SOME OBSERVATIONS ON THE VALUE OF URINARY GONADOTROPHIN ASSAYS AS AN INDEX OF PITUITARY FUNCTION IN MAN

By

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The main topics discussed in this communication are firstly, the relationship of urinary gonadotrophin assays to the treatment of recurrent or metastatic mammary carcinoma by bilateral adrenalectomy and oophorectomy, and secondly, the relationship of urinary gonadotrophin estimations to other hormone assays during the menstrual cycle.

I. METHOD OF ESTIMATION OF PITUITARY GONADOTROPHINS IN URINE

The method described by Loraine & Brown (1959) was used, results being expressed in terms of a standard prepared from menopausal and postmenopausal urine (HMG-20A). In assays conducted in patients with mammary carcinoma only the mouse uterus test was used as the end point of the bioassay; this method is not specific for either Follicle-Stimulating Hormone (FSH) or Interstitial-Cell-Stimulating Hormone (ICSH) but measures what may be conveniently designated as “total gonadotrophic activity”. In some of the assays performed during the menstrual cycle parallel assays were performed on the same urine samples by the mouse uterus and hypophysectomised rat prostate tests; the latter method is generally assumed to be specific for ICSH activity.

II. GONADOTROPHIN ASSAYS IN RELATION TO THE TREATMENT OF MAMMARY CARCINOMA BY BILATERAL ADRENALECTOMY AND OÖPHORECTOMY

The purpose of this investigation, details of which have already been described (Loraine, in press; Loraine, Douglas, Falconer & Strong, in press), was to study
the effect of bilateral adrenalectomy on gonadotrophin excretion and to ascertain whether such estimations might be of value in the management of patients treated in this way. All subjects included in this study had been treated earlier by one or more of the accepted palliative methods of therapy such as ovarian irradiation or the administration of oestrogens or androgens. They were either postmenopausal at the time the assays were performed or had been treated previously by ovarian irradiation or bilateral oophorectomy. If not removed previously, the ovaries were invariably removed at the time of adrenalectomy. Patients were divided into two groups depending on the course of their disease after adrenalectomy; these groups were designated respectively “remission” and “no remission”. Details of the clinical classification have been described elsewhere (Strong 1958; Loraine et al., in press).

Gonadotrophin assays were performed in 32 patients before adrenalectomy and oophorectomy; a total of 104 observations was made. It was found that, although the mean gonadotrophin excretion in the group subsequently designated “remission” was higher than that in the group designated “no remission”, the difference between these values was not significant ($P = 0.2-0.1$). Accordingly, it was concluded that, under the conditions of the investigation, such estimations were of little or no value in predicting the response of patients to this form of treatment.

Gonadotrophin excretion was studied in 37 patients following bilateral adrenalectomy and oophorectomy; a total of 96 observations was made. It was found that the mean gonadotrophin excretion in the group designated “remission” was considerably higher than that in the group designated “no remission”. The difference between these mean values was highly significant ($P < 0.001$). Possible reasons for the differing excretion patterns following adrenalectomy will be discussed.

### III. HORMONE ASSAYS DURING THE MENSTRUAL CYCLE

Two subjects will be considered.

(a) Hormone excretion in normally menstruating women.

(b) The effect of the progestational compound, norethisterone (17α-ethynyl-17β-hydroxy-19-norandrost-4-en-3-one) acetate*, on hormone excretion.

(a) **Hormone excretion in normally menstruating women**

A study of the urinary excretion of oestrogens, pregnanediol and pituitary gonadotrophins has been made by Brown, Klopper & Loraine (1958). Oestrogens were measured by the method of Brown (1955) and pregnanediol by the method of Klopper, Michie & Brown (1955). Most subjects kept basal temperature

* The norethisterone acetate was kindly supplied by Schering A. G. Berlin.
records and where possible, any change in basal temperature was correlated with the pattern of hormone excretion.

In none of the subjects studied did the urinary gonadotrophin peak at midcycle precede the oestrogen peak. Indeed, in some individuals the gonadotrophin peak occurred several days after the first oestrogen peak. In a proportion of subjects a gonadotrophin peak at midcycle was not observed although all the other evidence indicated that ovulation had occurred.

When gonadotrophin assays were conducted by the mouse uterus and hypophysectomised rat prostate tests, the results obtained agreed very closely at all stages of the cycle. This finding is compatible with the view that, throughout the cycle, a single gonadotrophin with two activities is being excreted. The fact that ICSH activity can usually be found in urine at all stages of the menstrual cycle conflicts with the generally accepted hypothesis that this hormone is secreted only at the time of ovulation and in the early luteal phase of the cycle.

One individual was artificially inseminated on the day of the expected midcycle oestrogen peak and became pregnant during the period of study. The first indication that conception had occurred was a sharp rise in urinary gonadotrophin excretion 9 days after insemination. It should be noted that, in this subject, previous inseminations performed at the time of the rise in basal temperature had been unsuccessful.

(b) The effect of norethisterone acetate on hormone excretion

The effect of this drug on the excretion of oestrogens, pregnanediol and gonadotrophins was studied in patients with dysmenorrhoea and with premenstrual tension (Brown, Fotherby & Loraine, unpubl.). In a subject with dysmenorrhoea norethisterone acetate, in a dosage of 6 mg/d orally from the 5th to the 25th day of the cycle, abolished the "luteal peak" of oestrogen excretion and prevented the luteal phase rise in urinary pregnanediol; the "midcycle peak" of oestrogen excretion was not affected. With a dosage of 12 mg/d both peaks of oestrogen excretion were abolished, the luteal phase rise in pregnanediol did not occur, and it was reasonable to conclude that ovulation had been inhibited. Similar results using a dosage of norethisterone of 12 mg/d were obtained in a patient with premenstrual tension.

Throughout the period of administration of the drug, urinary gonadotrophin excretion continued and, in some individuals, the levels tended to rise. This finding suggests that norethisterone acetate exerts its effect by a direct action on the ovary and not, as was previously supposed, by inhibiting the secretion of gonadotrophins by the anterior lobe of the pituitary gland.
REFERENCES