THE STIMULATING EFFECT OF CHORIONIC GONADOTROPHIN ON THE ADRENAL CORTEX

BY

W. P. PLATE

The ability of the adrenal cortex to produce androgenic and oestrogenic substances is at present generally accepted. The production probably takes place in one particular layer, often referred to as the X-zone and usually localized in the zona reticularis. Botella Llusia (1951, 1952) uses the term »sexual adrenal gland« and refers to the X-zone as the third gonad, contending that this layer may adopt the hormonal function in insufficiency of the sexual glands.

The problem chiefly investigated so far is that of the production in the adrenal cortex of androgenic substances, which are excreted in the urine as 17-ketosteroids (17 KS). This adrenal function is considered to be influenced by the anterior pituitary gland. In this respect, many investigators mention ACTH, which also stimulates the production of other adrenocortical hormones. Reifenstein, Forbes, Albright, Donaldson & Carroll (1945), Reifenstein (1950), however, pointed out that the production of androgenic substances in the adrenal cortex is attributable to the luteinizing hormone (ICSH or LH). In a schematic drawing of the action of anterior pituitary hor-
mones, *Heller & Nelson* (1948 a) queried the view of the relationship between ICSH and the adrenal cortex; in a later publication (1948 b) the query was omitted. *Howard, Sniffen, Simmons & Albright* (1950) contend that both ACTH and LH have a stimulating effect on the production of androgenic substances. *Albeaux-Fernet’s* article in the »Encyclopédie Médico-Chirurgicale« (1951) comprises a schematic survey indicating LH as the cortitrophic hormone governing the production of androgenic substances. *Siliotti & Prosdomi* (1951) observed that the administration of urine from pregnant women to rabbits was followed by a 100 per cent increase in the excretion of 17 KS; histological examination of the adrenal glands revealed hyperplasia of the zona fasciculata and the zona reticularis. *Santos Ruiz, Gomez Maestro & Botella Llusia* (1951) observed an increase in the excretion of 17 KS following the injection of chorionic gonadotrophin into normal young men and women; the increase was attributed to stimulation of the adrenal cortex by LH. This conclusion is incorrect, inasmuch as the chorionic gonadotrophin may have stimulated the gonads to produce androgenic substances. *Landing & Gold’s* observations (1951) are of interest in this respect: in three male children, autopsy revealed both adrenocortical hyperplasia and hyperplasia of the Leydig cells of the testis, while increased activity of the basophile cells and decreased activity of the eosinophile cells of the hypophysis was also demonstrated. The testicular and adrenocortical changes are probably both attributable to an overproduction of LH.

Experiments carried out by *Diczfalusy, Holmgren & Westman* (1950) give another aspect of the question. Administration of chorionic gonadotrophin to castrated rats did not stimulate adrenal production of androgenic substances when the animals were submitted to hypophysectomy. This led to the conclusion that stimulation of the adrenal cortex requires the combined action of ACTH and LH.

Beside these investigators, who contend that LH has a stimulating effect on the production of androgenic substances in the adrenal cortex, there are many others who reject this
theory. This was expressed by Selye (1948) and Li (1948) in a discussion following an address by Heller & Nelson (1948 b). Later on Selye (1951) has not entirely rejected the possibility that LH stimulates the adrenals. Sayers & Sayers (1948) emphasized that there exists only one adrenocorticotropic pituitary hormone. Férin & Devis (1949) observed no stimulation of the adrenal cortex following administration of large doses of chorionic gonadotrophin to a female castrate previously treated with oestrogenic substances; the excretion of 17 KS was decreased after the test. Kyle & O'Donovan (1950) observed only a slight increase in the excretion of 17 KS after the injection of fairly large doses of chorionic gonadotrophin in a woman with pituitary hypogonadism. However, with reference to the occurrence of signs of oestrogenic activity they state that: »Although the slight rise in 17 KS excretion suggested that there had been stimulation of adrenal androgen production, the evidence of estrin secretion during the course of therapy might indicate the androgenic material was being formed by the ovaries« (p. 335). Segaloff, Sternberg & Gaskill (1951) observed a rise in the excretion of 17 KS in four and a fall in two women with ovaries, who had received large doses of chorionic gonadotrophin. Although the authors maintain that only the adrenal cortex is involved in the production of androgenic substances, they point out that their experiments do not warrant the conclusion that chorionic gonadotrophin exerts an influence on the adrenal glands. However, the rise in the excretion of 17 KS may also be attributable to the ovaries (Plate, 1951).

