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Disturbed Endocrine Function in the Psychoses

I: Disordered Homeostasis or Disease Process?

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Plasma concentrations of prolactin, growth hormone, cortisol, TSH, and the neurophysins were measured over 17 hours in 98 newly admitted psychiatric patients and 35 control subjects. Seventy patients had been free of psychotropic medication for three months. Patients with schizoaffective mania (SAM) differed significantly from control subjects by increased plasma cortisol concentrations and decreased night-time TSH concentrations. The latter were also significantly lower than in both schizophrenic and manic disorder patients. Plasma cortisol was increased to a lesser extent in other psychotic subgroups, and increases in prolactin were most marked in the affective psychoses. There was little diagnostic specificity for psychoses other than SAM. Higher cortisol and prolactin levels may be due to the stimulatory effect of serotonergic pathways, but the neural mechanisms underlying lower night-time TSH levels in SAM are not known. The findings are not consistent with the view (a) that the hormonal changes of the psychoses simply reflect a non-specific response to stress, or (b) that the biological abnormalities of the psychoses can be accounted for by a single continuum of disturbance.

The most commonly described biological model of the psychoses assumes discrete disease entities, each with characteristic symptoms and signs arising from separate aetiologies. This view is supported by the distinctions that can be made between psychoses using, for example, family history data (Tsuang *et al*, 1980) or response to treatment (Taylor *et al*, 1974). In the absence of consistent neuropathological changes, the most plausible biological model of the psychoses implicates abnormalities in central neurotransmission, such as dopamine in schizophrenia (Snyder *et al*, 1974), and noradrenaline or serotonin in depressive illness (Charney *et al*, 1981). Much current biological research in psychiatry is, therefore, directed towards identifying the particular neurotransmitter disturbance that best explains the onset of each type of disorder and the mode of action of effective treatments.

One potentially informative approach is to test the hypothesis that the simultaneous investigation of many variables, each regulated by those neurotransmitters implicated in the psychoses, will separate a diagnostically heterogeneous population into groups characterised by specific clinical features. Multivariate analysis of this type has been widely used in psychopathological and socio-demographic studies in psychiatry, but, with few exceptions (e.g. Shagass *et al*, 1985), has been little used in biological research. If the approach was successful, the biological data would provide an important addition to the already extensive clinical criteria that distinguish between subtypes of psychoses, and might later be developed into rapid and reliable diagnostic tests (Kendell, 1982).

The secretion of pituitary hormones is regulated by the same neurotransmitters likely to be involved in the aetiology of the psychoses. We have tested the specific hypothesis that the measurement of plasma hormones over an extended (17-hour) sampling period would separate a diagnostically heterogeneous patient sample into groups that would correspond with the classification of the same sample using Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978). Previously, our psychoneuroendocrine studies have shown that in young men with mania, there is a selective increase in concentrations of plasma lutenising hormone (Whalley *et al*, 1985, 1987*a*, 1987*b*), that plasma cortisol was increased in many psychotic patients (Christie *et al*, 1986), and that there are characteristic hormonal changes in Alzheimer's disease (Christie *et al*, 1987).

We now report plasma concentrations of cortisol, growth hormone (GH), prolactin (PRL), thyroid-stimulating hormone (TSH), and oestrogen-stimulated neurophysin (ESN) in carefully diagnosed, drug-free psychotic patients. Plasma neurophysins were measured in preference to oxytocin and vasopressin because the neurophysins provide a more accurate index of their overall secretion. We know of no other study where all these pituitary hormones have been examined in the same patients.

The statistical analysis of these data presents several problems, partly because of the number of variables studied at several time points, and partly because of the number of groups. Firstly, we wished

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to determine whether hormonal data distinguished between diagnostic groups. Many hormones vary substantially by sex, age, and reproductive status, and so we excluded the gonadotrophins and reported these separately (Whalley *et al*, 1985). Multivariate statistical techniques can demonstrate overall differences between groups, and make appropriate adjustments for the effects of time, age, and sex. This approach represents the most satisfactory resolution of the conceptual and statistical problems arising during testing of the study hypothesis. Secondly, we wished to locate differences, where these existed, between diagnostic groups, and sought to do this by univariate one-way analysis of variance, corrected for the number of tests performed. Thirdly, we wished to classify systematically the complex endocrine data, using discriminant function analysis, and to compare the classification obtained with the categorisation of patients using RDC (see Whalley *et al*, 1989 – this issue, pp. 462–467).

