evidence of language-based cognitive impairment. In view of the dearth of developmental data, it is probably more appropriate to describe him as an 'adult autist' or, following the recommendation of a working party of the National Autistic Society, by the more clumsy term 'more able autistic adult'. Although he was described in the past as having schizophrenia, the evidence for this is unconvincing: in particular, there has never been incontrovertible evidence of first-rank symptoms, or other abnormal beliefs or perceptions. It could be argued that many of his features represent the indications of a defect state, but his non-delusional and lively fascination for the subjects mentioned above renders him unlike most cases of schizophrenia. In addition, the affect disturbance was a feature from very early age, and remains largely unaltered at the age of 44.

Finally, there was no evidence of 'relapse' when he was taken off medication, although behavioural changes occurred. These features do not support the diagnosis of schizophrenia.

The deficits consequent upon his disorder have an immediate bearing on his potential for dangerous behaviour. His impulsive attempts to silence sources of high-pitched sound are less frequent and his preoccupation with poisons and poisoning has remained rather more academic than applied. However, he is closely supervised and his environment prohibits access to many of the previous sources of irritation. His unusual candour reveals his strong dislikes readily, greatly facilitating his assessment, and although somewhat improved since admission, he is not felt to be ready to leave conditions of maximum security. It is anticipated that he will require long-term institutional care.

We submit the speculation that this association between Asperger's syndrome and violent behaviour is more common than has been recognised and that more such individuals are to be found in long-term care institutions of various sorts.

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(*Accepted 3 January 1985*)

British Journal of Psychiatry (1985), **147**, 569–573

Neuroendocrine Findings in Chronic Cocaine Abusers: A Preliminary Report

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This study examined the neuroendocrine status of 21 chronic cocaine abusers after cessation of use. Ending a binge of stimulant abuse is followed initially by a phase of severe dysphoria and hypersomnolence (the 'crash'), which lasts one or more days (Siegel, 1982). A second phase then consists of prolonged but less severe anergia and anhedonia, without hypersomnia (Siegel, 1982; Kleber & Gawin, 1984; Gawin & Kleber, 1984a; 1984b). Stimulant craving is low during the 'crash', but re-

emerges after one or two days of abstinence, during the second phase, leading to repeated cycles of abuse (Gawin & Kleber, 1984a; 1984b). Study of this latter phase might disclose neurophysiological adaptations in catecholaminergic systems, and we have postulated that such adaptations are associated with the cocaine craving that occurs during the second phase (Gawin & Kleber, 1984c). If so, reversing such neuro-adaptations could become a focus for research on treatments to facilitate abstinence.

There are no published neurophysiological or neurochemical investigations of chronic cocaine abusers, though increased REM sleep and decreased urinary MHPG excretion have been reported in four chronic amphetamine abusers after amphetamine discontinuation (Watson *et al*, 1972). The REM sleep changes persisted into the second phase, but MHPG changes did not. A six-day trial of cocaine in depressed patients showed similar REM sleep changes (Post *et al*, 1974), but there have not been any such observations in cocaine abusers.

Various evidence supports the possibilities that neurophysiological adaptations occur after prolonged cocaine administration and that neuroendocrine measures might reflect such changes. Central stimulants, including cocaine, increase dopaminergic and noradrenergic activity (Jaffe, 1980). Dopamine inhibits prolactin (PL) release, and both dopamine (DA) and norepinephrine (NE) stimulate growth hormone (GH) release. Consistent with this, acute administration of central stimulants causes a decrease in serum PL and an increase in GH (Brown *et al*, 1978). In animals, chronic cocaine administration causes β-adrenergic, α-adrenergic, and dopaminergic receptor supersensitivity (Kleber & Gawin, 1984), and increased NE and DA turnover (Roy *et al*, 1978). Neuroendocrine evaluations in animals or humans after chronic stimulant administration have not been done but, based on the receptor and turnover alterations after chronic cocaine administration in animals, prolonged increases in GH or decreases in PL could be expected after chronic cocaine abuse. Animal research has employed schedules of administration that differ substantially from the habits of human abusers, however, so that it is unclear if these results can be extrapolated to humans.

