Serum Thyrotropin in Hospitalized Psychiatric Patients: Evidence for Hyperthyrotropinemia as Measured by an Ultrasensitive Thyrotropin Assay

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In order to gather further insight into the basis for high serum T4 and/or T3 of psychiatric illnesses, we studied thyroid function in 84 consecutive newly hospitalized psychiatric patients (HPP) in a 12-week period. Serum T4 and T3 were measured by immunoassay and thyrotropin (thyroid-stimulating hormone [TSH]) by an ultrasensitive immunoradiometric assay. Serum T4 was in the normal range in 64 (76%) and elevated in 20 (24%); free T4 index was elevated in 13 of 75 (16%), total T3 in 12 of 60 (20%), free T3 index in seven of 56 (13%), and TSH in 14 of 84 (17%) cases so studied. Serum TSH was subnormal in only one case (1%). Among the 14 patients with elevated serum TSH, serum free T4 index was normal in 12 and elevated in two. High serum T4 (or free T4 index) and high serum TSH were not correlated significantly by χ^2 analysis. None of the patients with elevated TSH demonstrated goiter or antithyroglobulin or antimicrosomal antibodies. On repeat testing 7 to 21 days after admission, serum TSH (and/or T4) normalized in the three of five patients studied. Serum TSH response to 500 μg intravenous (IV) thyrotropin-releasing hormone (TRH) was normal (serum TSH post-TRH, 8 to 28 μU/mL) in two patients with elevated TSH and T4, one patient with normal TSH and high T4, and one patient with normal TSH and T4. One patient with suppressed serum TSH (0.1 μU/mL) had elevated serum T4 (16.9 μg/dL, normal 4.8 to 11.5). In conclusion, in HPP (1) elevated serum T4 (or free T4 index) is mainly associated with normal or elevated serum TSH; TSH is suppressed in only 1%; (2) the transiency of high TSH (and T4) and absence of goiter and antithyroid antibodies suggest that high TSH (and T4) values are a result of a central abnormality in the central nervous system (CNS)-hypothalamothyrotropic axis.

PREVIOUS STUDIES have documented transient increases in serum T4 and free T4 index, occasional increases in serum T3, and normal or suppressed serum thyrotropin (thyroid-stimulating hormone [TSH]) or TSH response to thyrotropin-releasing hormone (TRH) in newly hospitalized psychiatric patients (HPP).[1,2] The mechanisms underlying these abnormalities are not known. However, serum TSH was measured in previous studies[1] by an assay that had a detection threshold of about 5 μU/mL and, therefore, comparison with normal subjects was not feasible. TSH assays now available detect less than 0.1 μU/mL, permitting clear differentiation between low, normal, and high TSH.[3] The present study was undertaken to apply the new ultrasensitive TSH assay for gaining further insight into the basis for elevated serum T4 and/or T3 in psychiatric disorders.

MATERIALS AND METHODS

Patients

Eighty-four consecutive HPP admitted to the UCLA neuropsychiatric institute over a 12-week period (November 1985 through January 1986), who were clinically euthyroid and who gave an informed consent, were enrolled for the study. Blood was obtained from patients between 8 AM and 10 AM one day following their admission to the hospital. The proposed studies were approved by the Human Subject Protection Committee at UCLA. There were 37 men and 47 women. Ages of patients varied between 19 and 85 years. Psychiatric diagnoses included schizophrenia, schizo-affective disorder, psychosis, mania, obsessive compulsive disorder, dysthymic disorder, depression with or without agitation, dementia, bipolar disorder, and atypical affective disorder. Several patients were taking one or more of the following drugs: Ativan, Artane, chloral hydrate, Cogentin, Desyrel, Doxepine, Halcion, Haldol, lithium carbonate, Mellaril, Navane, Norpramin, prolixin, Ritalin, Serax, Stelazine, Tylenol, and Xanax (see Appendix for details). Control subjects were healthy volunteers or blood donors whose age ranged between 18 and 66 years. The ratio of women to men in control subjects approximated 1.5.

Thyroid Function Studies

Serum T4 and T3 were measured by radioimmunoassay kits (Ventrex, Portland, ME). Resin uptake of T3 and antithyroid antibodies were measured by kits available commercially (Ventrex, and Burroughs Wellcome, Dratford, UK). In selected cases, percent free T4 was determined by equilibrium dialysis.[4] Serum TSH was measured by an ultrasensitive immunoradiometric assay (IRMA) (Sucrosep, Boots-Celltech, Slough, UK), which has a sensitivity of 0.05 μU/mL or less.[3] Intraassay coefficient of variation was 8% for serum TSH of 0.6 μU/mL, 5.0% for serum TSH of 1.9 μU/mL, and 3.5% for serum TSH of 10.9 μU/mL; the mean coefficient of variation for all measurements within an assay was 5.5%. Similarly, between-assay coefficients of variation of the TSH assay were 8.0%, 5.0%, and 2.5% for serum TSH values of 0.6, 1.9, and 10.9 μU/mL, respectively, and the mean interassay coefficient of variation for all TSH measurements was 5.2%. Since intraassay and interassay coefficients of valuation were so similar, it was not considered necessary to run all samples and controls in the same assay run. Instead, quality of the TSH assay runs was monitored by values obtained in reference sera provided by the manufacturer of the kits and those prepared in-house in our laboratory. Serum TSH response to TRH was measured at 30 minutes after injection of TRH (500 μg intravenously [IV]).

