

## Observations of gonadotrophic and ovarian hormone activity during recovery from anorexia nervosa

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### Summary

Serum gonadotrophins and gonadal steroids were measured in six unmarried female patients with anorexia nervosa before and during treatment by feeding and psychotherapy, which led to restoration of weight to matched population mean levels. In three patients whose premorbid weight was normal, hormonal levels during treatment were initially low, but as weight was regained gonadotrophic levels increased and one patient showed cyclical activity. In three other patients who were premorbidly obese gonadotrophic levels did not appear to increase over the period of investigation. With the exception of one patient whose menstrual cycles were resumed during the period of investigation, gonadal steroid levels in general appeared to remain low although, subsequently, regular monthly menstrual bleeding occurred in some of these patients.

### Introduction

Primary anorexia nervosa, occurring in girls after puberty, is characterized by a return to prepubertal weight levels, amenorrhea, and a reversion to child-like behaviour. The disorder has been construed as a psychosomatic avoidance response to the events and consequences of puberty, and appears to be brought about largely as a result of a self-determined carbohydrate starvation. Individuals with anorexia nervosa usually avoid treatment, but if they can be persuaded to undergo it, they will usually accept the goal of a limited restoration of weight, but only to a level which will still leave them clinically 'pre-pubertal' and 'submenstrual' (Crisp, 1967, 1973).

During the advanced stages of anorexia nervosa, urinary gonadotrophin levels (Bell *et al.*, 1966; Rakoff, 1968; Russell, 1970) and serum luteinizing hormone (LH) levels (Marshall & Russell Fraser, 1971; Beumont, 1972) are low and probably account

for the amenorrhea. If clomiphene citrate, which normally stimulates pituitary gonadotrophin secretion, is administered at this stage, it fails to cause an increase in gonadotrophin secretion. However, when considerable weight has been regained the drug is effective (Marshall & Russell Fraser, 1971). From the results of these investigations it has been suggested that anorexia nervosa is also associated with a disturbance of hypothalamic function. The nature of the probable interaction between the psychological and hypothalamic disturbances, however, remains unclear.

In the present study six unmarried female subjects with anorexia nervosa were admitted to hospital for treatment aimed in the usual way at not only restoring their weight to exactly that of a healthy population (matched for sex, height and age at which the patient fell ill), but also at attempting, through discussions with them and their families, to enable them to develop a more realistic assessment of and capacity to cope with themselves and their environment in their renewed 'post-pubertal' state (Crisp, 1967).

The patients were each admitted for a period of 3-5 months. They remained in bed throughout the time of weight gain, eating a 2500-3000 calorie 'normal' diet daily, including adequate amounts of carbohydrate, and thereafter they were slowly mobilized as described elsewhere (Crisp, 1970). The levels of plasma luteinizing hormone (LH), follicle stimulating hormone (FSH) and ovarian steroid hormones in these patients before and during weight gain are presented in this paper.

### Patients and methods

Some of the clinical details of the six patients are given in Table 1. Blood samples for estimation of gonadotrophin and gonadal steroid levels were