Method

Subjects

Ninety-eight patients routinely admitted to hospital and 35 control subjects were studied. The sample contained 5–10% of acute psychotic patients admitted to the Royal Edinburgh Hospital during the study period, and was drawn from a larger sample of 137 newly admitted patients, of whom 39 were later removed for a history of endocrine, renal or liver disease, intercurrent physical illness, drug or alcohol addiction, or for taking oral contraceptives within 12 weeks. All patients understood that the research procedures were unrelated to their treatment, and gave their informed consent. In cases of doubt, only when both a relative and patient agreed was that patient included. The Present State Examination (PSE; Wing *et al*, 1974), completed within two weeks of admission, was assessed with the clinical history independently by two psychiatrists (JEC and LJW) six months after discharge, when patients were classified according to RDC, without knowledge of the results of the endocrine investigations. In three cases where raters disagreed, a third rater (IMB) arbitrated. The classification was, therefore, based on a standardised mental state (the PSE), and routine clinical observations, and allowance was made for any new information (for example, a previously concealed history of illicit drug use excluded one patient). There was good agreement between initial clinical diagnoses and the research classification. A notable exception was a young man with a first-onset psychosis initially thought to be schizoaffective disorder, manic subtype. His affective symptoms rapidly remitted, but he continued to exhibit many features of acute schizophrenia for several months in the absence of mood disorder. His final research classification was, therefore, changed from schizoaffective disorder, manic subtype, to acute schizophrenia.

Blood sampling

The control subjects were not admitted to hospital. All patients and controls were asked to fast from midnight before blood sampling. During the following day, all were offered the same hospital diet at the same times of day. There was, however, considerable variation between subjects in the extent to which they complied with this request, and this variation was greatest among the patient group. Within one week of admission, blood samples (10 ml) were withdrawn from an indwelling cannula, kept patent with a heparin lock, and placed in a forearm vein about 20–30 minutes before the first sample at 07.00 h, with further samples taken at 07.30, 08.00 (a.m.), 15.00, 15.30, 16.00 (p.m.), and 23.00, 23.30 and 24.00 h (e.v.). Blood was collected in lithium heparin-coated tubes containing 100 kallikrein-inhibiting units of aprotinin (Trasylol), and kept at 4°C for up to 24 hours until centrifugation at 1600 *g* and 4°C. The plasma was stored at −40°C until assay.

Hormone assays

Plasma concentrations of PRL, GH, TSH, nicotine-stimulated neurophysin (NSN), and ESN were measured with National Institute of arthritis, diabetes and digestive kidney diseases (NIADDK) radioimmunoassay kits. The reference preparations (and intra-assay and interassay % coefficients of variation, and lower limits of sensitivity were: PRL, hPRL-RP-1 (AFP-2312C) (3.9%, 8.9%, 70 mU/l); GH, hGH-HS2243E (9.0%, 10.4%, 1.6 mU/l); TSH, the WHO first international reference preparation 63/38, obtained from the National Institute of Biological Standards and Control (6.2%, 9.7%, 0.8 mU/l). The reference preparations for ESN (5.2%, 7.8%, 80 pmol/l) and NSN were those given to NIADDK by Dr A. Robinson, University of Pittsburgh. The NSN results were all at or close to the lower limit of sensitivity of the assay (20 pmol/l) and, therefore, were not included in the statistical analysis. Total cortisol concentrations were determined as previously reported (Christie *et al*, 1986).

Medication

Seventy patients, by their own account, had been free of all oral psychotropic medication for at least three months (a year for depot medication); four patients with major depressive disorder (psychotic subtype) who had received benzodiazepine medication (up to 20 mg daily) before admission were also included. The drug history was always later confirmed by hospital and general practitioner records and, in most instances, at interview with a close relative. Urine from a random sample of 26 patients believed to be drug free, collected on the day after admission, was also examined using the Toxi-lab System for the presence of drugs. This system detected no drugs other than nicotine, caffeine, and salicylates (one subject each). On the day of blood sampling, when there was a danger to the patient or others, 30 of the 70 patients who had otherwise been drug free (14 schizophrenic, 7 with manic disorder, 6 with schizoaffective disorder, manic subtype, 1 with schizoaffective disorder, depressive subtype, 1 with unspecified

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psychosis, and 1 with manic disorder, post-partum onset) were given 200–600 mg amylobarbitone.

