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Hormonal Effects of Apomorphine in Schizophrenia

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Summary: The hormonal effects of apomorphine, a direct-acting dopamine receptor agonist, in schizophrenic patients are of interest in view of the therapeutic efficacy of dopamine receptor antagonists. In this study, apomorphine (0.75 mg s.c.) and placebo were administered to unmedicated acute and chronic schizophrenics and controls. Apomorphine-induced prolactin suppression did not discriminate between the groups. However, an inverse relationship between basal prolactin levels and the severity of positive symptoms was detected in the patients with acute schizophrenia, consistent with a role for dopamine in the genesis of these symptoms. Growth hormone increments after apomorphine administration were blunted in the chronic schizophrenic patients, particularly those with 'negative' symptoms. It is argued that this blunting is not due to previous neuroleptic therapy and may represent evidence of structural change in the hypothalamus in this group of patients.

The dopamine-overactivity hypothesis of schizophrenia, first put forward by Randrup and Munkvad (1972), has been explored by several methods. The discovery of increased numbers of striatal dopamine receptors in the brains of schizophrenics (Owen *et al*, 1978; Lee *et al*, 1978) has focused attention on dopamine receptor function. This has stimulated interest in the endocrine responses to dopamine-receptor agonists in schizophrenia, although there is as yet no direct evidence of a change in receptor function in those brain areas concerned with endocrine regulation. There have been reports of differences between schizophrenics and controls in their responses to such agonists: see Rotrosen *et al* (1979) for a review. The nature of these differences, their relationship to clinical state and to drug therapy, and their implications in terms of the pathophysiology of schizophrenia remain to be determined.

Various dopamine agonists have been employed in such studies. The hormonal effects of amphetamines and L-DOPA are weak and inconsistent; and the effects of ergot derivatives, which are administered by mouth, are of gradual onset and prolonged duration. Apomorphine, on the other hand, is administered subcutaneously, is transported rapidly into the blood and the central nervous system, and is rapidly metabolized in the liver. It induces a prompt and large elevation of serum growth hormone (GH) in Man when given in doses of 0.25–1.5 mg s.c. (Lal *et al*, 1973), and the dose–response curve appears to be linear within this range (Cleghorn *et al*, 1983*a*). Although apomorphine induces reproducible growth hormone responses within individuals (Rotrosen *et al*, 1979), there are large differences *between* individuals, partly accounted for by differences in sex, levels of oestrogen and glucose, and posture (Ettigi *et al*, 1975). The GH response to apomorphine is consistently blocked by neuroleptics but not by other neuro-active drugs (Lal, Harvey and Bikadoroff, 1977), which suggests mediation by dopamine receptors. Since the response is not blocked by domperidone, a dopamine-receptor blocker which does not cross the blood-brain barrier (Laduron *et al*, 1979), a hypothalamic site of action is probable (Brown *et al*, 1982).

Apomorphine suppresses prolactin secretion in a variety of circumstances, e.g. pituitary cell culture-lines, animals, and human subjects with and without hyperprolactinaemia—for a review see Johnstone and Ferrier (1980). The effect is more marked when prolactin levels are high—there appears to be a lower limit of prolactin below which even massive doses of apomorphine will not suppress secretion. Apomorphine does not produce changes in other pituitary hormones (Johnstone and Ferrier, 1980).

Several studies have demonstrated that the GH response to apomorphine is blunted in patients with chronic schizophrenia (Pandey *et al*, 1977) although some such patients have an *exaggerated* response (Ettigi *et al*, 1976). It would appear from the cumulative data of several studies (Rotrosen *et al*, 1979) that in acute schizophrenia the mean increase in GH and the mean reduction in prolactin after apomor

phine are normal, but there is a wide scatter of response, with many patients above and below the control range. Short withdrawal times after neuroleptics have been suggested as the cause of this variability (Pandey *et al*, 1977). Another possible explanation (Cleghorn *et al*, 1983*b*) is that the clinical state of the patient at the time of testing determines magnitude of the GH response.

This study attempted to distinguish between these possible explanations by examining the hormonal response to apomorphine of male fasting schizophrenic patients, acute and chronic, who had been off medication for at least one month. The clinical state of the patients was assessed by means of videotaped interviews: the clinical effects of apomorphine are described in the preceding paper (pp. 341–348).

