THE EFFECT OF CYPROTERONE ACETATE
ON THE PLASMA GONADOTROPHIN RESPONSE TO
GONADOTROPHIN RELEASING HORMONE

By
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ABSTRACT
Cyproterone acetate (100–150 mg daily) was administered to 8 male patients with excessive libido. Within 3 months a significant fall \((P < 0.02)\) in plasma testosterone was demonstrated. The plasma luteinising hormone (LH) and follicle stimulating hormone (FSH) responses to gonadotrophin releasing hormone (LH/FSH-RH) were also significantly impaired \((P < 0.05)\). A direct correlation between the resting plasma testosterone level and the LH response to LH/FSH-RH was demonstrated \((r = 0.743)\). It is concluded that the fall in plasma testosterone levels in patients receiving cyproterone acetate may be attributed to suppression of LH release, rather than an antiandrogen effect on the testis or hypothalamus.

Cyproterone has been shown to have an antiandrogenic action in laboratory animals and inhibits the development of male sex organs \((Hamada et al. 1963)\). The acetate derivative produces a fall in plasma testosterone levels in man \((Murray et al. 1973)\) and has been used in the treatment of hypersexuality \((Laschet & Laschet 1967)\), sexual precocity \((Rager et al. 1973)\) and hirsutism \((Hammerstein & Cupceanu 1969; Ismail et al. 1974)\).

The mode of action of cyproterone acetate is imperfectly understood, although it is thought to have both antiandrogenic and progestogenic properties \((Brotherton 1974)\). A fall in urine FSH excretion has been demonstrated \((Vosbeck & Keller 1971)\) but not confirmed \((Brotherton 1974)\). Resting plasma
LH levels have not been significantly reduced (Murray et al. 1973). It was the aim of this study therefore to analyse the effect of cyproterone acetate on gonadotrophin secretion in greater detail by observing the gonadotrophin response to LH/FSH-RH in patients undergoing treatment for excessive libido.

**PATIENTS AND METHODS**

Eight male subjects (ages 21–58 years) with excessive libido were referred from the Department of Psychological Medicine for assessment of endocrine function. Plasma testosterone levels and LH/FSH-RH stimulation tests were carried out prior to starting cyproterone acetate and were repeated at 2-4, 5-8 and 9–12 monthly intervals thereafter. The daily dose of cyproterone acetate was 100 mg taken orally in two divided doses. Patient S. F. received 150 mg daily after 3 months on the above dose.

The LH/FSH-RH (100 μg) was administered intravenously. Details of the LH/FSH-RH test and plasma LH and FSH radioimmunoassay procedures have been referred to previously (Donald & Espiner 1974). Results were expressed in terms of

**Table 1.**

The effect of cyproterone acetate administration on plasma testosterone levels and the maximum plasma LH increment following LH/FSH-RH.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time (months)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0  1  2  3  4  5  6  7  8  9  10 11 12</td>
</tr>
<tr>
<td><strong>Plasma testosterone (ng/dl)</strong></td>
<td></td>
</tr>
<tr>
<td>H. C.</td>
<td>665 94 59 54 63</td>
</tr>
<tr>
<td>G. C.</td>
<td>894 643 643 496</td>
</tr>
<tr>
<td>P. E.</td>
<td>482 255 255 263</td>
</tr>
<tr>
<td>S. F.</td>
<td>326 153 153 147</td>
</tr>
<tr>
<td>L. G.</td>
<td>739 186 186 184 309</td>
</tr>
<tr>
<td>R. H.</td>
<td>665 359 359 187 879</td>
</tr>
<tr>
<td>W. P.</td>
<td>355 595 595 595</td>
</tr>
<tr>
<td>D. F.</td>
<td>1430 284 284 284</td>
</tr>
<tr>
<td><strong>LH increment (ng/ml)</strong></td>
<td></td>
</tr>
<tr>
<td>H. C.</td>
<td>94 42 146 146 146 146 146 146 146 146 146 146 146 146 146</td>
</tr>
<tr>
<td>P. E.</td>
<td>146 83 83 83 83 83 83 83 83 83 83 83 83 83 83</td>
</tr>
<tr>
<td>S. F.</td>
<td>198 52 52 52 52 52 52 52 52 52 52 52 52 52 52</td>
</tr>
<tr>
<td>L. G.</td>
<td>146 42 42 42 42 42 42 42 42 42 42 42 42 42 42</td>
</tr>
<tr>
<td>R. H.</td>
<td>115 31 31 31 31 31 31 31 31 31 31 31 31 31 31</td>
</tr>
<tr>
<td>W. P.</td>
<td>354 125 125 125 125 125 125 125 125 125 125 125 125 125 125</td>
</tr>
</tbody>
</table>

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the human pituitary gonadotrophin reference preparation LER 907 which is stated to contain 20 IU FSH and 48 IU LH per mg (bioassay 2nd IRP standard). Plasma testosterone was measured by radioimmunoassay using the Searle anti-testosterone serum and the assay procedure of Williams et al. (1974) with minor modifications. The paired Student’s t-test was used for calculations of statistical significance.