Statistical analysis

The data comprised five hormone values, each measured on nine occasions in 98 patients and 35 control subjects. The three values for each homone during the three collection periods (a.m., p.m., and e.v.) were averaged and transformed (see Table II) to normal distribution before analysis.

The SPSS-X statistical package was then used for analysis. Firstly, a multivariate repeated-measures analysis of covariance (MANOVA) by sex and diagnostic group (between-subject factors), time (a.m., p.m., and e.v. as a within-subject factor), and age as the covariate, was performed on the hormonal data. Certain symmetry conditions for the distribution of the variance and covariance matrices are required for the repeated-measures design (Scheffe, 1959; Huynh & Mandeville, 1979). The Box modified likelihood ratio criterion M (Box's M) was used to test whether these conditions were met. The analysis generated (a) multivariate significance tests of the effects of sex on the hormonal differences between diagnostic groups adjusted for age; (b) multivariate tests of the effects of diagnosis on hormonal measures over time adjusted for age and sex; (c) univariate statistics that have more statistical power than the one-way analysis of variance (ANOVA) described below.

The transformed data were entered into a one-way ANOVA, and the source of differences between diagnostic groups on each hormonal measure located by the multiple-range test of Duncan (Winer, 1971). Only those hormones determined by MANOVA to differ by diagnosis are reported during this stage of the analysis. The reliability of this choice was improved by lowering the nominal significance level ($P<0.05$) to $P<0.003$, to allow for the number of tests performed (Jacobs, 1971). Correlations between plasma cortisol and TSH concentrations were made by Pearson's method using transformed data.

Results

General health

Clinical examination and history showed no evidence of physical illness in any patient. All patients and control subjects were normotensive (systolic blood pressure less than 160 mmHg, diastolic less than 95 mmHg). Three patients were obese (two schizophrenic, one with schizoaffective disorder, depressive subtype), and four patients were underweight (one schizophrenic, two with major depressive disorder, psychotic subtype, one with manic disorder) as judged by standard tables for their height, body build, and age. There were no significant differences between patient groups in plasma sodium concentration or plasma T_4 (Table I). Plasma TSH concentrations were in the range 2.5–6 mU/l except in three patients, in each of whom one of nine plasma values was above 6 mU/l but below 9.8 mU/l. Further clinical assessment (Caldwell *et al*, 1985) of these patients showed no evidence or history of thyroid disease, and they were retained in the study.

Effects of amylobarbitone

Only psychotic patients were examined for the effects of amylobarbitone. One group ($n=28$) was drug free for at least three months before blood sampling, and the other ($n=36$) was treated by amylobarbitone on or immediately before the day of sampling, but was otherwise drug free. MANOVA detected no significant effects of amylobarbitone (Hotelling's $T^2=0.81$, $P<0.67$).

Diagnostic groups

Table II presents plasma hormone concentrations in each of the major drug-free diagnostic groups (57 patients). Significance tests were performed on transformed data (log: growth hormone, cortisol a.m., OSN, TSH; square root: prolactin e.v. and cortisol, p.m., e.v.; and reciprocal:

TABLE I

Characteristics of 57[1] drug-free psychotic patients, subdivided according to RDC

	n	*Weight (kg): range, mean ± s.d.*	*Na (mmol/l): range, mean ± s.d.*	*T_4 (mU/litre): range, mean ± s.d.*	*First episode: relapse*
Schizophrenia	26	47.0–96.8 66.0 ± 10.5	139–144 140 ± 1.9	60–121 94.4 ± 18.3	16:10
Schizoaffective disorder	9	43.5–65.7 56.0 ± 7.9	135–142 139.8 ± 2.3	61–136 97.8 ± 25.3	3:6
Major depressive disorder	10	44.6 ± 72.5 57.5 ± 10.0	133–142 139.7 ± 2.7	78–106 96.7 ± 0.8	3:7
Manic disorder	12	50.0–92.9 62.7 ± 13.9	137–143 141.3 ± 2.5	81–118 91.5 ± 14.9	4:8

1. Forty-one patients are omitted – these patients were either not drug free or were from smaller diagnostic groups.

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TABLE II

Median, first and third quartiles of plasma hormone concentrations, age and sex distributions by diagnostic group in 57 drug-free psychotic patients and 35 control subjects