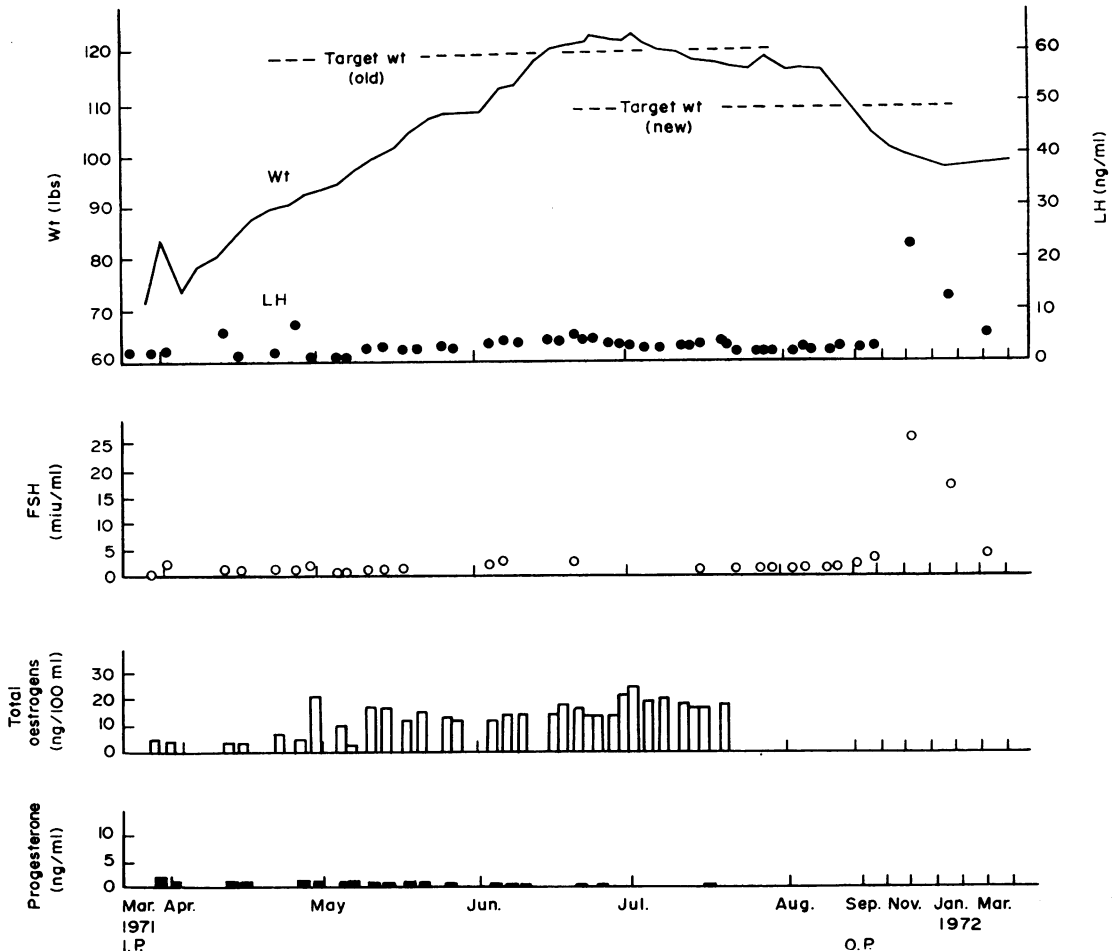


FIG. 1. Case no. 154. 17 years, height 5 ft 1½ in. Case nos. 154, 112 and 163 (Figs. 1-3) show a weight gain during treatment which is unaccompanied by marked changes in hormonal levels. These patients were pre-morbidly obese. The target weight for Case no. 154 was wrongly calculated in the first instance.

TABLE 1. Some data concerning age, weight and LH activity in relation to restoration of weight to mean pre-morbid weight (MPMW) levels

| Case no. | Age at investigation | Age at onset of anorexia nervosa | Feeding pattern: abstinence/vomiting | *Weight (kg) and % of normal |                | Occurrence of one or more LH peaks or high levels of serum LH in association with restoration of weight to MPMW |
|----------|----------------------|----------------------------------|--------------------------------------|------------------------------|----------------|---|
|          |                      |                                  |                                      | Before illness               | At time of LMP |   |
| 161      | 17                   | 16                               | Abst.                                | 68.0<br>(111%)               | 57.2<br>(103%) | +   |
| 155      | 15                   | 14                               | Abst.                                | 52.1<br>(95%)                | 50.8<br>(93%)  | +   |
| 103      | 20                   | 16                               | Abst.                                | 50.8<br>(96%)                | 49.9<br>(94%)  | +   |
| 112      | 16                   | 13                               | Abst.                                | 64.0<br>(122%)               | 52.0<br>(100%) | -   |
| 163      | 15                   | 14                               | Abst.                                | 70.0<br>(144%)               | 68.0<br>(140%) | -   |
| 154      | 17                   | 15                               | Abst.                                | 66.7<br>(130%)               | 57.2<br>(114%) | -   |

\* Mean matched population weights obtained from Standard Tables (Kemsley, 1966).

obtained usually at 3- or 4-day intervals throughout the period of the in-patient treatment, and thereafter whenever possible. Plasma was separated within 1 hr of blood collection and stored at  $-23^{\circ}\text{C}$ .