Method

Subjects

Three groups of subjects were studied: (1) 15 chronic schizophrenics (2) 15 acute schizophrenics and (3) 10 controls. Full details are furnished in the preceding paper.

The 15 male 'chronic' schizophrenics conformed to the criteria of Feigher *et al* (1972) for the diagnosis of schizophrenia. These patients had been free of neuroleptic drugs for at least a year prior to study: five patients had never been treated with neuroleptic drugs.

The 15 male 'acute' schizophrenics had symptoms with an onset within the preceding month. These patients had features of nuclear schizophrenia on the Present State Examination (Wing *et al*, 1974). The patients had been off medication for at least one month prior to study: nine of them had never received neuroleptics.

Experimental procedure

The following procedure was carried out on all subjects:

(1) The subject fasted from 10 p.m.: at 8.00 the next morning a butterfly cannula was inserted into a forearm vein and kept patent with dilute heparinized saline which was discarded prior to sampling.

(2) Venous samples were taken at 8.30 and 8.45.

(3) A semi-standardized interview was carried out by a psychiatrist on each schizophrenic subject, and recorded on videotape. In the case of controls a short perception test was carried out at this time (listening to a tape-recording and listing the frequency of key words).

(4) A further venous sample was taken at 9.00 a.m. This was immediately followed by the administration of 1 ml s.c. of either 0.75 mg apomorphine or 1.0 ml of an identical vehicle into the upper arm, the choice of drug or placebo being determined by a random schedule.

(5) The patient then lay recumbent for 30 minutes—during this period venous samples were taken 15 and 30 minutes after the injection. Side-effects experienced by the subjects (drowsiness, nausea, vomiting, or yawning) were assessed during this time.

(6) The schizophrenics were then interviewed again, and the interview, lasting 5–10 minutes, was videotaped. The perception test was repeated on the controls.

(7) Two further venous samples were obtained, 45 and 60 minutes after the injection of drug/placebo.

(8) On the following day the procedure was repeated with either placebo or apomorphine whichever, had not been administered the previous day.

(9) Sera was prepared from venous samples by standing them at 4°C and centrifuging at 3000 r.p.m. Aliquots were stored at −40°C until assayed.

(10) Videotapes were rated according to the scheme devised by Krawiecka *et al* (1977). Eye blink-rates were measured from the videotapes by counting blinks with the aid of a microcomputer programme.

Radio-immunoassays

Growth hormone (GH), prolactin (PRL) and luteinizing hormone (LH) were estimated by double-antibody radio-immunoassay (RIA) as described by Cotes *et al* (1978). The standards used for RIA were:

GH—2nd UK Working Standard.

PRL—International Reference Preparation of Human Prolactin for Immunoassay (75/504).

LH—1st IRP Human Pituitary LH for Immunoassay (MRC 68/40).

The mean within-assay coefficient of variation was 5%. The coefficients of variation for high-, medium- and low-quality controls for GH, PRL and LH are given in Table I. Oestradiol was estimated in the pre-placebo sample at the WHO Collaborating Centre, Chelsea Hospital for Women, London SW3, by a method adapted from Emment *et al* (1972).

All incubations were carried out in two replicate tubes. Potency estimates were derived from observations of radio-activity counts bound, using a computer program written by Dr R. Wootton based on the 4-parameter log-dose logit response standard curve of Healey (1972). For estimates of each substance, all the samples from each patient were estimated in a single assay which contained samples from both patients and controls.

Analysis of data

Baseline prolactin levels have a strong effect on apomorphne-induced suppression of prolactin. We also found that prolactin levels fell after placebo (see

TABLE I

Radio-immunoassay of growth hormone, prolactin and luteinizing hormone: coefficients of variation for high-medium- and low-quality controls

	GH	PRL	LH
High	14%	12%	10%
Medium	8%	8%	8%
Low	10%	10%	10%

Fig 1). In view of these effects, we used three different measures to assess apomorphine-induced suppression of prolactin: (a) the percentage reduction at 60 minutes post-apomorphine compared to 0 minutes; (b) the absolute reduction, in mIU/l, between these two times; and (c) the percentage reduction between these times after apomorphine *minus* the percentage reduction after placebo.