RESULTS

Resting plasma testosterone levels and the maximum plasma LH increment following LH/FSH-RH administration, both before and during cyproterone acetate administration, are shown in Table 1. It will be seen that all 8 patients showed a diminished LH response to LRF after 2–4 months of cyproterone acetate therapy and 7 showed a fall in plasma testosterone concentration. However 2 patients subsequently showed a more than two-fold rise in plasma testosterone during continued cyproterone acetate therapy.

![Bar chart](https://example.com/bar_chart.png)

**Fig. 1.**
Effect of cyproterone acetate on mean basal levels of plasma testosterone and mean maximum plasma LH increments following LH/FSH-RH. The bars represent standard errors.
A significant fall in the mean basal plasma testosterone level was observed (Fig. 1) both at 2–4 and 5–8 months after starting cyproterone acetate ($P < 0.02$ and $< 0.05$ respectively). The mean plasma LH increment following LH/FSH-RH was significantly less at 2–4 months ($P < 0.05$) but the difference just failed to reach significance at 5–8 months.

The mean basal plasma LH level was 40.5 ng/ml ($\pm 8.3$ SEM) prior to treatment, 26.3 ($\pm 9.8$ SEM) at 2–4 months and 31.7 ($\pm 11.1$ SEM) at 5–8 months. No significant change in basal plasma LH or FSH levels was observed. The mean plasma FSH increment following LH/FSH-RH prior to treatment was 60.0 ng/ml ($\pm 23.4$ SEM), and 15.0 ng/ml ($\pm 8.3$ SEM) 2–4 months following treatment. The release of FSH following LH/FSH-RH administration was significantly reduced following cyproterone acetate ($P < 0.05$).

The correlation between the maximum increment in plasma LH following LH/FSH-RH and the corresponding basal testosterone value (see Table 1) was analysed. If the pre-treatment values are included $r = 0.743$, if excluded, $r = 0.533$ ($P < 0.01$). Hence a significant positive correlation between plasma testosterone and the LH response to LH/FSH-RH has been demonstrated during treatment with cyproterone acetate.

**DISCUSSION**

There is now little doubt that the administration of cyproterone acetate results in a fall in plasma testosterone levels (Murray et al. 1973), a conclusion which is confirmed by this study. However it does not necessarily follow that cyproterone acts only by inhibiting plasma testosterone levels. Indeed, the reduction in libido which was noted by the patients in this study was more marked than might have been expected from the testosterone levels alone, as the levels in 4 patients failed to fall below the lower limit of the normal range (230 ng/dl). This perhaps suggests that the antiandrogenic effect of cyproterone acetate in inhibiting the action of testosterone is also important. Unfortunately the reduction in libido was not readily accepted by some of the patients who admitted to irregularities in tablet taking. However the failure to exclude such patients would increase the significance of any changes which were observed as all results were included in the statistical analyses. It is possible that the two-fold rise in plasma testosterone levels which was observed in 2 patients may have been due to irregular tablet taking. However the recovery in plasma testosterone levels may also be due to the development of tolerance to this drug (Davies 1974; Ho 1971). In order to increase the accuracy of administration further studies are in progress using a long acting intramuscular preparation of cyproterone acetate.

The significant fall in the plasma LH response to LH/FSH-RH in patients
receiving cyproterone acetate suggests that this drug inhibits the release of pituitary gonadotrophins. Had the reduction in plasma testosterone levels been due to direct inhibition of testicular function, then the LH and also the FSH responses to LH/FSH-RH would have been increased (Donald & Espiner 1974). A similar result would have been expected had there been any interference with the inhibitory action of testosterone at hypothalamic level. Furthermore, the correlation which we have demonstrated between basal plasma testosterone levels and the LH response to LH/FSH-RH confirms that plasma LH and testosterone are positively related during cyproterone acetate therapy. Hence we conclude that the action of cyproterone acetate in lowering plasma testosterone levels in man, is the result of decreased gonadotrophin release from the pituitary, rather than an antiandrogen effect on the testis or hypothalamus.

ACKNOWLEDGMENTS

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REFERENCES

Ho S.: Congress Report, Schering AG., Cyproterone Acetate Symposium, Berlin,
Ismail A. A. A., Davidson D. W., Souka A. R., Barnes E. W., Irvine W. J., Kilimnik H.

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