ANOVA and the Mann-Whitney *U* test). The ANOVA was significant ($P<0.001$), and differences in TSH concentrations were located between ATD and MDD ($P<0.001$), ATD and control subjects ($P<0.001$), and ATD and other dementia patients ($P<0.02$), but there was no difference between MDD and control subjects ($P=0.41$). The mean age of ATD female patients was 61.7 (s.d. = 4.8) years, MDD, 62.4 (s.d. = 11.7) years, other dementia patients, 64.3 (s.d. = 5.5) years and control subjects, 56.2 (s.d. = 6.0) years. Age differences (ANOVA $P=0.04$) were located between control subjects and ATD ($P<0.05$) and controls and OD ($P<0.01$), but not between the patient groups. TSH concentrations certainly increase with age, especially in women, but the Wickham community survey (Tunbridge *et al*, 1977) clearly showed that the prevalence of raised TSH concentrations (> 6 mU/l) is similar in the age groups 45–54 years (9.6%), 55–64 years (10.0%), and 65–74 years (8.0%); thus it is unlikely that the slightly lower mean age in our control subjects is meaningful.

TSH concentrations were similar in all four groups of male subjects: ATD, $n=11$, median = 4.5 mU/l, range = 3.0 to 5.7 mU/l; MDD, $n=4$, median = 3.4 mU/l, range = 2.6 to 4.3 mU/l; other dementia patients, $n=11$, median = 3.7 mU/l, range = 3.1 to 9.0 mU/l; control subjects, $n=6$, median = 4.4 mU/l, range = 2.8 to 7.1 mU/l. There was a significant difference in TSH concentrations between female and male ATD patients ($P<0.002$).

We have measured thyroid antibodies in all additional ATD patients and the surviving patients in the original series, including five of the female ATD patients with raised TSH concentrations. One female ATD patient (TSH 10.2 mU/l) was positive for microsomal antibodies, but none of the others were positive for thyroid antibodies. All patients had T_4 and T_3 values within the normal ranges. We have also measured TSH concentrations in nine of the female ATD patients (five with raised TSH concentrations) over a period of 1 to 4 years, and found that TSH concentrations declined in all cases with progression of the dementia; it is not surprising, therefore, that severely demented patients fail to show raised TSH concentrations. A further female ATD patient with high TSH concentrations, positive thyroid antibodies, but initially normal T_4 and T_3 was excluded from the study because on repeat testing 6 months later her T_4 and free T_4 were in the hypothyroid range. The upper limit for the euthyroid range for the TSH radioimmunoassay used in this study is 6.5 mU/l.

Thus, we reaffirm our previous conclusions and suggest that plasma TSH concentrations together with growth hormone and oestrogen-stimulated neurophysin concentrations are useful in differentiating presenile ATD from other causes of dementia and major depressive disorder.

J. E. CHRISTIE
L. J. WHALLEY
J. BENNIE
G. FINK

MRC Brain Metabolism Unit
Royal Edinburgh Hospital
Edinburgh EH10 5HF

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Down's Syndrome with Mania

SIR: Cook & Leventhal (*Journal*, February 1987, **150**, 249–250) seem to suggest that they have disproved the hypothesis that Down's syndrome precludes the development of mania. The position is not as simple as they would like us to believe.

Firstly, the case they have reported, and the cases reported by Rollin (1946) to which they refer, are more likely to be hypomanic than full-blown manic. Acute mania, apart from heavy sedation, often requires seclusion in the initial stages.

Secondly, post-mortem studies of the brains of patients with Down's syndrome clearly show the cell loss in the noradrenergic system of locus ceruleus and dorsal motor vagus, not only in the middle-aged, but also in younger patients (Mann *et al*, 1985). This loss may not be sufficient to prevent, but probably is sufficient to modify, the manic picture. Hence the absence of a full-blown manic picture in Down's syndrome.