Group	n	Mean age (s.d.)	Sex M:F	Prolactin: mU/l			Growth hormone: mU/l			Cortisol: nM			Thyroid stimulating hormone: pmol/l			Oestrogen-stimulated neurophysin: pmol/l		
				a.m.	p.m.	e.v.	a.m.	p.m.	e.v.	a.m.	p.m.	e.v.	a.m.	p.m.	e.v.	a.m.	p.m.	e.v.
Schizophrenia	26	30 (12)	21:5	543*	322	357	4.6	5.4	5.0	498***	285***	200***	4.0	3.8	4.3**	133	125	129
				382	250	284	2.8	3.5	2.8	288	215	98	3.5	3.1	3.8	108	91	91
				692	419	464	6.7	8.8	9.0	616	336	353	4.7	4.1	5.1	191	154	170
Major depressive disorder, psychotic subtype	10	45 (11)	3:7	460*	385*	443	12	7.8	4.6	499***	285***	240***	3.2	3.1	3.6***	170	179	166
				309	284	347	3.2	4.8	2.8	295	184	156	2.9	2.8	3.1	108	102	127
				1083	846	655	14	9.2	6.5	519	373	308	4.0	3.9	4.2	297	324	218
Schizoaffective disorder, manic subtype	9	38 (12)	5:4	525*	308	326	3.5	5.6	4.8	646*	454*	413*	3.3	2.9	3.1*	266	224	208
				366	217	277	2.9	2.6	3.4	622	368	305	3.0	2.6	2.6	112	112	120
				1089	371	347	7.3	7.5	8.4	686	520	486	4.4	3.1	3.2	436	423	444
Manic disorder	12	38 (18)	8:4	506*	340*	441	4.6	5.0	5.4	543***	262***	239***	4.2	3.6	4.0**	137	121	108
				343	305	368	2.4	4.5	3.0	466	213	121	3.6	3.8	3.7	96	91	85
				742	716	716	8.3	9.5	15	584	347	349	5.8	4.4	5.5	172	162	139
Controls	35	41 (13)	15:20	305	249	287	3.7	4.3	3.8	404	205	132	3.9	3.4	4.2	125	125	141
				228	217	238	2.9	3.0	3.4	321	179	82	3.4	3.1	3.7	100	91	100
				420	298	445	6.0	5.3	7.8	495	271	166	4.4	4.0	5.1	232	191	199
		F[1]		7.0	5.9	3.6	1.6	0.8	0.4	6.5	9.4	7.9	2.4	4.0	7.4	2.0	2.2	2.1
		p(d.f.4,87)[2]		<0.002	<0.001	<0.02	<0.12	<0.56	<0.77	<0.001	<0.001	<0.001	<0.04	<0.005	<0.001	<0.009	<0.007	<0.02
		Transformation		$1/x$	$1/x$	$\sqrt{x}$	ln$x$	ln$x$	ln$x$	ln$x$	$\sqrt{x}$	$\sqrt{x}$	ln$x$	ln$x$	ln$x$	ln$x$	ln$x$	ln$x$

1. F values are from a one-way analysis of variance for each hormone.
2. The corrected significance level is $P<0.003$.
*$P<0.01$ patient group v. controls; **$P<0.01$ v. SAM; ***$P<0.05$, patient group v. controls.
Transformation to normal distribution are reciprocals ($1/x$), logE (ln$x$) or root ($\sqrt{x}$). All statistics were performed on transformed data.

prolactin a.m. and p.m.). The covariance matrices generated for each of the diagnostic groups did not differ significantly from each other (Box's $M=214$, $P<0.36$), and so met requirements for the multivariate analysis.

The MANOVA showed that the hormonal differences between diagnostic groups remained when the effects of sex, age, and time were adjusted for. Prolactin and growth hormone were affected by sex. There was a significant covariance between plasma growth hormone concentration and age ($P<0.001$). There was no significant interaction between sex, diagnosis, and time adjusted for age for any hormone.

The ANOVA detected significant ($P<0.003$) between-groups F ratios for prolactin a.m., p.m., cortisol a.m., p.m., e.v., and TSH e.v. Duncan's multiple-range test located the source of these differences between groups ($P<0.01$) as follows: for prolactin (a.m. and p.m.) major depressive disorder, psychotic subtype, and manic disorder; for cortisol a.m., manic disorder and schizoaffective disorder, manic subtype (SAM); for cortisol p.m., e.v., SAM; for TSH e.v., SAM. Scheffe's procedure detected significant ($P<0.01$) differences for TSH e.v. between SAM and schizophrenia, and between SAM and manic disorder (Table II). There were no significant correlations between plasma cortisol and TSH concentrations within the total study population or in any single diagnostic subgroup.