*Plasma LH* was estimated by radioimmunoassay using a double antibody technique. The antiserum showed no cross reaction with pure FSH or with thyroid stimulating hormone. The second international reference preparation of human menopausal gonadotrophin (2nd IRP-HMG) was used as a standard. Plasma 'pools' were included with each assay in order to check both intra- and inter-assay variation.

*Plasma FSH* was similarly measured by a double antibody radioimmunoassay. The antibody used showed a small degree (4%) of cross reaction with pure LH which, for the purposes of this study, was considered negligible. 2nd IRP-HMG was used as a standard. Plasma 'pools' used in the LH assays were also used in all the FSH assays.

*Plasma total immunoreactive oestrogens* were

estimated by the radioimmunoassay techniques of Hotchkiss, Atkinson & Knobil (1971) without chromatographic separation of the oestrogens. The antiserum used was relatively specific for oestradiol with only a 5% cross reaction with oestrone.

*Plasma progesterone* was estimated by competitive protein binding (Johansson, 1969).

## Results

In three patients (Case nos. 154, 112 and 163) with anorexia nervosa no obvious increases in LH levels and no typical preovulatory peaks were recorded at any time during the period of weight gain or its maintenance over several months (Figs. 1-3). In one of these subjects (Case no. 154) however, there was some evidence of a temporary increase in plasma LH as her weight fell 10% below the target weight after having been maintained at this level for some months. From Table 1 it can be seen that the pre-morbid weights of these patients were considerably higher than the means of matched populations and

