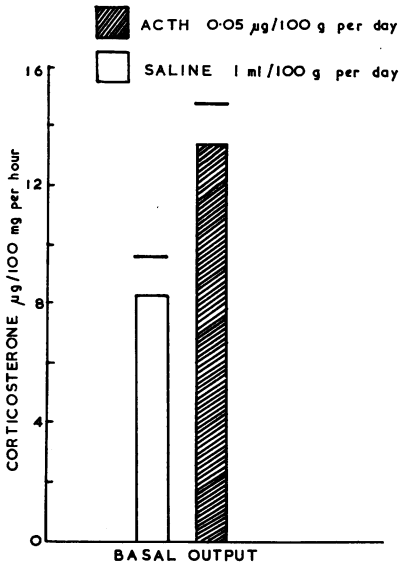

Fig 2 *Basal output of corticosterone (µg/100 mg adrenal tissue per hour). Basal production* in vitro *of corticosterone in µg/100 mg per hour from adrenals taken from rats treated with ACTH 0.05 µg/100 g per day and control rats given saline over a similar period*

In the rats treated with the larger dose of ACTH the HPA system was depressed, releasing less corticosterone into the plasma when challenged with ether than the control animals. This suppression was due to the failure of the hypothalamo-pituitary complex of the HPA system since, after a small single test dose of ACTH, the adrenals of the animals treated with the prolonged high dose produced a similar rise in plasma corticosterone to that of the control animals. However, in the rats treated with the prolonged small dose of ACTH, the whole HPA system appeared to be functionally intact, as shown by the same tests as before (Fig 1). Further, when the adrenals of the rats treated with the small dose were removed, quartered and incubated *in vitro*, the basal corticosterone production rate per unit weight of adrenal tissue was increased by approximately 65% over the saline control animals as shown in Fig 2.

The resting level of plasma corticosterone is always significantly higher in the animals treated with the small dose of ACTH than in the animals treated with saline or those with the high dose of ACTH. However, the basal corticosterone production rate is greatly increased due to the prolonged action of corticotrophin on the adrenal gland. Ács *et al.* (1967) studied the effect of long-term corticotrophin treatment on corticosteroid binding capacity of transcortin and found that ACTH given over a long period depresses the plasma transcortin concentration. Although in the present study transcortin levels were not measured, it might be tentatively suggested that the transcortin levels are not affected by the small dose of prolonged ACTH but are depressed by the high dose of prolonged ACTH, even in the presence of a high corticosterone production rate.

From these preliminary studies it is suggested that it may be possible to avoid hypothalamo-pituitary impairment and transcortin deficit in patients treated with prolonged intermittent ACTH and yet maintain the required improvement in the patient's endogenous steroid production by reducing the dose of ACTH given daily. There may be a certain critical dose margin above which hypothalamo-pituitary suppression occurs and below which there is an effect on the adrenal steroid production alone.

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Plasma Œstrogen and Luteinizing Hormone Concentrations in Thyrotoxic Menstrual Disturbance

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The interaction between the thyroid gland and the hypothalamo-pituitary-gonadal axis is poorly understood. Plasma luteinizing hormone levels are raised in female thyrotoxics (Akande & Hockaday 1972) but the relationship between luteinizing hormone (LH) and œstrogen levels in these patients has not been elucidated.

Materials and Methods

Six female thyrotoxic patients in the reproductive age were studied as outpatients. They kindly agreed for blood samples to be collected daily at a constant time of day for 28 days before commencement of therapy. Plasma was separated within one hour and kept frozen at −23°C until assayed. Plasma was similarly obtained from 6 volunteer euthyroid female controls with no history of menstrual abnormality. They were of comparable age and parity to the patients.