Investigation of human cocaine abusers can provide data on whether neuroendocrine changes consistent with the adaptations observed in animals occur in this abuse. Assessments of human abusers cannot, however, provide unquestionable evidence that cocaine is the cause of any observed abnormalities. The stresses of addiction, other drugs abused, street adulterants, and many other factors might also cause neuroendocrine changes. Positive findings would at least provide a starting point, but would require further investigations to ascertain causation: the present study was undertaken to investigate whether such a starting point exists. We examined PL, GH, and post-dexamethasone cortisol in 21 chronic cocaine abusers. Dexamethasone suppression testing was included to assess noradrenergic function further. The study design required that strong cocaine craving occurred in the second phase, and that 'crash' symptoms had ended, before evaluations were done.

Method

Subjects

Subjects were 21 out of 24 consecutive, self-referred, chronic cocaine users entering out-patient treatment at the Drug Dependence Unit of the Connecticut Mental Health Center: 15 subjects were male and six female. Mean age was 27.4 years (range 20–37), and average duration of cocaine use was 3.4 years (range 1.6–14). All subjects met our minimal treatment criteria of at least weekly street cocaine use, with total reported use in the three months prior to treatment of at least 14 grams. For all subjects, cocaine was the primary substance of abuse. Subjects who were dependent on another substance or who had any history of drug withdrawal phenomena were excluded (one subject (No. 9) had a history of heroin addiction and naltrexone treatment, but had used neither of these in the 14 months prior to treatment, and was therefore included). Illness or medical treatments with possible effects on endocrine measures were ruled out for all patients by history taking and by physical, and routine hospital laboratory evaluations. All subjects were at greater than 90% of baseline body weight and described eating regularly during the period of abstinence preceding testing. All denied use of medication or drugs with possible long-term effects on neuro-hormones (especially barbiturates, benzodiazepines, marijuana, opiates, and phencyclidine) for at least ten days prior to testing, and from all medication or drugs during the period of cocaine abstinence preceding testing. Urine drug screens done at the time of testing confirmed the subjects' reports, and extra urine drug screens done, when possible, before this period also confirmed their reports.

Timing

Subjects were tested between four and ten days after their last cocaine use; the length of abstinence for each subject is shown in the Table. Blood was drawn for hormone assays when subjects experienced at least three consecutive nights of normalised sleep following the conclusion of post-cocaine 'crash' symptoms; they also had to describe experiencing significant cocaine craving before testing. In no case did this require more than seven days of abstinence. Variation in timing of testing also reflects

logistical constraints (e.g. weekends). A detailed discussion of considerations of time factors in assessments of cocaine abusers appears elsewhere (Gawin & Kleber, 1984a).

Chemical analyses

Blood samples were spun immediately after collection at 3,000 rpm for 20 minutes in a refrigerated centrifuge, and plasma stored at 2–4°C until assay. All assays were done blindly in duplicate. Samples were drawn at 12.30 pm (+/− 90 minutes)—except for post-dexamethasone cortisols which were done at 9.00 am and 4.00 pm (+/− 15 minutes). Dexamethasone was provided in standard 1 mg dosage for self-administration at 11 pm on the night preceding am and pm cortisol samples. Plasma PL, GH and cortisol were measured via RIA using commercial assay preparations (PRL No. 09100, Serono Laboratories, Inc., 280 Pond Street, Randolph, MA 02368; Chromocode-Human Growth Hormone. No. KT-12002. Bio-Ria, 10900 Hamon Street, Montreal, Canada H3M 3A2; Gamma Coat-Cortisol No. CA549. Travenol Laboratories, Inc., Cambridge, MA 02139). Inter-assay coefficients of variation within the range of results were less than 9.6% for all measures. Normal ranges (means +/− 2 s.d.) for the laboratory and procedures used is 0.0–5.0 ng/ml for growth hormone, 2–25 ug/dl for cortisol, and 5.0–14.2 ng/ml (males) and 5.0–25.0 ng/ml (females) for PL. A 5 ug/dl post-dexamethasone cortisol cut-off was employed.

Results

Mean plasma PL was decreased in male cocaine abusers (9.8 (+/− 2.4) vs. 5.3 (+/− 1.6); $t = 6.6$; $P<0.001$) compared to healthy, age-matched, laboratory controls. Female plasma PL variation was greater and our female sample too small for meaningful statistical comparisons. Mean plasma GH (both sexes) was increased in the cocaine abusers (1.6 (+/− 0.65) vs. 4.2 (+/− 4.9); $t = 2.4$; $P<0.01$). Cocaine use characteristics and individual neuroendocrine values are presented in the Table: 35% of the sample had plasma PL values below the normal range (corrected $\chi^2 = 26.3$; $P<0.01$), 20% had increased plasma