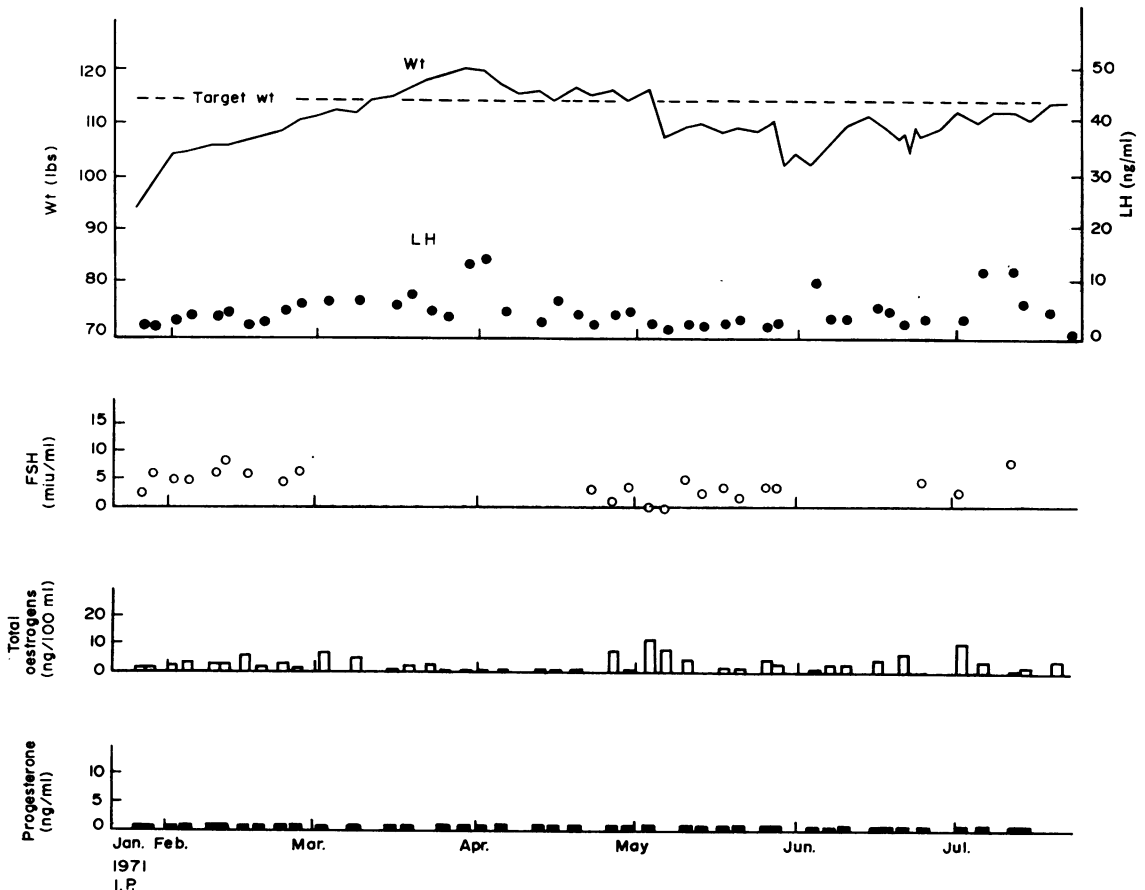


FIG. 2. Case no. 112. 16 years, height 5 ft 4 in.

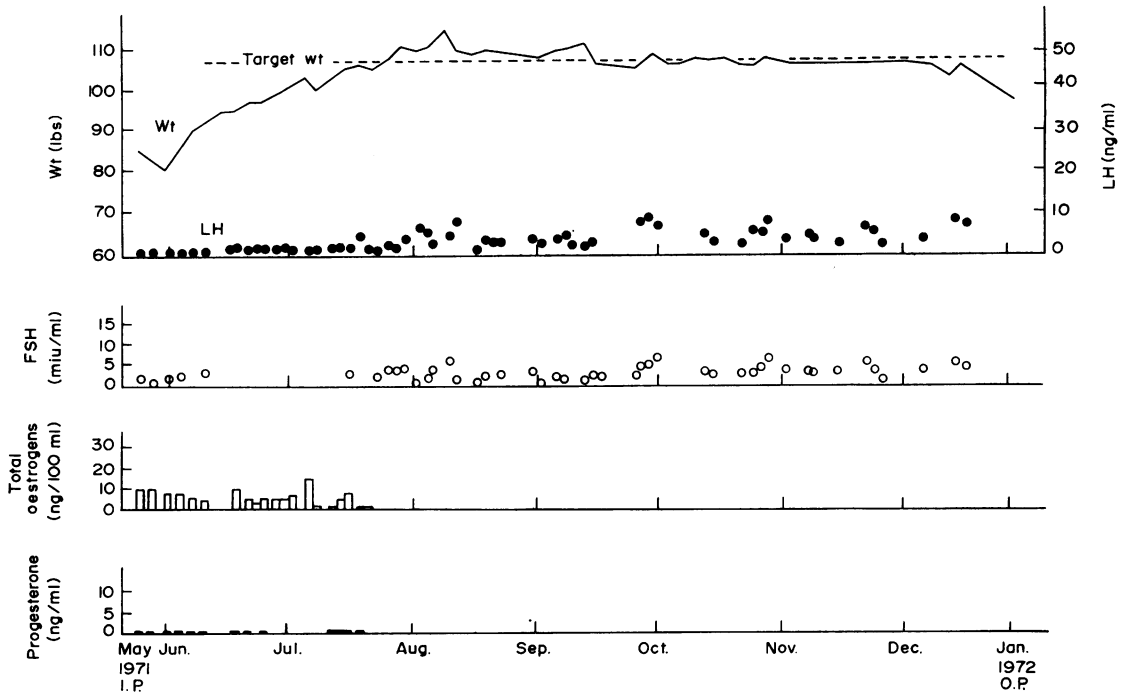


FIG. 3. Case no. 163. 15 years, height 5 ft 2 in.

also that, at the time of their LMP, their weights had been above such levels. In three other patients (Case nos. 161, 155 and 103) there was evidence of considerable LH activity occurring for the first time as weight increased to within 20% or so of the target weight (Figs. 4-6). At this time occasional LH levels occurred which appeared to reach peak proportions, particularly in patient no. 103, who commenced to menstruate regularly during the course of treatment. The premorbid weights of these patients were close to matched population mean weights (Table 1).

Plasma FSH levels tended to be higher in those subjects who had displayed an increase in LH levels. Raised FSH levels were found in patient no. 154 coincidentally with the single phase of high plasma LH levels, to which reference was previously made.