Plasma œstrogens were measured by the dextran-coated charcoal radioimmunoassay method described by Hotchkiss *et al.* (1971) without the chromatographic separation of œstradiol. The

Table 1

Mean plasma total immunoreactive œstrogens and luteinizing hormone levels in 4 thyrotoxic and 6 euthyroid females in phases of the menstrual cycle

	Follicular phase (excluding Day −1 and Day 0)	*Day −1*	*Day 0 (LH peak)*	*Day +1*	*Luteal phase (excluding Day 0 and Day +1)*
Total œstrogens (ng/100 ml):					
Thyrotoxic females	28.1±3.4	92.8±14.0	71.9±19.3	39.0±23.6	36.0±9.4
Euthyroid females	13.1±1.6	48±3.6	26.4±1.8	8.3±3.1	22.3±2.1
P value (Student's *t* test)	<0.001	<0.001	<0.001	<0.02	<0.02>0.01
Luteinizing hormone (miu/ml IRP2 HMG):					
Thyrotoxic females	23.7±2.9	35.0±13.9	82.5±15.0	43.0±11.8	22.3±2.8
Euthyroid females	10.9±1.0	38.5±7.7	125.0±34.0	20.0±7.0	9.0±1.5
P value (Student's *t* test)	<0.001	>0.9 (n.s.)	0.05<*P*<0.1 (n.s.)	<0.01	<0.001

n.s. = not statistically significant

results, therefore, represent the total immunoreactive œstrogens. The antiserum (a gift from Dr G E Abrahams) is specific for œstrogens and reacts with œstradiol-17β more than any other œstrogen. There was no significant cross reaction with other steroids. The water blank for the method was 5.0±1.8 pg/ml. The results were corrected for the water blank. The recovery of œstradiol added to water was 98±5% and to pooled plasma obtained from male subjects was 94±4% over the range 100–1000 pg.

The LH assays were performed by the double antibody radioimmunoassay technique described by Midgley (1966) and modified in Oxford (Naftolin 1970) by a further extension of the incubation period. All samples from one patient were estimated in the same assay in duplicate. Most assays included specimens from euthyroid controls as well as thyrotoxic patients. The second international reference preparation of the human menopausal gonadotrophin was used as standard.

Results

Plasma total immunoreactive œstrogen concentrations were raised in all the thyrotoxics. The mean levels in the follicular and luteal phases in 4 patients with hypomenorrhœa were 28.1±3.4 ng/100 ml and 36.0±9.4 ng/100 ml respectively in comparison with normal values of 13.1 ± 1.6 ng/100 ml and 22.3±2.1 ng/100 ml (Table 1). In this group of patients and in all the normal controls an œstrogen peak occurred the day before the LH peak. However, in 2 thyrotoxic patients who had just developed amenorrhœa œstrogen peaks occurred without ensuing LH peaks.

Plasma LH levels were also raised in all the thyrotoxic patients (Table 1). In the 4 thyrotoxics with hypomenorrhœa the mean LH levels in the follicular and luteal phases of the cycle were 23.7±2.9 miu/ml IRP-2 HMG and 22.3±2.8 miu/ml respectively in comparison to normal values of 10.9±1.0 miu/ml and 9.0±1.5 miu/ml. In the 2 thyrotoxics with amenorrhœa the LH values were also raised (mean 21.3±1.6 miu/ml) but interestingly showed greater day-to-day variability than in menstruating women. Mid-cycle LH peaks were present in hypomenorrhœic thyrotoxics but not in those who had developed amenorrhœa.

One possible explanation for these observations is that in thyrotoxicosis the feedback effects of œstrogen on the hypothalamo-pituitary LH releasing apparatus (negative and positive 'feedbacks') are blunted. To test this hypothesis, small doses of œstradiol benzoate (125 and 250 µg) were injected into postmenopausal euthyroid and thyrotoxic females. The results obtained from these tests show a greater suppressibility of LH in response to œstradiol injection in euthyroid compared to thyrotoxic postmenopausal females.

An alternative explanation of all the results could stem from the large increase in œstrogen binding globulins in thyrotoxicosis.

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Cyclic Adenosine Monophosphate in Human Adipose Tissue

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With the realization of the importance of 3'5'-adenosine cyclic monophosphate (C-AMP) in mediating the cellular response to many hormones (Robison *et al.* 1968, Jost & Rickenberg 1971) has come the need for a simple rapid assay for the