Raised basal GH levels have been shown to reduce GH response to apomorphine, but none of our subjects had baseline GH levels greater than 3 mIU/l. As our measure of GH increment we took the highest GH level after-apomorphine *minus* the baseline level (the mean of three pre-drug levels). There was no change in GH secretion after placebo.

Differences between hormonal responses were assessed by Student's *t*-test. Relationships between non-parametric clinical data (clinical ratings, frequency of side-effects) and hormonal data were assessed using Spearman's rank correlation. The main relationships examined were between clinical ratings and (a) GH increments, (b) basal prolactin levels (c) apomorphine induced prolactin suppression; in these cases partial correlation coefficients were employed to determine whether relationships were dependent or independent of age. Subsequently, other relationships were examined (e.g. between blink-rates or oestradiol levels and the above variables); thus a large number of variables were compared and caution is needed in the interpretation of positive results, some of which may have occurred by chance.

Results

Responses of controls

The mean GH and prolactin responses to apomorphine in normal subjects are shown in Fig 1.

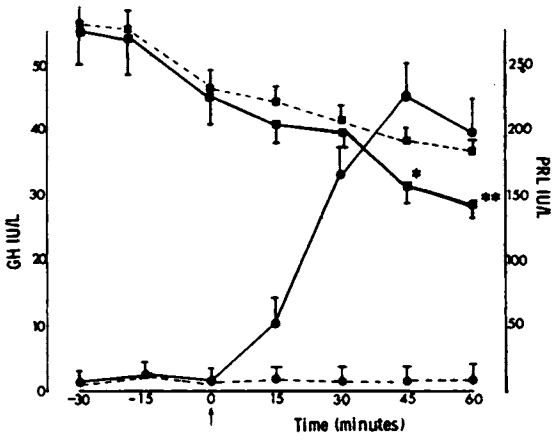

FIG 1.—Levels of growth hormone and prolactin (mean ± S.E.M.) before and after apomorphine and placebo in ten control subjects. Statistically significant differences between drug and placebo are marked *($P < 0.05$) and **($P < 0.01$).

TABLE II

Basal and post-apomorphine levels of growth hormone, prolactin, luteinizing hormone and oestradiol (basal only) in two schizophrenic groups and a control group. Figure represent mean ± S.E.M.

	GH		Prolactin			LH		
	Basal (mIU/litre)	Peak minus basal (mIU/litre)	Basal (mIU/litre)	60 minutes after APO (mIU/litre)	Reduction %	Basal (IU/litre)	60 minutes after APO (IU/litre)	Basal E_2 (pmol/litre)
Controls ($n = 10$)	1.1 ±0.3	48 ± 6.4	225 ± 14	159 ± 9.6	29% ± 2.4	5.5 ±0.5	5.4 ±0.3	60.1 ± 9.5
Acute schizophrenics ($n = 15$)	1.4 ±0.2	53 ± 9.4	248 ± 33	152 ± 21	38% ± 4	5.9 ±0.8	5.7 ±0.7	52.1 ± 7.3†
Chronic schizophrenics ($n = 15$)	2.4 ±0.7	*31 ± 5.0	158 ± 11	122 ± 8.5	24% 3.1	6.9 ±0.7	6.7 ±0.6	71.1 ± 5.9

*Significant ($P < 0.05$) compared with acute schizophrenics or controls
†$n = 10$

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The mean increase in the level of GH was statistically significant 15 minutes after the injection of apomorphine, and remained so. The response was large but variable, with a peak at a mean of +45 minutes: in eight out of ten controls, levels peaked at +45 minutes, the other two peaking at +30 minutes and +60 minutes.

Prolactin suppression was a slower and less marked phenomenon: there was no statistically significant reduction in prolactin secretion until 45 minutes after the injection.

LH levels were unaffected by apomorphine (see Table II).

Responses of schizophrenics

The hormonal responses of the acute and chronic schizophrenics are depicted in Figs 2 and 3 and summarised in Table II. The timing of the changes in GH and prolactin levels in schizophrenics was similar to that in controls.

(1) *Growth hormone.* There was no significant difference in the mean baseline level of GH between the groups studied (see Table II). A scattergram of peak GH increments after apomorphine for all three groups is shown in Fig 3. There was no significant differences in the increment between acute schizophrenics and controls, but the chronic schizophrenic group's mean peak GH increment was reduced compared with both other groups ($P < 0.05$).