TABLE
Summary of cocaine use and neuroendocrine findings

	Sex		Total cocaine use		Abstinence	Post-dexamethasone cortisol					
Subject	M/F	Method[1]	3 mo (gm)*	1 wk*	duration (days)	Growth hormone	Prolactin	Cortisol	(9 am)	(4 pm) LFT[2]	Follow-up[3]
1	M	IV/S	300	30	4	0.9	9.8	16.0	no test[4]	5.7 +	WNL
2	F	IV/IN	90	6	4	19.0	7.4	6.5	1.2	1.8	no abst.
3	M	IV/IN	60	5	5	2.0	4.8	14.8	2.0	2.2 +	no abst.
4	M	IV/S	45	3.75	4	0.9	5.5	12.9	1.2	1.1	—
5	F	IV	40	3	8	4.1	6.4	12.5	no test	no test +	—
6	M	IV/IN	36	4	7	0.7	5.4	9.0	1.3	1.2 +	—
7	M	IV	35	3	6	no test	2.8	14.3	2.0	2.1	WNL
8	M	IV	25	2	4	2.7	4.8	12.6	no test	no test	no abst.
9	F	IV	20	2	10	1.4	5.9	21.9[5]	1.7	5.0	WNL
10	M	IV	14	1.5	4	9.7	no test	6.3	2.1	1.6 +	no test
11	F	S	100	14	5	1.4	7.9	8.9	33.1	8.8	WNL
12	F	S	90	6	4	11.5	10.6	21.2	2.1	7.9	WNL
13	M	S/IN	90	14	7	1.6	4.5	14.0	1.6	1.7	no abst.
14	F	S/IN	35	3	6	2.4	6.3	18.3	2.4	6.6	no abst.
15	M	IN	80	7	5	3.3	5.7	11.3	2.7	7.4	WNL
16	M	IN	65	4	5	1.3	4.1	7.8	2.0	2.2	WNL
17	M	IN/S	60	8	5	1.1	5.7	14.3	39.0	41.5	WNL
18	M	IN	60	7	5	12.5	4.9	8.0	1.8	1.9	WNL
19	M	IN	60	6	5	0.8	3.6	8.0	1.2	1.2	WNL
20	M	IN/IV	30	3	5	2.5	6.3	18.3	1.8	1.9	—
21	M	IN	25	2	5	3.3	5.7	11.3	2.7	7.4	WNL

1. Method: IV—intravenous; S—smoking cocaine base; IN—intranasal. When more than one method is noted the second represents between 15 and 40% of the subject's cocaine administration.
2. This category is included because most IV drug users have LFT elevations and these could affect DST cortisol levels. However, for this sample only one DST + (number 1) user had such abnormalities and he demonstrated normalisation of DST with abstinence >4 weeks while LFTs remained elevated.
3. Retests of abnormal values occured after four weeks of abstinence. (Some patients were treated with lithium or desipramine). No abst. = patient had no period of abstinence lasting this long. All abnormal values are underlined. WNL = within normal limits.
4. No test—laboratory error or patient unavailability at test time.
5. Base-line cortisol on patient number 9 was done one week after dexamethasone administration, following mishandling of the first cortisol sample.

* Preceding abstinence

https://doi.org/10.1192/bjp.147.5.569 Published online by Cambridge University Press

growth hormone levels (corrected $\chi^2 = 5.5$; $P<0.05$), and 42% had abnormal dexamethasone suppression. Base-line cortisols were normal in all subjects.

In all, 80% of the sample displayed one or more abnormal neuroendocrine values. Neuroendocrine abnormalities were re-tested, and returned to normal in all subjects (n = 11) reporting >4 weeks of abstinence.

Discussion

Decreased plasma PL and increased plasma GH levels were observed in this preliminary study, consistent with animal studies showing neurophysiological alterations in dopaminergic and noradrenergic systems after chronic cocaine exposure. However, the methodological shortcomings of the research on recently active drug users preclude firm conclusions being reached.

Several individual subjects showed clearly abnormal plasma PL and GH levels, as well as alterations in dexamethasone suppression, while others did not. This could reflect heterogeneity within our sample, based on differences in the purity of cocaine obtained, chronicity of use, routes of administration, self-report accuracy, sensitivity to cocaine effects, and degrees of dependence. Other shortcomings of out-patient clinical studies which are unrelated to cocaine abuse itself, such as possible undetected use of other drugs or medication, differences in diurnal patterns, sleep habits, diet, or psychosocial stressors, and the possibility of pre-existant endocrinopathy, could also have affected the results.