In summary, the largest single source of differences between diagnostic groups was attributable to the SAM patients. These were characterised by increased cortisol and decreased TSH e.v. concentrations when compared with control subjects. The SAM patients also had significantly lower plasma TSH e.v. concentrations than those with either schizophrenia or manic disorder. These differences could not be attributed to the effects of amylobarbitone, age, or sex.

Effects of time

Over time (a.m., p.m., and e.v.) there were significant differences between diagnostic groups (Hotelling's $T^2=0.84$, $P<0.001$). These were located to prolactin, $F=2.8$, $P<0.03$; cortisol, $F=7.8$; $P<0.001$; and TSH, $F=6.0$, $P<0.001$. Our sampling points were too few to fit cosine functions to the data of a circadian rhythm in hormone secretion (Monk & Fort, 1983). Inspection of individual profiles of plasma cortisol showed that during the night-time (23.00–24.00 h) sampling period, 1 of 35 controls and 21 of 57 psychotic patients had an average cortisol concentration more than two standard deviations above the control mean. These 21 patients comprised four with major depressive disorder (psychotic subtype), eight with schizophrenia, six with schizoaffective mania, and three with manic disorder.

Discussion

These results show that the endocrine disturbances of the psychoses do vary according to the nature of the illness. When allowance was made for the age and sex differences between diagnoses, SAM could be distinguished, using endocrine data alone, from other psychoses.

We could not establish that other factors, not involved in the diagnostic classification of patients but known to influence plasma hormones, had contributed to these endocrine differences. The general health (Amico *et al*, 1984; Semple, 1986) of each group appeared similar, and no differences were found after adjustments were made for the effects of age and sex. The fact that blood sampling and diagnostic procedures were carefully standardised substantially reduced these sources of bias. Differences between control subjects and psychotic patients may, however, have been attributable to the stress of hospital admission or altered motor activity associated with illness. Because blood samples were obtained one to seven days after admission to hospital and the RDC required an illness duration of at least two weeks, our patients cannot be considered to be acutely stressed in a way comparable to experimental studies of the endocrine effects of stress (e.g. Hodges *et al*, 1962; Rubin *et al*, 1970; Miyabo *et al*, 1976; Johansson *et al*, 1983; Brooks *et al*, 1986). Our previous analysis of the cortisol data (Christie *et al*, 1986) showed that increased cortisol secretion was unrelated to the time of blood sampling in relation to hospital admission and to correlates of stress, such as psychic or somatic anxiety and agitation. Increased cortisol secretion was, however, closely related to some of the features of psychosis.

Thus, the present and previous (Christie *et al*, 1986) data show that increased plasma cortisol and prolactin concentrations in psychotic subjects are not simply the effects of stress. Our data that show that increased cortisol secretion is a feature of psychosis but is not specific for major depression are consistent with those of several recent studies (Pfohl *et al*, 1985; Halbreich *et al*, 1985*a*,*b*; Rubin *et al*, 1987).

Plasma TSH concentrations also showed evidence of specificity. Significant decreases were found in SAM during the night-time sampling period (e.v.), a time when in controls, schizophrenic and manic patients, plasma TSH showed a consistent night-time rise. Comparable decreases in plasma TSH have been reported previously (Golstein *et al*, 1980; Kjellman *et al*, 1984; Unden *et al*, 1987) in patients with major depressive disorder, but there are no similar studies in schizoaffective mania. In a review of the TSH response to TRH in depressed patients, Loosen & Prange (1982) noted the suggestion that TSH secretion may be suppressed by increased circulating plasma cortisol (Otsuki *et al*, 1973; Nicoloff *et al*, 1979). A possible explanation of lower plasma TSH in SAM could, therefore, be based upon such a putative suppressive effect of cortisol on TSH release.

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We regard this explanation as unlikely, since we could detect no significant intercorrelations between plasma cortisol in TSH in any of our diagnostic subgroups or in the total population. Winokur *et al* (1983) reached a similar conclusion when considering the interactions between plasma anterior pituitary hormone concentrations and responses to TRH in depressed patients. On the basis of these results, we concluded that disturbances in cortisol and TSH detected in SAM are specific for SAM and do not simply reflect an increase in plasma cortisol that, in turn, suppresses TSH secretion.

