Prolactin and gonadotrophin activity in females treated for anorexia nervosa

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Introduction

Although here is some agreement that in anorexia nervosa there is a major disturbance of function at the hypothalamic level, its precise nature remains obscure. Evidence that hypothalamic control of prolactin and gonadotrophic hormones is mediated through relatively discrete mechanisms (McNeilly, 1974) suggested that a study of these hormones during treatment of anorexia nervosa might help clarify the issue. Since phenothiazines are known to influence prolactin secretion in normal and psychiatric populations (Beumont *et al.*, 1974), these drugs were taken into account during the present investigation as a necessary aspect of treatment.

Patients and methods

Thirteen female patients were selected on the basis of consecutive admission to hospital. Treatment, apart from psychotherapy, involved all patients in remaining in bed and consuming a normal diet until they reached their target weight, i.e. matched population mean weight (Crisp, 1967). The dose of phenothiazines was related to the patient's mental state: the more restless and distressed the patient, the higher the dosage. Ten patients were on chlor-

promazine, two on perphenazine and one on both chlorpromazine and trifluoperazine.

The mean age of patients on admission to the study was 20 years 1 month; mean weight on admission to the study was 40.8 kg; and mean target weight was 53.4 kg.

Blood for hormonal assay was collected from each patient at intervals of approximately 3 weeks, usually, but not always, in the morning. The mean number of samples per patient was approximately five with a total of sixty-eight samples collected over a period of 11 months. Blood was centrifuged and the plasma frozen within 2 hr of collection. Plasma LH (luteinizing hormone) and FSH (follicle stimulating hormone) were measured by double antibody radioimmunoassay as described by McNeilly and Hagen (1974). Prolactin was measured using the homologous antibody technique described by McNeilly (1973). Units of measurement throughout were: prolactin ng/ml; FSH mu/ml; LH mu/ml.

Results

The mean weight of patients on leaving the study was 51.4 kg, 2.0 kg short of mean target weight and reflecting a mean weight gain of 12.6 kg. Table 1

TABLE 1. Relationship between premorbid weight, plasma prolactin and LH levels at various stages of treatment and immediate outcome

Patient no.	Premorbid wt*	Admission		Intermediate		Target		Return of menses
		Prolactin (ng/ml)	LH (mu/ml)	Prolactin (ng/ml)	LH (mu/ml)	Prolactin (ng/ml)	LH (mu/ml)	
1	95	8	5	2.5	4	10	22	+
2	95	—	—	16	15	17	6	+
3	100	7	2	8	5	8.5	20	+
4	100	15	1	12	2	9	4	—
5	105	8	9	7.5	8	0	7	+
6	110	8.5	0	14	0	†	†	—
7	110	11	0	24	0	7	7	—
8	110	9	5	9.5	10	8	24	+
9	115	9	0	38	0	12	0	—
10	120	5	2	23	0	†	†	—
11	125	9	8	53	15	7	34	+
Mean		9.0	3.2	18.9	5.4	8.7	13.8	

* % Matched population mean weight.

† Patient left hospital before target weight reached.

shows the basic data: prolactin and LH levels reported are those within 10 days of admission to hospital; the mean of those intermediate between the admission level and the level at target weight; and those at or above target weight. Data on FSH levels are omitted here since they largely paralleled and were less complete than those on LH. Patients 12 and 13 are omitted from Table 1: 12, because she had recently had a modified leucotomy and 13, because blood was analysed only after she had reached target weight. Both subjects are referred to later.

Since previous work has suggested an association between premorbid weight of anorexia nervosa patients and whether or not LH/FSH activity is resumed on restoration of normal weight (Crisp *et al.*, 1973), this factor was again examined. Those five patients (Table 1) premorbidly less than 10% overweight showed no intermediate rise in prolactin levels whereas the six patients premorbidly 10% or more overweight shows a significant rise ($t=2.80$, $P<0.05$). In both groups, however, mean prolactin levels at target weight fell to levels below those on admission. Taking admission levels into account, the intermediate rise in prolactin levels in the more obese group is significantly different ($t=2.45$, $P<0.05$) from the small decrease in the less obese group.

There is a non-significant trend for menstruation to return more frequently in the less obese group (four out of five versus two out of six).

If the patients are divided into two groups according to whether or not menstruation resumed within 3 months of leaving hospital, intermediate LH levels are significantly higher in the menstruating group (9.5 ± 2.70 versus 0.4 ± 0.51 , $P<0.005$). This trend is still apparent at target weight, but there are insufficient data for statistical analysis. There is a non-significant trend towards higher intermediate prolactin levels in the non-menstruating group.

The data in Table 1 show that there is no overall relationship between prolactin levels and weight. Table 2, however, shows a clear relationship between prolactin and phenothiazine dosage. All thirteen patients are included. Since for most patients the daily dose varied throughout treatment in relation to their emotional state, a comparison of the overall mean dose for each patient with their overall mean prolactin level would have been of little value. Instead, the table shows the highest recorded (peak) prolactin level for each patient, and the dose of phenothiazine given on that day. For those patients receiving 100 mg of less chlorpromazine (or its equivalent) per day, the mean prolactin level was 11.7 ng/ml; for those receiving more than 100 mg daily the mean prolactin level was 65.3 ng/ml. The likelihood of this association arising by chance is

TABLE 2. Relationship between chlorpromazine dosage and prolactin levels

Patient	Daily chlorpromazine (mg)	Prolactin (ng/ml)
5	0	5
13	0	9.7
3	50*	9.1
8	75	10.0
4	75	10.4
2	100	17.0
1	100*	21.0
10	150	37.1
9	225	55.4
7	250*	36.4
11	300	47.2
6	400	30.0
12	800	175.8

* Approximate equivalent of other phenothiazines.

remote ($P<0.05$), and there is also a consistent relationship between prolactin levels and chlorpromazine dosage ($r=0.93$, $P<0.001$).