Reports on the production of oestrogenic substances by the adrenal cortex are much less numerous. All observations are based on the view that, beside the gonads, only the adrenal cortex is capable of producing oestrogens. Plate (1950) observed a case of severe metrorrhagia caused by oestrogenic substances which could only have been produced by the adrenal cortex. Pundel (1952) also observed marked oestrogenic activity in a female castrate. Botella Llusia (1952) administered chorionic gonadotrophin to castrated white mice
and came to the conclusion that the adrenal glands secreted androgens in males and oestrogens in females. *Jayle* (1952) observed an increase in oestrogenic substances after administration of mare serum gonadotrophin to castrated rabbits. It should be borne in mind, however, that the crude serum gonadotrophin used in these experiments may have contained ACTH.

We believe we have demonstrated stimulation of the adrenal cortex in two women treated with large doses of pure human chorionic gonadotrophin (pregnyl) after operative castration.

**Case report.**

A (1951-431). On September 14th, 1950, a woman of 51 underwent supravaginal hysterectomy and resection of both adnexa for diffuse myomatous changes in the uterus. In order to determine the effect of chorionic gonadotrophin on the ovaries, she was given 20,000 I. U. pregnyl daily for 4 pre-operative days (*Plate*, 1951). The adrenal function was determined with the aid of the *Thorn* test with adrenaline, which was positive, and with the *Robinson-Power-Kepler* test, both components of which were negative. A daily dose of 20,000 I. U. pregnyl was administered on November 7th, 8th and 9th, 1951. The excretion of 17 KS in the urine was determined at various intervals by *Dingemanse’s* method (1952), the results being corrected by means of the *Pincus* reaction; total determination was completed by fractional determination of most of the samples of urine. Oestrogenic substances in the urine were repeatedly determined by the method described by *De Jongh & Laqueur* (1938). The results are given in Table 1. The figures show that the injection of chorionic gonadotrophin is followed by an increase in the excretion of 17 KS in all fractions; this can only be a result of stimulation of the adrenal cortex. Fractional determination revealed that the fractions IV (androsterone) and V (aetiocholanolone) were invariably present. The theory that these fractions originate exclusively from androgenic substances produced by the gonads is therefore no longer tenable. *Nuyens* (1950) showed that these fractions do appear in the urine of castrates, as was the case with our patient. This inevitably leads to the conclusion that these 17 KS may also originate from the adrenal cortex.

Injection of pregnyl, however, not only stimulates the adrenal cortex to produce androgenic substances, but also causes an increase in the production of oestrogens. This was pointed out by *Dubois* (1952) at a meeting of the Dutch Endocrinological Society.
Table 1.

<table>
<thead>
<tr>
<th>Date</th>
<th>I. U. pregnyl</th>
<th>mg. 17-ketosteroids in 24 hrs urine</th>
<th>I. U. oestrogens in 24 hrs urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total content I II III IV V VI VII VIII</td>
<td></td>
</tr>
<tr>
<td>3rd Nov.</td>
<td></td>
<td>7.7 0.5 1.3 2.3 2.8 0.6 0.2</td>
<td>25 neg.</td>
</tr>
<tr>
<td>7th Nov.</td>
<td>20.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8th Nov.</td>
<td>20.000</td>
<td>12.9 1.1 2.8 3.1 3.7 1.7 0.5</td>
<td></td>
</tr>
<tr>
<td>9th Nov.</td>
<td>20.000</td>
<td>15.3 0.9 0.1 3.2 4.4 4.5 1.0 1.2</td>
<td>50 pos.—100 neg.</td>
</tr>
<tr>
<td>10th Nov.</td>
<td></td>
<td>11.7 0.7 0.4 1.6 3.4 2.9 1.7 1.0</td>
<td></td>
</tr>
<tr>
<td>20th Dec.</td>
<td>12.0</td>
<td></td>
<td>25 pos.—50 neg.</td>
</tr>
</tbody>
</table>

Female castrate of 51, treated with 60.000 I. U. pregnyl.
(chorionic gonadotrophin)

Before the administration of pregnyl, the vaginal smear showed a predominance of small basal cells. After administration of chorionic gonadotrophin, an oestrogenic effect was demonstrable: the cells were larger, increased in number and were arranged in groups; acidophile cells were also found, some of which had a pyknotic nucleus. Earlier experiments with the administration of pregnyl to castrates led to the conclusion that the changes in the vaginal smear

Table 2.