Total oestrogens tended to remain low in most subjects throughout the investigation although they were within the range of values observed for the early follicular phase of a normal menstrual cycle. In one patient (Case no. 154) oestrogen levels appeared to increase coincidentally with a gain in weight, although a concomitant increase in gonadotrophic levels was not observed. In only one patient (Case no. 103), who began to menstruate after weight gain, was there evidence of cyclical activity; however, Case no. 161 may have had a mid-cycle peak of oestrogen which was not apparently followed by

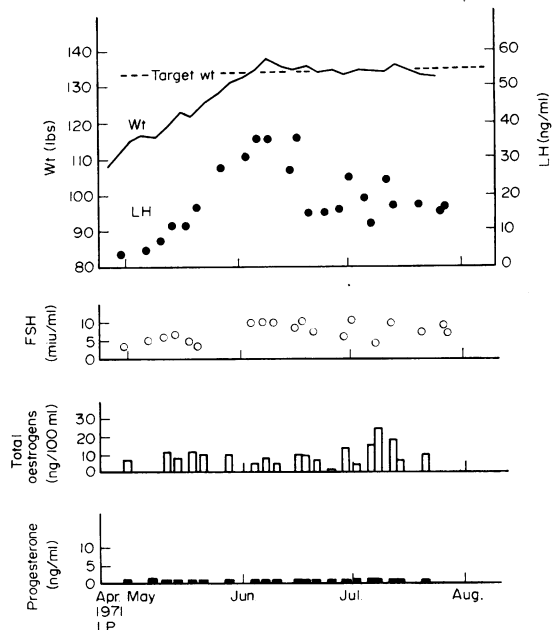


FIG. 4. Case no. 161. 17 years, height 5 ft 10 in. Case nos. 161, 155 and 103 (Figs. 4-6) show marked increases of plasma gonadotrophins coincidental with weight gain during treatment. Apparently only Case no. 103 shows evidence of steroid and gonadotrophic cyclicity. These patients had 'normal' premorbid weights.