The condensed data as displayed in Table 1 fail fully to reveal the different patterns of change in prolactin and LH levels in individual patients during the intermediate period. In fact, it was possible to discern patterns. Five patients (Nos 1, 2, 3, 5 and 8) showed highly consistent and generally very low prolactin levels throughout, with a rise in LH levels as target weight approached. Only one of these was in the more obese group, and all resumed menstruation. Five patients (Nos 4, 6, 7, 9 and 10) showed inconsistent prolactin levels with peaks up to 55.4 ng/ml and no rise in LH levels as target weight approached. Two of these discharged themselves prematurely, and none resumed menstruation. Four were in the more obese group. Two patients (11 and 12) had inconsistent prolactin levels with very high peaks and a return of LH activity and menstruation. Patient 11 was premorbidly obese, 12 was not. The full data for these two are shown in Table 3.

Patient 13, for whom full data are available only around target weight, is of interest. At target weight, which she maintained for some months, she showed LH and FSH levels within normal limits, but no signs of menstruation. She had a poorly developed left breast but a normal right breast, suggesting some 'target organ resistance'.

Discussion

The results show that premorbid obesity is significantly associated with higher prolactin levels and phenothiazine dosage during weight-gain, and more weakly associated with a failure to resume gonadotrophic and menstrual activity. The meaning of these associations may be revealed through

TABLE 3. The full data on patients 11 and 12

Patient no.	Weight (kg)	Daily chlorpromazine	Prolactin ng/ml	LH mu/ml	FSH mu/ml
11 (Target weight 50.0 kg)	41.5	150	8.7	9.0	0.0
	43.2	150	87.8	16.0	0.6
	47.8	300	47.2	25.0	1.6
	49.5	300	25.4	0.0	0.0
	51.8	300	7.4	38.0	1.6
12 (Target weight 54.5 kg)	40.5	75	7.7	12.8	0.0
	44.5	150	24.8	15.2	1.7
	49.0	150	24.4	5.6	0.0
	51.0	200	18.4	15.2	1.6
	54.0	200	18.9	16.0	0.6
	55.5	800	175.8	36.0	3.5

consideration of the pattern of hormone changes in the different individuals and groups.

Two main groups of patients have been defined in this study. One group requires small doses of phenothiazines, has consistently low prolactin levels, is not very obese premonstrally and more often resumes menstruation on reaching target weight or soon afterwards. The other group requires considerably more phenothiazines, has sharp peaks of prolactin activity, tends to premonstrous obesity, fails to resume gonadotrophic and menstrual activity, and is more at risk for premature discharge.

One reason for failure to resume gonadotrophic activity in the more obese group might be a higher 'threshold' for the rekindling of 'pubertal' changes (Crisp, 1967) which initially occur at a mean weight of about 47 kg in the normal female population (Frisch and Revell, 1971) but which, after secondary amenorrhoea, are found to recur at a higher level (Frisch and McArthur, 1974). Furthermore, premonstrous obese subjects, who are particularly likely to adopt an anorexic posture of periodic overeating or sustained overeating and vomiting as a means of weight control, are usually the most restless and the most desperate and fearful about their capacity to maintain such control, especially when their weight reaches target levels. They, and other anorexics also, often reveal related anxiety about their emerging sexuality at this stage both in terms of its biological reality and its complex experiential effects.

However, premonstrous obesity does not appear to be the only determinant of a stormy weight-gain period or return of menstruation. Patient no. 12 was premonstrously 5% below target weight, yet was chronically distressed at the experience of weight-gain and unable to sustain it after achieving it on successive occasions with intensive refeeding and psychotherapy. She was eventually advised to undergo modified leucotomy and accepted this. Her talk after operation suggested that a profound fear of sexuality had to be resolved before full recovery could occur. It is noteworthy that peak

prolactin levels occurred at a time when gonadotrophic activity was also at peak. She finally killed herself, having made previous attempts earlier in her illness, about a year after leucotomy, which suggests that she had not learned to cope with those changes in her which may partly have been facilitated by the operation (Crisp and Kalucy, 1973). Patient no. 4 was not premonstrously obese, yet failed to resume gonadotrophic activity or menstruation after reaching target weight.

Presumably some factor other than an increase in menarchal weight threshold is involved in the failure to menstruate at target weight of those premonstrously obese. That such a factor may be present even in those premonstrously massively obese is suggested by the data on patient 11, who, although premonstrously very obese, resumed gonadotrophic activity well short of target weight.

This factor is unlikely to be phenothiazine dosage since Beumont (1974) has shown clearly that phenothiazines generally have little effect on LH levels in a psychiatric population. Furthermore, the data on patient 11 suggest that a rise in prolactin preceded increased phenothiazine dosage. The general reciprocity between prolactin and LH levels in those patients who fail to menstruate is of interest here.

It may be that high arousal and any associated emotional distress can itself inhibit gonadotrophic activity, presumably operating through the cortico-hypothalamic neuronal network. Certainly, arousal is known to modulate hypothalamic functions both in animals and man. The implication is that two important factors operate in the suppression of gonadotrophic activity in anorexics, both of which are related to premonstrous obesity. One appears mainly constitutional and is linked to menarchal weight thresholds and subsequent related growth, weight and fatness characteristics; the other is linked mainly to levels of arousal and emotional distress (which were often related to such factors as premonstrous obesity and its psychological meaning to the patient), mediated by hypothalamic or cortico-hypothalamic

activity and the relationship of these to appetite. This latter mechanism may have been specifically interrupted by modified leucotomy in patient no. 12 and is also always a necessary focus of psychotherapy in anorexia nervosa.

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