<table>
<thead>
<tr>
<th>Date</th>
<th>I. U. pregnyl</th>
<th>mg. 17-ketosteroids in 24 hrs urine</th>
<th>I. U. oestrogens in 24 hrs urine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total content I II III IV V VI VII VIII</td>
<td></td>
</tr>
<tr>
<td>19th Jan.</td>
<td></td>
<td>6.3 0.6 0.7 1.3 2.0 1.5 0.1 0.1</td>
<td>10 neg.</td>
</tr>
<tr>
<td>21st Jan.</td>
<td>20.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22nd Jan.</td>
<td>20.000</td>
<td>7.0 0.5 0.1 1.0 1.3 2.2 1.5 0.1 0.3</td>
<td>25 neg.</td>
</tr>
<tr>
<td>23rd Jan.</td>
<td>20.000</td>
<td>9.4 0.8 0.2 0.8 1.9 3.1 2.1 0.5</td>
<td>25 neg.</td>
</tr>
<tr>
<td>24th Jan.</td>
<td>20.000</td>
<td>8.2 0.6 0.6 1.7 3.2 1.8 0.1 0.2</td>
<td>20 neg.</td>
</tr>
</tbody>
</table>

Female castrate of 23, treated with 60.000 I. U. pregnyl.
(chorionic gonadotrophin)
were caused by a direct action of gonadotrophin on the vaginal wall. At present, however, it is believed that these changes develop under the influence of oestrogenic substances produced by the adrenal cortex.

B (1952-33). In 1949, a woman of 23 underwent two operations, during which both adnexa were resected for inflammation. In April, 1951, metrorrhagia following the use of oestrogens necessitated curettage; in accordance with expectations, microscopical examination revealed hyperplasia of the uterine mucosa. This castrate was given an injection of 20,000 I. U. pregnyl on January 21st, 22nd and 23rd, 1952. The results of determinations of the excretion of 17 KS and oestrogenic substances are given in Table 2.

This patient also showed an increase in the excretion of 17 KS in nearly all fractions. After administration of pregnyl, testing of oestrogenic substances at 10 I. U. was omitted by mistake; an increase of these hormones could therefore not be established with certainty. In the vaginal smear, however, as was the case in the first patient, it was possible to demonstrate oestrogenic activity.

The effect of pregnyl on the adrenal cortex is probably also demonstrable in the following case, although an effect on the gonads cannot be excluded with certainty.

<table>
<thead>
<tr>
<th>Date</th>
<th>I. U. pregnyl</th>
<th>mg. 17-ketosteroids in 24 hrs urine</th>
<th>I. U. oestrogens in 21 hrs urine</th>
<th>mg. 11-oxytocorticoids in 21 hrs urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>24th Mar.</td>
<td>20,000</td>
<td>3.8 0.3 0.4 0.8 1.1 0.9 0.1 0.2 0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31st Mar.</td>
<td>20,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st Apr.</td>
<td>10,000</td>
<td>3.1</td>
<td></td>
<td>50 neg. 0.42</td>
</tr>
<tr>
<td>2nd Apr.</td>
<td>10,000</td>
<td>5.9 0.3 0.6 0.9 1.7 1.2 0.9 0.2 0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd Apr.</td>
<td>10,000</td>
<td>4.8</td>
<td></td>
<td>50 pos. 0.31</td>
</tr>
<tr>
<td>4th Apr.</td>
<td>20,000</td>
<td>5.1 0.5 0.8 1.0 1.4 1.0 0.2 0.2 50 pos.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5th Apr.</td>
<td>4.6</td>
<td>0.1 0.1 0.6 1.0 1.1 1.0 0.2 0.2 0.41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eunuchoid man of 21, treated with 70,000 I. U. pregnyl: (chorionic gonadotrophin)
C (1952-Ve). The patient was a man aged 21, with a eunuchoid physique and marked infantilism of the external genital organs: small penis, a very small testis in the right half of the scrotum and probably only an epididymis in the left half. These atrophic testes were considered to be unsuitable for biopsy. The pubic hair was extremely scanty. The condition showed no improvement after treatment with gonadotrophic hormones (pregnyl and gestyl). The patient could practically be regarded as a castrate. He was given large doses of pregnyl on March 31st, 1952, and on subsequent days. The excretion of 17 KS, oestrogenic substances and 11-oxycorticosteroids was determined at various intervals. The latter determination was made by the method of Heard & Sobel (1946). The results of this investigation are given in Table 3.

In this case, too, the excretion of 17 KS was increased in all fractions. The increase in oestrogens was considerable. This shows that chorionic gonadotrophin can stimulate the production of oestrogenic substances in the male too. Injection of pregnyl caused no changes in the excretion of 11-oxycorticoids.

**SUMMARY**

Two female castrates and a eunuchoid man with marked atrophy of the genital organs were treated with large doses of chorionic gonadotrophin. A rise in the excretion of 17 KS was observed in all patients, while the oestrogens were increased in one woman and in the man. These changes are attributable to stimulation of the adrenal cortex by chorionic gonadotrophin.

We are indebted to »Organon Ltd.« for making available pregnyl in ampoules of 20.000 I. U.

**REFERENCES**


