-trihydroxy-pregnane-11,20-dione; ATHF: 3α,11β,17,21-tetrahydroxyallopregnane-20-one; A: Androsterone; 3α-hydroxy-5-androstan-17-one; E: Etoiocholanolone; 3α-hydroxyetiocholane-17-one; D: Dehydroisoandrosterone; 3β-hydroxy-Δ4-androstene-17-one.
Table 1.—Clinical Status of Patients with Chronic Myelogenous Leukemia

<table>
<thead>
<tr>
<th>Subject, Age and Sex</th>
<th>Creatinine (Gm./24 hr.)</th>
<th>Hb (g)</th>
<th>WBC x 10^3</th>
<th>Liver/Spleen Costal Margin</th>
<th>Antecedent Therapy</th>
<th>Duration of Disease (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. S., 72, M</td>
<td>102</td>
<td>2.3</td>
<td>13</td>
<td>36</td>
<td>0/3</td>
<td>Busulfan 60</td>
</tr>
<tr>
<td>K. N., 53, M</td>
<td>85</td>
<td>1.7</td>
<td>12</td>
<td>11</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>D. V., 58, M</td>
<td>66</td>
<td>1.3</td>
<td>12</td>
<td>130</td>
<td>8/10</td>
<td>144</td>
</tr>
<tr>
<td>M. E., 65, M</td>
<td>61</td>
<td>0.9</td>
<td>9</td>
<td>210</td>
<td>0/5</td>
<td>Leukopheresis 3</td>
</tr>
<tr>
<td>L. N., 73, M</td>
<td>57</td>
<td>0.8</td>
<td>10</td>
<td>44</td>
<td>8/8</td>
<td>7</td>
</tr>
<tr>
<td>H. N., 52, F</td>
<td>44</td>
<td>0.8</td>
<td>14</td>
<td>10</td>
<td>2/0</td>
<td>Busulfan 18</td>
</tr>
<tr>
<td>W. R., 38, F</td>
<td>95</td>
<td>1.4</td>
<td>12</td>
<td>83</td>
<td>8/8</td>
<td>Busulfan 24</td>
</tr>
<tr>
<td>F. A., 47, F</td>
<td>52</td>
<td>0.9</td>
<td>12</td>
<td>36</td>
<td>0/7</td>
<td>7</td>
</tr>
<tr>
<td>H. O., 67, F</td>
<td>50</td>
<td>0.5</td>
<td>9</td>
<td>50</td>
<td>10/20</td>
<td>10</td>
</tr>
</tbody>
</table>

Patients Acutely Ill at Time of Study

<table>
<thead>
<tr>
<th>Subject, Age and Sex</th>
<th>Cretinine (Gm./24 hr.)</th>
<th>Hb (g)</th>
<th>WBC x 10^3</th>
<th>Liver/Spleen Costal Margin</th>
<th>Antecedent Therapy</th>
<th>Duration of Disease (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. I., 52, M</td>
<td>60</td>
<td>1.2</td>
<td>12</td>
<td>11</td>
<td>2/6</td>
<td>Cyclophosphamide 42</td>
</tr>
<tr>
<td>H. Y., 63, M</td>
<td>69</td>
<td>1.1</td>
<td>13</td>
<td>32</td>
<td>0/16</td>
<td>72</td>
</tr>
<tr>
<td>M. Y., 63, F</td>
<td>57</td>
<td>0.9</td>
<td>10</td>
<td>130</td>
<td>0/2</td>
<td>1</td>
</tr>
</tbody>
</table>

Under Treatment with Busulfan at Time of Study

<table>
<thead>
<tr>
<th>Subject, Age and Sex</th>
<th>Cretinine (Gm./24 hr.)</th>
<th>Hb (g)</th>
<th>WBC x 10^3</th>
<th>Liver/Spleen Costal Margin</th>
<th>Antecedent Therapy</th>
<th>Duration of Disease (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U. N., 16, M</td>
<td>70</td>
<td>1.6</td>
<td>14</td>
<td>42</td>
<td>0/11</td>
<td>Busulfan 6</td>
</tr>
</tbody>
</table>

Other pertinent clinical data: L. N., 73, M had essential hypertension; F. A., 47, F had past history of Graves' disease; B. I., 52, M had herpes zoster and hematuria from cyclophosphamide cystitis; H. Y., 63, M was severely cachectic; M. Y., 63, F had thrombophlebitis with fever.