Thirdly, they quote Prange *et al* (1974) to suggest a heightened association between Down's syndrome and bipolar affective illness. This is not relevant. There is no clinical evidence of this. In fact, Prange *et al* hypothesised that reduced indolamine activity accompanied by increased catecholamine may heighten this association. It is well established (Yates *et al*, 1980, 1983) that in Down's syndrome not only noradrenaline but other catecholamine activity is reduced.

I would suggest that post-mortem studies of the brains of patients with Down's syndrome have given

a lead in the further understanding of the amine hypothesis of affective illness, especially mania.

IQBAL SINGH

Leavesden Hospital
College Road
Abbots Langley
Herts WD5 0NU

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Dopamine Hypothesis of Neuroleptic Drug Action

SIR: The October issue (*Journal*, **151**, 455–465) contained three articles discussing the merits of the dopamine hypothesis of neuroleptic drug action. Since it is but a small step from there to a dopamine hypothesis of schizophrenia, and since various theorists and textbook authors have made that step, it seems appropriate to ask whether a better understanding of neuroleptic action is likely to tell us more about the underlying cause or causes of schizophrenia. I think that there are three reasons for pessimism in this regard. Firstly, the positive psychotic symptoms that respond to neuroleptic treatment are non-specific even when they are of the 'first rank', occurring in affective and organic disorders as well as in schizophrenia. Secondly, acute psychotic symptoms seem to be the least heritable component of schizophrenia, suggesting that they are only loosely related to the underlying biological predisposition. Finally, the severity of acute psychotic symptoms is a poor predictor of progressive decline with accumulating negative symptoms – a feature that seems much more distinctive of schizophrenia than the acute psychotic episodes themselves.

In the light of these considerations, it seems possible that a better understanding of neuroleptic drug action may reveal little about the origins of schizophrenia, just as an understanding of the actions of aspirin reveals little about the origins of influenza. A dopamine (or calcium-activated potassium conductance) hypothesis may no more explain schizophrenia than a prostaglandin hypothesis explains influenza. Of course, the treatment of positive psychotic symptoms is extremely valuable, and a better understanding of drug action may lead to future improvements in symptomatic treatment. At the same time, however, we may need to recognise that the search for better neuroleptics is relatively unlikely to lead to a specific treatment for schizophrenia, just as the search for a better febrifuge is unlikely to lead to a specific treatment for influenza.

Given the need for effective treatments for schizophrenia's relatively distinctive negative symptoms, the most appropriate research strategy may be to concentrate primarily on the correlates and origins of those features that generally distinguish schizophrenia from other psychotic disorders. Positive symptoms are striking and easily recognised, but they may be as much of a distraction to researchers as they are to patients. How intact are the research community's filters in the face of such absorbing noise?

ROBERT GOODMAN

The Hospital for Sick Children
Great Ormond Street
London WC1N 3 JH

Lithium, Psoriasis, Abnormal Glucose Tolerance, and Thyroid Dysfunction

SIR: We wish to report a patient exhibiting several unusual effects related to treatment with lithium.

Case report: A fifty-year-old man presented to this unit in February 1974 because of heavy drinking. He was noted to have had psoriasis since his early teenage years, characterised by minimal skin lesions but severe, disfiguring nail changes.

In 1975 he developed a depressive illness, and despite treatment with antidepressants continued to be subject to frequent severe fluctuations of mood. Lithium carbonate was commenced in November 1976. His mood swings became less marked, and he remained euthyroid for five years. In May 1982 he presented complaining of headache. There were no clinical signs, but his free thyroxine index was marginally raised. Three weeks later he was admitted as an emergency to a general hospital with chest pain thought to be cardiac in origin. He was noted to have lost a stone in weight over the preceding month, and complained of thirst. On examination he was flushed and sweating with a marked fine tremor and palpable goitre. His pulse was 136/min and blood pressure 160/80. Reflexes were bilaterally brisk. ECG showed sinus tachycardia but no ischaemia. Elevated serum thyroxine confirmed the clinical diagnosis of thyrotoxicosis.

Throughout the hospital stay, intermittent glycosuria occurred and an oral glucose tolerance test was abnormal. This was thought to be secondary to hyperthyroidism, and glibenclamide was commenced. He remained hyperthyroid