There was a large *variation* in the GH increment in the acute schizophrenic group (1–120 mIU/l). When compared with the variation within the control group, this just failed to reach statistical significance ($F = 3.24$, d.f. = 2,12: $F = 3.28$ for $P = 0.5$).

(2) *Prolactin.* There was no difference in basal prolactin levels between acute schizophrenics and controls, but levels were significantly lower in the chronic schizophrenic group than in either of the others ($P < 0.05$). This no doubt reflects the greater age of this group.

There was no statistically significant difference between the groups in the reduction in prolactin after apomorphine either in percentage terms or in absolute terms, i.e. mIU/litre (Fig 3). The mean placebo-corrected reduction in prolactin after apomorphine (per cent reduction in 60 minutes after drug *minus* per cent reduction in 60 minutes after placebo) was 23 per cent ± 4 per cent in acute schizophrenics, 17 per cent ± 6 per cent in chronic schizophrenics, and 21 per cent ± 8 per cent in controls, which on analysis revealed no significant differences between the groups.

As can be seen from Fig 3, there was a very large variation in the magnitude of prolactin reduction within each group. There was a highly significant relationship between the apomorphine-induced reduction in prolactin and the basal level of prolactin ($r = 0.91$, $n = 40$, $P < 0.001$)—the reduction was greatest where basal levels were highest and least when basal levels were lowest.

(3) *Luteinizing hormone.* Mean LH levels before and after apomorphine and placebo are given for all three groups in Table II. Apomorphine produced no change in LH secretion in any of the groups.

(4) *Oestradiol.* Pre-placebo oestradiol (E_2) levels are shown in Table II. There was no statistical difference between the groups.

Correlations between clinical and hormonal variables

All subjects (incuding controls)

(1) *Age.* Significant negative correlations were found between age and (a) basal prolactin level ($r = -0.43$, $n = 40$, $P < 0.01$), (b) apomorphine-induced prolaction suppression, however calculated (e.g. between percentage reduction and age, $r = -0.41$, $n = 40$, $P < 0.01$) and (c) GH increment ($r = -0.37$, $n = 40$, $P < 0.05$).

In view of the close relationship between basal prolactin and apomorphine-induced prolactin suppression, it is likely that the effect of age on suppression is mediated by the effect on baseline prolactin levels. The significant negative correlation between age and the GH response is difficult to interpret, since it was found across the group of 40 subjects as a whole and was not seen within any of the individual groups. It may be an effect of illness rather than age.

(2) *GH increments.* There was no relationship between the increase in GH secretion after apomorphine and (a) prolactin suppression, (b) oestradiol levels, or (c) the side-effects of apomorphine administration (sedation, nausea, yawning or vomiting).

Correlations in schizophrenics

Symptom ratings (on the Krawiecka scale) of the pre-placebo videotape were compared with hormonal responses to apomorphine. Symptoms were divided into two groups—positive symptoms and negative symptoms—as described in the preceding paper (pp. 341–348).

(1) *GH increments.* There was a significant relationship between GH increments and positive-symptom ratings for both schizophrenic groups taken together ($r = 0.36$, $n = 30$, $P < 0.05$, Spearman's rank correlation). However, it was found that this relationship was based on the effects of age on both variables: while GH increments were found to fall with increasing age in the schizophrenic groups, the frequency of positive symptoms also fell with increasing age. Analysis of these correlations by the method of partial coefficients reduced the relationship between GH increments and positive symptoms to a non-significant level.