Given these multiple sources of heterogeneity, scattered findings might be expected. That conceptually plausible findings emerged at all, in a sample selected only on the common basis of recent cocaine abuse, is compelling but requires replication. These findings provide a foundation for further studies to isolate causative elements. However, certainty about whether cocaine causes clinically significant neuro-adaptation will require primate studies with multiple and naturalistic cocaine self-administration paradigms, due to the ethical and logistical difficulty of replicating such patterns in humans in a pure research setting. Such studies should utilise experimental designs which, unlike previous animal work, reflect human abuse characteristics. Such work could also repeat assays and generate important data on the temporal course of any post-cocaine neurochemical adaptations, and on concurrent behavioural changes.

The findings presented are the first, to our knowledge, that have been reported in human cocaine abusers consistent with the possible existence of a neuro-adaptive state associated with such drug taking. If this state is corroborated by appropriately designed studies and corresponds to the clinical difficulties of cocaine craving and addiction, it could have important implications for the treatment of cocaine abuse. For example, tricyclic antidepressants cause neuroreceptor alterations opposite to those reported after chronic cocaine in animals (Kleber & Gawin, 1984) and have been reported to reduce cocaine craving in open pilot trials (Gawin & Kleber, 1984c).

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*Reprints

(*Accepted 12 December 1984*)

British Journal of Psychiatry (1985), **147**, 573–575

Response to Sequential Administration of Clomipramine and Lithium Carbonate in Treatment-Resistant Depression

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Treatment-resistant depression remains a significant clinical problem (Shaw, 1977); none of the currently available treatments for depression claim a 100% response rate. Often, particular treatment regimes for treatment-resistant depression such as a monoamine oxidase inhibitor (MAOI) and a tricyclic antidepressant (TCA) in combination, or stereotactic surgery, involve increased risk of immediate or long-term complications. A number of recent reports have stated that where depression has not responded to TCAs, it has responded if lithium carbonate was added (Heninger *et al*, 1983; de Montigny *et al*, 1983). It has been postulated that the administration of a three-week course of TCAs, followed by these in combination with lithium, is effective in relieving treatment-resistant depression. This is because of the added enhancing effect of lithium carbonate on serotonin-containing neurones, in the setting of the TCA having already sensitised forebrain neurones to serotonin (de Montigny *et al*, 1981). The following case is that of a 73-year-old man with major depression. This persisted for ten months without significant response to three courses of electroconvulsive therapy (ECT), (two unilateral and one bilateral), amitriptyline (AMT) in doses of up to 200 mg, and tranylcypromine in doses of up to 50 mg daily. He subsequently responded, one week after lithium had been added to a three-week course of clomipramine. This case would appear to describe the phenomenon previously reported, but we believe it to be the first report of the use of clomipramine, a drug with predominantly serotonergic effects, in sequential combination with lithium carbonate in the treatment of resistant depression.

Case history

Mr L J is a 73-year-old married, retired post office technician, who was admitted to the intensive care unit of a general hospital, following an overdose of 60 × 20 mg tablets of temazepam. There was a three-month history of increasing depressive symptoms, with diurnal mood variation, early morning wakening, poor appetite, intermittent suicidal ideation, low energy, and a complete loss of pleasure in his usual activities.

Prior to his illness, the patient's personality had been characterised by obsessional traits; he had been a very capable but overly-meticulous man in his working life, although quiet and reserved socially. He had few friends and few outside interests since his retirement, eight years prior to admission. He was the youngest of six children, and was now the only surviving member of his family. He had two children, and was in regular social contact with them. During the three months before admission, he became concerned over his wife's health and his ability to care for her. He was preoccupied with his inability to complete his taxation forms, and this, together with mounting concerns over personal poverty, immediately preceded his overdose.

There was a past history of four severe depressive episodes: initially in his late teens, then when aged 41, at the age of 54, and finally at 61 years; these had lasted about three months each. On these occasions he had been treated with ECT, and for the last 12 years, had been on a maintenance antidepressant (AMT, up to 100 mg). There was a family history of severe depression, a brother having committed suicide in his mid-40s after several severe depressive episodes treated with ECT, but no other family member having been affected.

He was transferred to the psychiatric unit. Mental state examination revealed a weary looking, elderly man, with both psychomotor retardation and marked agitation. His affect was depressed and he was preoccupied with themes of poverty, including ideas of a delusional intensity. On