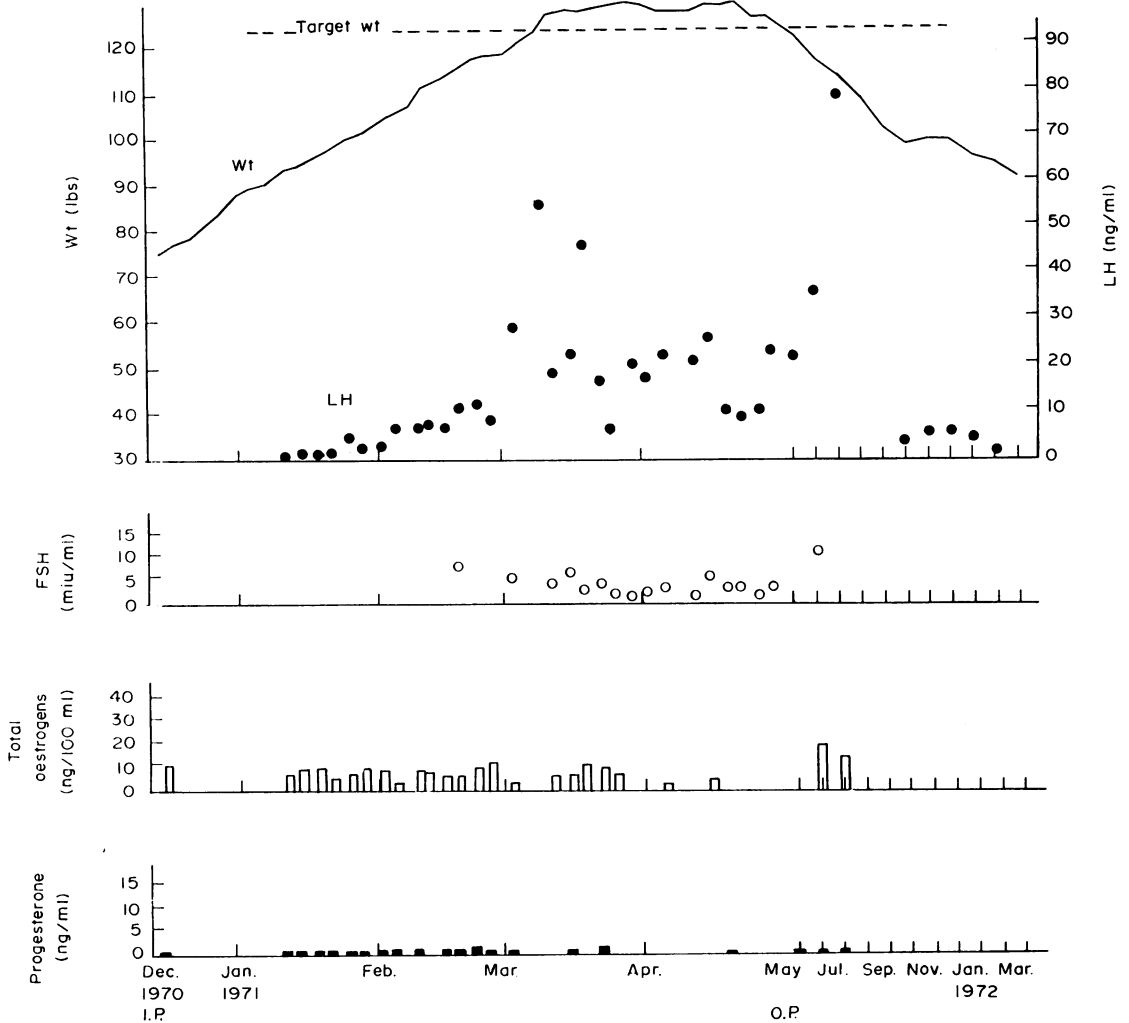


FIG. 5. Case no. 155. 15 years, height 5 ft 6½ in.

peak levels of gonadotrophins or a progesterone response.

Although sampling was incomplete the data suggests that plasma progesterone levels remained low (i.e. within the range of values for the follicular phase of a menstrual cycle) in almost all the patients throughout the investigation.

### Discussion

Of the six patients with anorexia nervosa who were studied, three had increased levels of LH and FSH with occasional peak values towards the end of the period of weight gain, while one returned to cyclical activity. These patients were characterized by having had normal premorbid weights. Three other patients who did not show a rise in plasma LH levels or,

apparently, any gonadotrophic peaks on restoration of their weights to normal levels were markedly obese premorbidly and had experienced their last menstrual periods at weights well above their matched population mean weight. In spite of the fact that a full daily assessment of hormone levels was not possible these findings suggest that, at least initially, the nutritional stimulus to renewed gonadotrophic activity in the individual patient appears to depend upon her premorbid weight. However, although cyclical activity appears not to be always immediately re-established in the premorbidly obese patients merely by restoration of their weight to matched population mean levels, it has been reported that over a longer period of time (e.g. a year) such activity often returns if the patients manage to