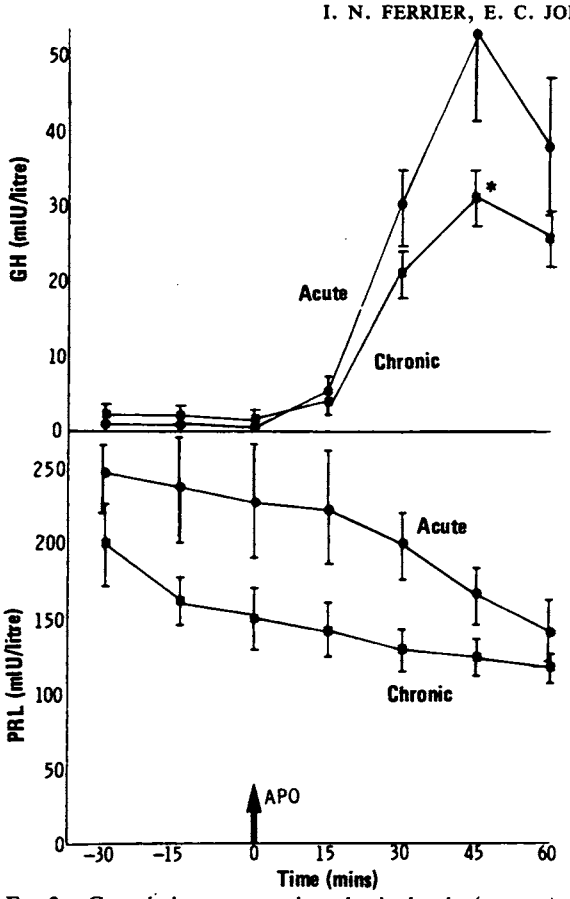

FIG 2.—Growth hormone and prolactin levels (mean ± S.E.M.) before and after apomorphine (APO) in 15 acute and 15 chronic schizophrenics. *The GH peak is significantly lower in the chronic group ($P < 0.05$) than in the acute schizophrenics or the controls.

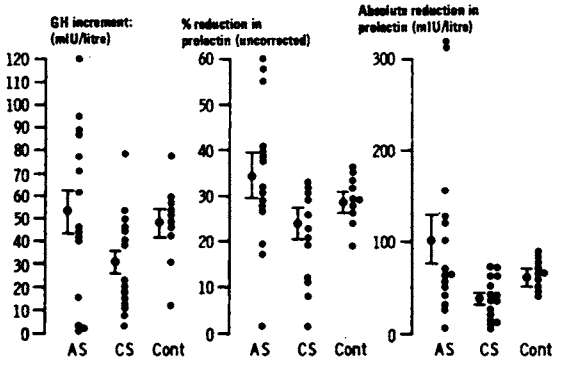

FIG 3.—Scattergram of changes in growth hormone and prolactin after apomorphine in 15 acute schizophrenics (AS), 15 chronic schizophrenics (CS) and 10 controls (Cont).

There was also a relationship between GH increments and *negative* symptoms, which remained significant following partial correlation coefficient analysis ($r = -0.40$, $n = 30$, $P < 0.05$). Moreoever, this inverse relationship was also seen within the chronic patient group alone ($r = -0.56$, $n = 15$, $P < 0.05$).

(2) *Prolactin levels.* Significant negative correlations were established in the acute schizophrenic group between positive symptom score and basal prolactin level, and between positive-symptom score and apomorphine-induced prolactin suppression ($r = -0.56$, $n = 15$, $P < 0.05$ for both measures, Spearman's rank correlation). These correlations were not present in the *chronic* schizophrenic group, or in the two schizophrenic groups combined.

(3) *Eye blink-rates* There was no correlation between eye blink-rates before or after apomorphine (nor the percentage change) and any other variable measured.

Discussion

This study revealed that: (a) there is a blunted GH response to apomorphine in chronic schizophrenic patients which is significantly related to the presence of negative symptoms; (b) the GH response to apomorphine in acute schizophrenics is very variable—no clinical correlate of this variability was established; and (c) basal prolactin secretion and prolactin levels after apomorphine did not discriminate between the clinical groups studied, but were lower in those acute patients with a greater score for positive symptoms.

The hormonal effects of apomorphine in normal control subjects parallel those previously described in other studies. There was a large variable increment in GH levels which peaked at +45 minutes. The variability of GH levels after apomorphine was striking, even though most of the known factors which affect this response were controlled for (i.e. only male subjects were studied, and all subjects were fasting and recumbent throughout the procedure). Oestradiol levels were not found to be related to the GH increment in this study, whereas Ettigi *et al* (1975) found large differences in the GH response to apomorphine between males and females, and between females on and off oestrogen supplementation. It is probable that oestrogens do suppress the GH response (there is supporting animal evidence), but that the effect of oestrogens was not seen in the present experiments because the range of oestradiol levels in this group of male subjects was limited.