We did not find changes in either growth hormone or the neurophysins. In an intensive study of growth hormone secretion in major depressive disorder, Mendlewicz *et al* (1985) detected hypersecretion of growth hormone. Table II shows that there were no significant differences between diagnostic groups in the present study, although the highest median values were found in the morning samples from depressed patients. After adjusting for the effects of age and sex, there were no significant differences. Failure to detect a significant difference when it is, in fact, present between study populations can arise because, as in our case, the study sample is small. We are not able to exclude this potential source of error.

Our knowledge of the neurotransmitter control of pituitary hormone secretion is not sufficiently advanced to allow firm interpretation of our data in terms of central neurotransmitter dysfunction. However, these data do identify questions which could be answered by further basic and clinical research. For example, the increased prolactin concentrations, which our data suggest are a general feature of psychosis, together with the findings that prolactin concentrations are unchanged or increased in schizophrenia (Meltzer *et al*, 1974; Johnstone *et al*, 1977; Gruen *et al*, 1978), acute paranoid psychoses (Ohman & Axelsson, 1978), major depressive disorders (Mendelwicz *et al*, 1980; Unden *et al*, 1987), and manic disorder (Cookson, 1985), suggest that the generally accepted version of the dopamine hypothesis of schizophrenia needs to be re-evaluated. Similarly, the older view, based on early animal experiments, that increased plasma cortisol secretion reflects decreased central noradrenergic and/or serotonergic activity, must be carefully re-evaluated in view of the fact that recent studies show that noradrenaline stimulates cortisol secretion (Tuomisto & Mannisto, 1985), and that cortisol and prolactin secretion is stimulated by central serotonergic activation (Rivier & Plotsky, 1986; Goodwin *et al*, 1987).

Further biological studies in heterogeneous samples of psychotic subjects are likely to clarify the issues raised here. We have found that a single functional psychiatric disorder, SAM, can be separated from neighbouring syndromes by biological data and this finding requires replication. As our understanding of the neuroendocrine control of hormone secretion progresses, it may be possible to identify precisely the neurobiological abnormalities that underlie the differences we have detected.

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References

ALLEN, P., BATTY, K., DODD, C., *et al* (1985) Dissociation between emotional and endocrine responses preceding an academic examination in medical students. *Journal of Endocrinology*, **114**, 166–176.

AMICO, J., CORDER, C., MCDONALD, R., *et al* (1984) Levels of the oxytocin associated and vasopressin associated neurophysins in plasma and their responses in essential hypertension. *Clinical Endocrinology*, **20**, 289–297.

BROOKS, J., HERBERT, M., WALDER, C. P., *et al* (1986) Prolactin and stress: some endocrine correlates of pre-operative anxiety. *Clinical Endocrinology*, **24**, 653–656.

CALDWELL, G., GOW, S. M., SWEETING, V. M., *et al* (1985) A new strategy for thyroid function testing. *Lancet*, *i*, 1117–1119.

CHARNEY, D. S., MENKES, D. B. & HENNINGER, G. R. (1981) Receptor sensitivity and the mechanism of action of antidepressant treatment. *Archives of General Psychiatry*, **38**, 1160–1180.

CHRISTIE, J., WHALLEY, L., DICK, H., *et al* (1986) Raised plasma cortisol concentrations are a feature of drug-free psychotics and are not specific for depression. *British Journal of Psychiatry*, **148**, 58–65.

——, ——, BENNIE, J., *et al* (1987) Characteristic plasma hormone changes in Alzheimer's disease. *British Journal of Psychiatry*, **150**, 674–681.

COOKSON, J. (1985) The neuroendocrinology of mania. *Journal of Affective Disorders*, **8**, 233–241.

GOLSTEIN, J., VAN CAUTER, E., LINKOWSKI, P., *et al* (1980) Thyrotrophin nyctohemeral pattern in primary depression: differences between unipolar and bipolar women. *Life Sciences*, **27**, 1695–1703.

GOODWIN, G. M., FAIRBURN, C. G. & COWEN, P. J. (1987) The effects of dieting and weight loss upon neuroendocrine responses to tryptophan, clonidine and apomorphine in volunteers: important implications for neuroendocrine investigations in depression. *Archives of General Psychiatry*, **44**, 952–957.

GRUEN, P., SACHAR, E., ALTMAN, N., *et al* (1978) Relation of plasma prolactin to clinical response in schizophrenic patients. *Archives of General Psychiatry*, **35**, 1222–1227.