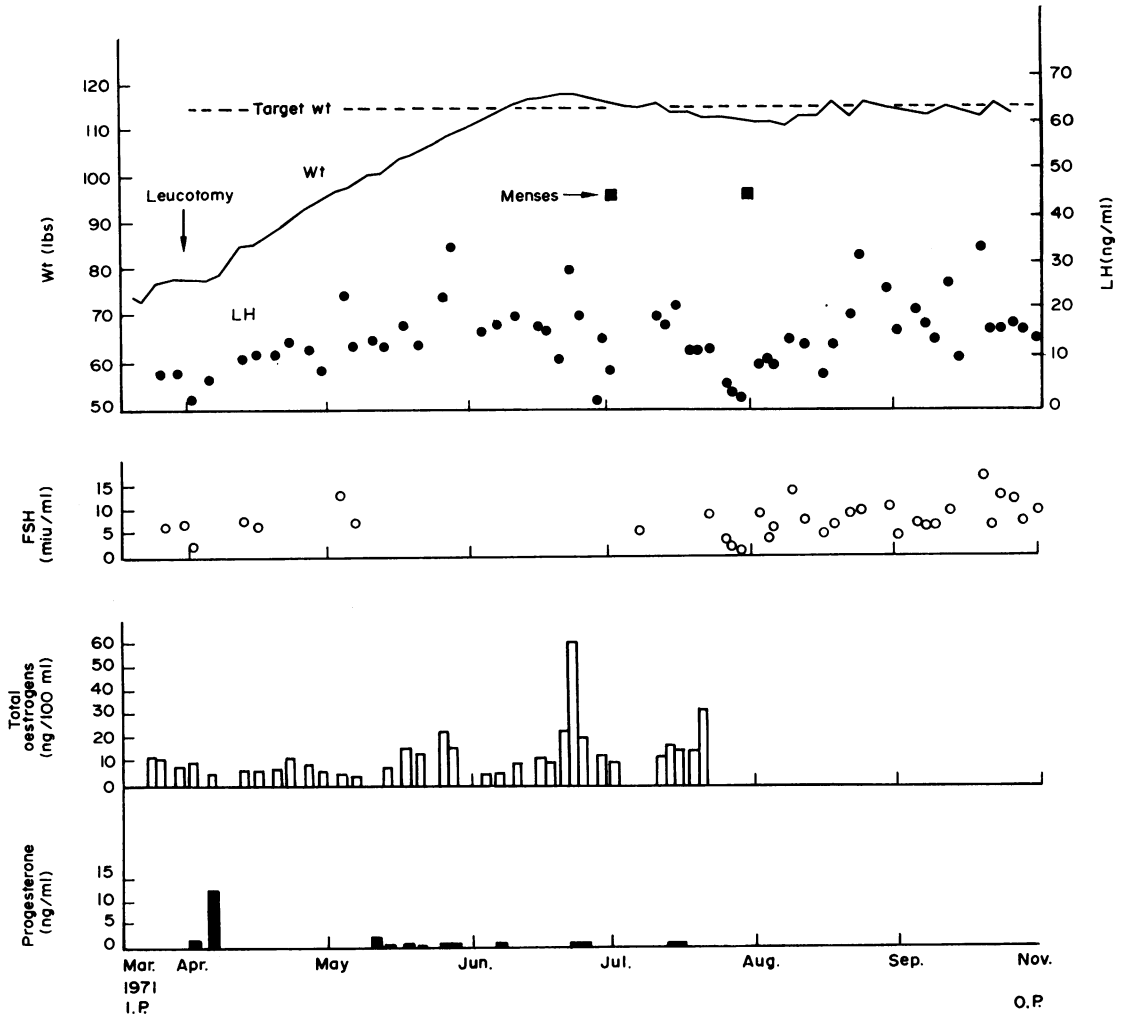


FIG. 6. Case no. 103. 20 years, height 5 ft 4 in.

maintain a normal post-illness weight along with a normal dietary intake and adequate social adjustment (Crisp & Stonehill, 1971).

It has been shown that the LH response to clomiphene citrate in patients with anorexia nervosa is dependent on their weight. Patients with low weights are unresponsive to the drug, whilst those whose weight has been completely or partially restored show the expected response (Marshall & Russell Fraser, 1971; Beumont, 1972). On the evidence of these findings it has been suggested that hypothalamic activity in the early stages of anorexia nervosa is abnormal and recovers during weight gain. However, clomiphene is used to test the function of the hypothalamic-pituitary axis (Newton & Dixon, 1971) and does not test specifically the function of the anterior pituitary in terms of gonado-

trophic output. Nevertheless, we are in agreement that the more primary defect in anorexia nervosa is likely to be at the hypothalamic level and that it is governed by both psychological and nutritional factors, especially carbohydrate starvation.

In anorexic patients during weight gain it has been reported that urinary oestrogens (Bell *et al.*, 1966) and plasma oestradiol (Beumont, 1972) increase coincidentally with the increase in LH levels. In two out of our three patients in whom LH levels increased along with a gain in weight, a concomitant increase in ovarian steroids during the period of investigation did not apparently occur. This finding suggests the possibility that in certain patients ovarian tissue may be unresponsive, at least initially, to the rising levels of gonadotrophin. Two years later, however, these two patients are doing well and have regular men-

strual cycles. Meanwhile, if this initial unresponsivity is caused by a lowered nutritional status then pituitary tissue might be expected to be similarly affected. A study of anorexic patients is now in progress to determine whether anterior pituitary activity when stimulated specifically by the gonadotrophic releasing hormone is in fact altered during the initial course of treatment involving restoration of weight to matched population mean levels as described above.

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