There was a strong relationship between baseline prolactin level and the specific reduction in prolactin associated with apomorphine—the higher the prolactin level the greater the reduction. This is in agreement

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with previous reports (e.g. Rotrosen *et al,* 1978) and fits in with observations from dose–response studies that there is a prolactin level below which even massive doses of apomorphine do not suppress the prolactin level any further (Cleghorn *et al,* 1983*a*).

The lack of any relationship between apomorphine-induced prolactin suppression and apomorphine-induced GH secretion, in either the schizophrenics or the controls, suggests that these two hormonal responses are mediated differently. There is experimental evidence to support this contention: apomorphine directly suppresses prolactin secretion from pituitary cells *in vitro* but has no effect on GH secretion under these circumstances. Several other lines of evidence indicate that apomorphine-induced GH secretion is mediated at the hypothalamic level. For example, Brown *et al* (1982) have demonstrated that domperidone, a peripheral dopamine blocker, eliminates the prolactin response to apomorphine but not the GH response: this indicates that the dopamine receptors controlling prolactin release are peripheral (located within the pituitary and/or the median eminence) while those involved with GH are on the inside of the blood-brain barrier, perhaps in the anterior hypothalamus where dopamine receptors have been described by List and Seeman (1981).

No clear evidence emerged of any abnormality or change in receptor sensitivity in acute schizophrenia. GH increments after apomorphine showed a substantial variation in the group of patients with acute schizophrenia, but the difference from the controls was not statistically significant. The cause of this variability, which has been reported in other studies (Pandey *et al,* 1977; Rotrosen *et al,* 1979), is not clear. The period of withdrawal from drugs in the above studies was short and variable and this led the authors to suggest that neuroleptic withdrawal induced pituitary receptor super-sensitivity in some of the schizophrenic patients, leading to variable responses in the groups as a whole. However, all the patients in the present study had been off drugs for at least a month, and nine patients had never received neuroleptics. Since variability was still pronounced, drug withdrawal effects seem an unlikely cause of these differences in response.

Another question to be considered is whether the GH increment after apomorphine in acute schizophrenics is related to clinical state; are large GH increments found in a particular sub-group of patients, or are they related to a particular group of symptoms? No such clinical correlate emerged in the present study: no relationship was detected between GH secretion and clinical symptoms (e.g. grouped positive or negative symptoms or individual symptoms) in the acute patient group. The group with high GH-output were clinically indistinguishable from the group with low GH-output in terms of age, symptoms, previous episodes, etc. Studies of larger numbers of patients may be needed before some of these issues are adequately resolved. Cleghorn *et al* (1983*b*) have suggested that the clinical factor governing GH secretion after apomorphine is not clinical state as such, but whether this state is changing; i.e. whether the patients are relapsing or remitting. Unfortunately the present study provides no data to confirm or refute this hypothesis. The magnitude of the GH response to apomorphine does not appear to predict subsequent clinical response to drugs (Rotrosen *et al,* 1979).

We did find, in the acute schizophrenic group, significant negative correlations for positive-symptom score with both prolactin secretion and apomorphine-induced prolactin suppression; i.e. the greater the positive-symptom score, the lower the basal prolactin and the smaller the apomorphine-induced reduction in prolactin secretion. Since there is a close relationship between prolactin suppression and basal prolactin levels, the main relationship is probably between basal levels and symptoms: this is of theoretical interest, since dopamine tonically inhibits prolactin secretion, and dopamine has been implicated in the genesis of positive symptoms (Crow, 1980).

A similar relationship between positive symptoms and basal prolactin levels has previously been reported in a group of unmedicated chronic schizophrenics by Johnstone *et al* (1977). More recently, Kleinman *et al* (1982) have reported that there is an inverse relationship between positive symptoms and prolactin secretion only in those schizophrenics with normal computerised axial tomography (CAT) scans. It is apparent that the relationship between positive symptoms of schizophrenia and prolactin secretion is a weak one and is not applicable to individual patients. This is perhaps not surprising, since so many factors may influence both prolactin secretion and postive symptoms.

Basal prolactin levels were lower in the *chronic* schizophrenic patients, and this is the likely cause of the smaller degree of apomorphine-induced prolactin suppression in this group. Basal prolactin levels are known to be lower in chronic, as opposed to acute, schizophrenics (Meltzer *et al,* 1974)—an effect probably related to age.