HALBREICH, U., ASNIS, G. M., SHINDLEDECKER, R., *et al* (1985*a*) Cortisol secretion in endogenous depression. I. Basal plasma levels. *Archives of General Psychiatry*, **42**, 904–908.

——, ——, ——, *et al* (1985*b*) Cortisol secretion in endogenous depression. II. Time-related functions. *Archives of General Psychiatry*, **42**, 909–914.

https://doi.org/10.1192/bjp.155.4.455 Published online by Cambridge University Press

HODGES, J., JONES, M. & STOCKHAM, M. (1962) Effect of emotion on blood corticotrophin and cortisol concentrations in man. *Nature*, **193**, 1187–1188.

HUYNH, H. & MANDEVILLE, G. K. (1979) Validity conditions for repeated measures designs. *Psychological Bulletin*, **86**, 964–973.

JACOBS, K. W. (1971) A table for the determination of experiment-wise error rate (alpha) from independent comparisons. *Educational Psychological Measurements*, **36**, 899–903.

JOHANNSSON, G. G., KARONEN, S-L. & LAAKSO, M-L. (1983) Reversal of an elevated plasma level of prolactin during prolonged psychological stress. *Acta Psychiatrica Scandinavica*, **69**, 491–502.

JOHNSTONE, E., CROW, T. & MASHITER, K. (1977) Anterior pituitary hormone secretion in chronic schizophrenia: an approach to neurohumoral mechanisms. *Psychological Medicine*, **7**, 223–228.

KENDELL, R. E. (1982) The choice of diagnostic criteria for biological research. *British Journal of Psychiatry*, **39**, 1334–1339.

KENDLER, K. S. (1987) The impact of diagnostic misclassification on the pattern of familial aggregation and co-aggregation of psychiatric illness. *Journal of Psychiatry Research*, **21**, 55–91.

KJELLMAN, B., BECK-FRIIS, J., LJUNGGREN, J-G., *et al* (1984) Twenty-four-hour serum levels of TSH in affective disorders. *Acta Psychiatrica Scandinavica*, **69**, 491–502.

LOOSEN, P. T. & PRANGE, A. J. (1982) Serum thryrotropin response to thyrotropin-releasing hormone in psychiatric patients: a review. *American Journal of Psychiatry*, **139**, 405–416.

MASON, J. W., MOUGEY, E. H., BRADY, J. V., *et al* (1968) Thyroid (plasma butanol-extractable iodine) responses to 72 hour avoidance sessions in the monkey. *Psychosomatic Medicine*, **30**, 682–695.

——, HARTLEY, L. H., KOTCHEN, T. A., *et al* (1973) Plasma thyroid stimulating hormone response in anticipation of muscular exercise in the human. *Journal of Clinical Endocrinology and Metabolism*, **37**, 403–406.

MELTZER, H. Y., SACHAR, E. J. & FRANTZ, A. G. (1974) Serum prolactin levels in unmedicated schizophrenic patients. *Archives of General Psychiatry*, **31**, 564–569.

MENDELWICZ, J., VAN CAUTER, E., LINKOWSKI, P., *et al* (1980) The 24-hour profile of prolactin in depression. *Life Sciences*, **302**, 1091–1092.

——, LINKOWSKI, P., KERKHOFS, M., *et al* (1985) Diurnal hypersecretion of growth hormone in depression. *Journal of Clinical Endocrinology and Metabolism*, **60**, 505–512.

MIYABO, S., HISADA, T., ASATO, T., *et al* (1976) Growth hormone and cortisol responses to psychological stress: comparison of normal and neurotic subjects. *Journal of Clinical Endocrinology and Metabolism*, **42**, 1158–1162.

MONK, T. H. & FORT, A. (1983) 'Cosina': a cosine curve fitting programme suitable for small computers. *International Journal of Chronobiology*, **8**, 193–205.

NICOLOFF, J., FISHER, D. & APPLEMAN, M. (1979) The role of glucocorticoids in the regulation of thyroid function in man. *Journal of Clinical Investigation*, **49**, 1922–1929.

OHMAN, R. & AXELSSON, R. (1978) Relationship between prolactin response and anti-psychotic effect of thioridazine in psychiatric patients. *European Journal of Clinical Pharmacology*, **14**, 111–116.

OTSUKI, M., DAKODA, M. & BABA, S. (1973) Influence of glucocorticoids on TRH induced TSH response in man. *Journal of Clinical Endocrinology Metabolism*, **36**, 95–102.