TetrahydroMetabolites of Hydrocortisone

The urinary excretion of hydrocortisone metabolites is summarized in table 2 for all subjects with myelogenous leukemia. All 4 groups, “well” men, “well” women, acutely ill subjects, and the single man under chemotherapy treatment, showed the tendency for higher levels of tetrahydrocortisol than tetrahydrocortisone compared with normal subjects. Of 13 patients studied, THF was greater than THE in 7, and the 2 metabolites were equal in 4. In the 2 groups of “well” patients, the urinary excretion of the sum of the 3 metabolites, THF, THE, and ATHF, was within the normal range, and there was no difference between men and women. However, although the excretion of THF by men with chronic lymphatic leukemia and men with chronic myelogenous leukemia was near to control normal values, there appears to be a distinction between the “low normal” values in lymphatic leukemia and the “high normal” values in myelogenous leukemia. The 3 acutely ill subjects each showed a distinct elevation of urinary THF and the sum of all 3 metabolites. The single subject under treatment with busulfan showed...
distinctly subnormal values for the hydrocortisone metabolites. The excretion of ATHF did not vary greatly in any of these groups.

**Androsterone, Etioccholanolone and Dehydroisoandrosterone**

The metabolites of “adrenal androgens,” D, E and A, were probably not significantly different from normal in the 5 men studied. It is difficult to be certain about this conclusion because of the pronounced influence of aging upon this portion of the adrenal secretion. It may be noted that the 2 most elderly subjects excreted appreciable quantities of these metabolites; indeed, one was exactly the same as a man half his years.

The women subjects were so disparate in age and exhibited such variation in production of these metabolites that interpretation of the findings is precluded. A more extended examination of these metabolites in women patients with this disorder is most desirable.

**Comparison with Other Conditions**

Table 3 compares the mean values for metabolites of hormones found in the chronic myelogenous leukemia patients with those previously reported for chronic lymphatic leukemia. Included also are values for normal subjects, men with prostatic cancer and women with breast cancer. The latter 2 groups are significant since they are patients of roughly comparable age and severity of illness. The hydrocortisone metabolites of the prostatic cancer patients are recorded for the postorchiectomy study since the preoperative values are considered to reflect a degree of adrenal hyperfunction resultant from anxiety and pain.6

**Discussion**

Comparison of endocrine functions in chronic lymphatic and chronic myelogenous leukemia may possibly shed light on the marked differences in the clinical course of these diseases of the hematopoietic system, and might be of
Table 3.—Comparison of Mean Values for Steroid Hormone Metabolites of Patients with Chronic Leukemia, Breast Cancer, Prostate Cancer and of Normal Subjects

<table>
<thead>
<tr>
<th>Metabolites (mg./Gm. creatinine)</th>
<th>THF</th>
<th>THE</th>
<th>ATHF</th>
<th>Total</th>
<th>A</th>
<th>E</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelogenous leukemia</td>
<td>1.7</td>
<td>1.4</td>
<td>0.6</td>
<td>3.7</td>
<td>1.2</td>
<td>2.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Lymphatic leukemia(^1)</td>
<td>1.1</td>
<td>0.9</td>
<td>0.5</td>
<td>2.5</td>
<td>0.7</td>
<td>0.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Prostate cancer(^4)</td>
<td>1.4</td>
<td>1.6</td>
<td>0.6</td>
<td>3.6</td>
<td>0.9</td>
<td>1.8</td>
<td>2.7</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelogenous leukemia</td>
<td>1.6</td>
<td>1.5</td>
<td>0.5</td>
<td>3.6</td>
<td>0.6</td>
<td>1.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Lymphatic leukemia(^1)</td>
<td>1.8</td>
<td>1.6</td>
<td>0.7</td>
<td>4.1</td>
<td>0.5</td>
<td>0.7</td>
<td>1.2</td>
</tr>
<tr>
<td>Breast cancer(^1)</td>
<td>1.5</td>
<td>1.7</td>
<td>0.7</td>
<td>3.9</td>
<td>0.4</td>
<td>0.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Normal men and women(^3)</td>
<td>1.4</td>
<td>1.7</td>
<td>0.7</td>
<td>3.8</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^1\)Hydrocortisone metabolites of 4 men 7-10 days after orchiectomy; androgen metabolites of 10 men age 50-63 yrs. before orchiectomy.

