Nevertheless, the standard deviation remains high in the ATD group and suggests that there is still considerable positive skewness, even if this single outlier is removed. Since it is not essential to remove the outlier, the Mann-Whitney tests remain valid and show a statistically raised TSH level at each time of day, in both sexes together and in females in particular. This has come about because there is a general shift upwards as well as a single grossly elevated value. What is incorrect is to interpret Table II in Christie *et al's* paper as meaning that TSH is raised *threefold* in females suffering with ATD.

Although the authors comment that this one patient with a high TSH level was euthyroid, they have not documented this satisfactorily. Hypothyroidism, reflected in elevated TSH levels, can occur in the presence of normal tri-iodothyronine (T_3) and thyroxine (T_4) levels and in the absence of overt clinical features. However, under these circumstances, elevated TSH levels are strongly correlated with the presence of thyroid antibodies (Tunbridge *et al,* 1977). The measurement of thyroid antibodies would therefore have helped to clarify the thyroid status of this one patient with high TSH levels. Furthermore, accurate assessment of clinical and biochemical thyroid status (including auto-antibodies) is mandatory in any study of this type, particularly in the presence of marginally elevated TSH levels.

In general, the basal TSH levels seem considerably higher in absolute terms than the levels one would expect to see in the most sensitive TSH assays. This does raise some questions about the actual TSH assay used. What is the normal cut-off for primary hypothyroidism with this assay?

Our group has also investigated thyroid function in 21 elderly patients with severe senile dementia of the Alzheimer type (Thomas *et al,* 1987). There was no substantial or statistically significant difference in basal TSH levels between patients and controls. The TSH response was blunted in the patient group, but all differences were small in biological terms and were within the laboratory's normal range, emphasising (in our study) the relative normality of neuroendocrine function, particularly thyroid status, in ATD.

ROGER THOMAS
BRIAN HARRIS
ROBERT NEWCOMBE
MAURICE SCANLON

Neuroendocrine Research Unit
University of Wales College of Medicine
Heath Park
Cardiff

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SIR: Dr Thomas and colleagues challenge the presentation of TSH data in our report. We would like to respond with some additional data that clarify and extend our finding of raised TSH concentrations in women with presenile Alzheimer-type dementia (ATD).

Firstly, we have deliberately studied a population of demented patients with a presenile onset and do not suggest that we can at this stage extrapolate our finding to the senile ATD population. Secondly, the patients studied were at an early stage of illness, but it is precisely at this time that there is a need for improved diagnostic tests, to help especially in the differential diagnosis of dementia and when distinguishing early dementia from depression.

We have considered whether recent weight change may have influenced our finding by examining the weekly weight records of the ATD patients during their repeated admissions to the research ward, and found that the weights of ATD patients remain remarkably constant over periods of up to 4 years. Weight gain was rarely, if ever, reported by the relatives of any of our ATD patients at the time of referral but, of course, weight loss is common during the latter stages of dementia and in the depressed patients and may tend to lower TSH concentrations in that group.

We have now extended our original study, and Dr Thomas's next four points are best answered by examining the original in conjunction with additional data for morning TSH concentrations. In the female subjects, morning TSH concentrations (mean of 3 samples) were: ATD, $n=19$, median = 5.5 mU/l, range = 3.4 to >50 mU/l; major depressive disorder (MDD), $n=16$, median = 3.8 mU/l, range = 2.6 to 4.9 mU/l; other dementia patients (primarily multi-infarct dementia), $n=8$, median = 4.7 mU/l, range = 3.3 to 5.7 mU/l; healthy control subjects, $n=15$, median = 4.2 mU/l, range = 2.1 to 5.9 mU/l. TSH concentrations greater than 6 mU/l were found in 9 female ATD patients (6.3, 7.3, 8.0, 8.1, 8.3, 8.8, 10.2, 15.1 and >50 mU/l respectively) but in none of the MDD, other dementia patients, or control subjects. The TSH concentrations in our ATD women are skewed and, as before, non-parametric statistics were used (the Kruskal-Wallis

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