PFHOL, B., SHERMAN, B., SCHLECHTE, J., *et al* (1985) Pituitary-adrenal axis rhythm disturbances in psychiatric depression. *Archives of General Psychiatry*, **42**, 897–903.

RIVIER, C. L. & PLOTSKY, P. M. (1986) Mediation by corticotrophin releasing factor (CRF) of adenohypophysial hormone secretion. *Annual Reviews in Physiology*, **48**, 475–494.

RUBIN, R. T., MILLER, L. G., CLARK, B. R., *et al* (1970) The stress of aircraft carrier landing I. Corticosteroid responses in naval aviators. *Psychosomatic Medicine*, **32**, 581–588.

——, POLAND, R. E., LESSER. I. M., *et al* (1987) Neuroendocrine aspects of primary endogenous depression. I. Cortisol secretory dynamics in patients and matched controls. *Archives of General Psychiatry*, **44**, 328–336.

SCHEFFE, H. (1959) *The Analysis of Variance*. New York: Wiley.

SCHLEIFER, S. J., KELLER, S. E., SIRIS, S. G., *et al* (1985) Depression and immunity. *Archives of General Psychiatry*, **42**, 129–133.

SEMPLE, G. G. (1986) Hormonal changes in non-endocrine disease. *British Medical Journal*, **293**, 1049–1052.

SHAGASS, C., ROEMER, R. A., STRAUMANIS, J. J., *et al* (1985) Combinations of evoked potential amplitude measurements in relation to psychiatric diagnosis. *Biological Psychiatry*, **20**, 701–722.

SNYDER, S. H., BANERJEE, S. P., YAMAMURA, H. I., *et al* (1974) Drugs, neurotransmitters and schizophrenia. Phenothiazines, amphetamines and enzymes synthesizing psychotomimetic drugs aid schizophrenia research. *Science*, **184**, 1243–1253.

SPITZER, R., ENDICOTT, J. & ROBINS, E. (1978) Research Diagnostic Criteria: rationale and reliability. *Archives of General Psychiatry*, **35**, 773–782.

TAYLOR, M. A., ABRAMS, R. & GAZTANGA, C. (1974) Manic-depressive illness and acute schizophrenia, a clinical, family history and treatment response study. *American Journal of Psychiatry*, **131**, 678–682.

TSUANG, M., WINOKUR, G. & CROWE, G. (1980) Morbidity risks of schizophrenia and affective disorders among first-degree relatives of patients with schizophrenia, mania, depression and surgical conditions. *British Journal of Psychiatry*, **137**, 497–504.

TUOMISTO, J. & MANNISTO, P. (1985) Neurotransmitter regulation of anterior pituitary hormones. *Pharmacological Reviews*, **37**, 249–332.

UNDEN, F., LJUNGGREN, J., KJELLMAN, B., *et al* (1987) Unaltered 24h serum PRL levels and PRL response to TRH in contrast to decreased 24h serum TSH levels and TSH response to TRH in major depressive disorder. *Acta Psychiatrica Scandinavica*, **75**, 131–138.

WHALLEY, L., CHRISTIE, J., BENNIE, J., *et al* (1985) Selective increase in plasma luteinizing hormone in drug-free young men with mania. *British Medical Journal*, **290**, 99–102.

——, ——, ——, *et al* (1987*a*) Case report. Elevated plasma luteinizing hormone concentrations, cryptorchidism and mania. *Psychoneuroendocrinology*, **12**, 73–77.

——, KUTCHER, S., BLACKWOOD, D. H. R., *et al* (1987*b*) Increased plasma LH in manic–depressive illness: evidence of a state-independent abnormality. *British Journal of Psychiatry*, **150**, 682–684.

——, CHRISTIE, J. E., BLACKWOOD, D. H. R., *et al* (1989) Disturbed endocrine function in the psychoses: II. Discriminant function analysis of multihormone data. *British Journal of Psychiatry*, **155**, 462–467.

WINER, B. J. (1971) *Statistical Principles in Experimental Design*, p. 184. New York: McGraw Hill.

WING, J., COOPER, J. & SARTORIUS, N. (1974) *The Description and Classification of Psychiatric Symptoms: An Instruction Manual for PSE and CATEGO System*. London: Cambridge University Press.

WINOKUR, A., AMSTERDAM, J. D., OLER, J., *et al* (1983) Multiple hormonal responses to Protirelin (TRH) in depressed patients. *Archives of General Psychiatry*, **40**, 525–531.

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