\(^3\)Ten women age 50-60 yrs., otherwise unselected; unpublished data from these laboratories.

\(^4\)These values vary with age and sex.

value for the etiology of these disorders. For example, the sex difference in incidence of chronic lymphatic leukemia and a sex difference in hydrocortisone metabolism in this disease contrast sharply with the absence of both findings in chronic myelogenous leukemia. Again, chronic lymphatic leukemia with hydrocortisone production low in men, and metabolism disturbed in both sexes, is characterized by a high incidence of hemolytic anemia, a condition responsive to treatment with corticoids. In chronic myelogenous leukemia, with hydrocortisone production normal in amount, hemolytic anemia is uncommon. Further, chronic lymphatic leukemia often shows a therapeutic response to corticoid treatment whereas chronic myelogenous leukemia does not, and may even be aggravated by corticoid administration.

In an attempt to understand the disturbances of hydrocortisone metabolism in the two leukemic states, several factors warrant consideration: (1) pituitary-adrenal failure does not seem to play a role in the diminished steroid production in men with chronic lymphatic leukemia, since acute illness in both myelogenous and lymphatic leukemia is able to provoke a substantial rise in hydrocortisone production; (2) the low corticoid excretion in men with chronic lymphatic leukemia does not result from chronic illness itself. The present group of subjects with chronic myelogenous leukemia who constitute an almost ideal control study of patients with a similar disease and degree of illness, do not have depressed corticoid production; (3) the role of the lymphatic tissues in the peripheral metabolism of hydrocortisone may be important, since it has been shown that these tissues are active in this metabolic sequence.\(^7\)\(^-\)\(^8\) There are also differences between normal and neoplastic lymphatic tissues in the biotransformation of steroids; (4) hypermetabolism may play a key role in the present findings. This disturbance more common in chronic myelogenous leukemia than in chronic lymphatic leukemia, has been shown to be capable of producing a 50-75 per cent increase in hydrocortisone production.\(^9\) It is possible that the differences in hydrocortisone production observed in the two types of leukemia might be explicable on the basis of differences in the degree of hypermetabolism. The results in the single patient studied while under bulsulfan therapy are
compatible with this viewpoint and confirm the previous observation,
the remission induced, with the associated reduction of a hypermetabolic
state to normal, resulted in a decrease of hydrocortisone production to the
range characteristic of chronic lymphatic leukemia without hypermetabolism.

The changes in androgen excretion in the two types of leukemia are harder
to interpret, because of the small numbers of subjects and the marked in-
fluence of age and sex on the normal course of androgen production, in
contrast to their lack of influence on hydrocortisone production. In any case,
the impairment in the functional level of this portion of the adrenal secretion
in lymphatic leukemia appears established. The tentative conclusion is drawn
that androgen secretion is normal in myelogenous leukemia. These facts may
suggest possible therapeutic measures and it is hoped to explore some of
these in future studies.

Summary

Individual metabolites of steroid hormones were isolated and measured
from the urine of patients with chronic myelogenous leukemia. The results
were compared with earlier studies of patients with chronic lymphatic leu-
kemia, men with prostatic cancer, women with breast cancer and normal
men and women. The metabolites of hydrocortisone were in the normal range
for the patients with chronic myelogenous leukemia but the amount of tetra-
hydrocortisol was generally greater than that of tetrahydrocortisone. There
was no evidence for a sex difference in the production of these metabolites.
The tentative conclusion was drawn that metabolites of the “adrenal andro-
gen” were also in the normal range in chronic myelogenous leukemia. These
results contrast with those in chronic lymphatic leukemia patients where a
sex difference in production of hydrocortisone was evident and the metabolites
of “adrenal androgens” were at low levels in both sexes.

Acknowledgment

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REFERENCES


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