The differences between the groups in prolactin suppression following apomorphine were not statistically significant for any of the measures used. Such results are in general agreement with those previously published (reviewed by Rotrosen *et al,* 1979). Maximum suppression of prolactin following apomorphine does not occur until about 90 minutes after the injection (Rotrosen *et al,* 1979): more prolonged sampling periods than those employed here may

therefore be necessary to detect changes in the prolactin response to apomorphine in schizophrenia.

As can be seen from Fig 3 and Table I, GH increments after apomorphine were significantly reduced in the chronic schizophrenics compared with the acute schizophrenics and the controls. Blunting of the GH response to apomorphine in chronic schizophrenics has been demonstrated in some previous studies (Pandey *et al*, 1977; Rotrosen *et al*, 1979), but not in all (Meltzer *et al*, 1982). The pathophysiological basis of this blunting is not clear. Rotrosen *et al* (1979) suggest that it is due to pathological sub-sensitivity of pituitary dopamine receptors schizophrenia, induced by chronic neuroleptic therapy. The evidence cited in favour of this contention is: (a) that Ettigi *et al* (1976) found a relationship between blunted GH responses and duration of neuroleptic therapy; and (b) that chronic neuroleptic therapy in rats appears to induce sub-sensitivity of dopamine receptors in the pituitary (Friend *et al*, 1978). However, there are several reasons to doubt the validity of this explanation. *Firstly;* the results of Ettigi *et al* may relate not to the duration of neuroleptic therapy, but to the chronicity of the illness. Meltzer *et al* (1982) have described such a relationship in a large study. *Secondly;* in the present study, three of the five chronic schizophrenics who had never been treated with neuroleptic drugs had GH responses well below the control mean. Moreover, blunting of the GH responses to apomorphine was related to the negative symptoms of schizophrenia. These symptoms, characteristic of chronic schizophrenia, are associated with cognitive impairment (Owens and Johnstone, 1980) and perhaps with structural changes in the brain (Crow, 1982). *Third;* although Friend *et al* (1978) detected biochemical evidence of neuroleptic-induced sub-sensitivity, there is pharmacological evidence (Lal, Brown *et al*, 1977) of functional *super*-sensitivity of this system to dopamine agonists in rats following neuroleptic withdrawal. Comparable evidence is not yet available in man, but the small study of Brambilla *et al* (1979) suggested that GH responses to L-DOPA were *enhanced* in the period following neuroleptic withdrawal. *Fourth;* and most crucially; it is unlikely that pathology of the pituitary dopamine receptor is involved in the mediation of this abnormality, since most evidence (Brown *et al*, 1978; Brown *et al*, 1982) points to a hypothalamic site of action for apomorphine in the induction of GH secretion.

The exact mechanism by which apomorphine acts on the CNS to elicit a surge of GH from the pituitary is not clear. It is virtually certain that apopmorphine does not elevate GH by an action on central nigrostriatal dopamine pathways: see Brown *et al* (1978) for a review. The effect appears to be mediated either via dopamine pathways within the hypothalamus (and associated receptors), or perhaps by an action on the hypothalamic releasing-hormones involved in GH regulation.

The cause of a reduced GH response to apomorphine in chronic schizophrenia, which has now been reported by several groups, thus remains unclear. In view of the relationship between blunted response and length of illness (Meltzer *et al*, 1982) and that between blunted response and negative symptoms (this study), it is conceivable that a degenerative or destructive process in the hypothalamus, or a closely related structure, underlies these impairments. The significance of this finding is open to doubt until further research can answer some of the questions above. Post-mortem examinations of pituitary dopamine receptors from schizophrenics should throw light on some of these issues. How these findings in a selected (drug-free) group of chronic schizophrenics relate to the deficits and impairments of the chronic schizophrenic population as a whole is a further problem.

In conclusion: we found no evidence of a change in dopamine-receptor sensitivity in schizophrenia such as might be predicted from post-mortem biochemical studies of the brains of schizophrenics. We did detect a blunting of the GH response to apomorphine in chronic schizophrenics, which was associated with negative symptoms; this may reflect the presence of hypothalamic damage. In acute schizophrenics we found relationships between positive symptoms and both basal prolactin and apomorphine-induced prolactin suppression which are consistent with a role for dopamine in the genesis of these symptoms. These distinct patterns of endocrine response may act as markers for different pathophysiological processes underlying these symptoms.

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