Statistical Analyses

The data in the groups were reduced to mean ±SEM and the group means were compared by Student's two-tailed *t* test. A *P* value of less than .05 was considered statistically significant. Correlation studies among certain parameters, eg, TSH and T4, were conducted

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using χ^2 analysis and/or regression analyses using the method of least squares.

RESULTS

Among the 84 HPP serum T4 was in the normal range (4.8 to 11.5 μg/dL) in 64 (76%) and elevated (11.6 to 16.7 μg/dL) in 20 (24%); free T4 index was elevated in 13 of 75 (16%), total T3 was elevated in 12 of 60 (20%), free T3 index was elevated in seven of 56 (13%), and TSH was elevated in 14 of 84 (17%) cases so studied (Fig 1). The mean (±SEM) serum T4 concentration (μg/dL) of 9.6 ± 0.29 in HPP was significantly ($P < .001$) higher than 8.2 ± 0.12 in normal subjects. The resin uptake of T3 was determined in 75 HPP and 243 control subjects. The mean (±SEM) value of 0.94 ± 0.011 in HPP was slightly but significantly lower than the corresponding value of 1.0 ± 0.004 in control subjects. Despite this difference, the mean free index T4 index in HPP was significantly higher than that in control subjects (9.2 ± 0.29 *v* 8.2 ± 0.12, $P < .005$) (Fig 2). The dialyzable fraction of T4 (DFT4) was studied simultaneously by equilibrium dialysis in 35 patients (24 with high T4 and 11 with normal T4) and 17 normal subjects. For convenience sake, the data in all patients and control subjects were arbitrarily expressed as percent of mean normal value (0.02%). The mean (±SEM) DFT4 in HPP of 92.3% ± 4.2% (range, 60% to 130%) did not differ significantly from that of 100% ± 7.1% (range, 75% to 140%) in normal subjects. On the other hand, the mean total T3 (147 ± 4.7 *v* 108 ± 1.2 ng/dL), the mean free T3 index (137 ± 4.2 *v* 108 ± 1.2), and the mean TSH (2.7 ± 0.22 *v* 1.9 ± 0.07 μU/mL) values in HPP were significantly ($P < .001$) higher than corresponding values in normal subjects (Fig 2). When studied by regression analysis, there was a significant negative correlation between serum TSH and free T4 index ($r = -0.20$, N = 75, $P < .005$), but not between TSH and free T3 index ($r = -0.13$, N = 56, P = NS) in HPP. None of the patients demonstrated goiter as examined by one of us (T.S.H.) and the physician taking care of the patient. Antithyroglobulin and antimicrosomal antibodies were measured simultaneously in all patients with high serum TSH (n = 14) or high serum T4 (n = 20), 12 patients with normal T4, and 17 normal subjects. They were undetectable in all instances except two cases, both of which were among the group of patients with normal T4; one of these patients had barely detectable antithyroglobulin antibody, while the other had minimal titer of antimicrosomal antibody.

Figure 3 compares the thyroid function tests in patients with high serum T4 (N = 20) and those with normal serum T4 (N = 64). The mean free T4 index and free T3 index were higher in patients with high T4. However, the mean serum TSH values in these two groups did not differ significantly from each other.

Table 1 describes the data on seven patients with elevated free T3 index. Serum total T4, and total T3 were also supranormal in all of these patients. However, free T4 index was clearly elevated in only four of them. Two patients in this group had elevated serum thyroxine-binding globulin (TBG), related to either ongoing or recently discontinued use of estrogen (case no. 1 and 2, Table 1). Serum TSH was clearly supranormal in two patients, whereas it was clearly in the normal range in four patients and supressed in one case.

Among the 14 patients with elevated serum TSH (range, 4.6 to 12 μU/mL), there were five men of 23 to 85 years of age and nine women of 28 to 65 years of age. Psychiatric diagnosis in patients with elevated TSH included schizophrenia (two cases), depression (four) bipolar disorder (three), obsessive compulsive disorder (with or without depression) (two), dementia (two), and personality disorder (one). Three of 14 patients were taking lithium-containing drugs, while 11 others did not ingest lithium. One of 14 patients was taking amphetamines. Serum free T4 index was normal in 12 cases and elevated in two cases. It ranged from 7.0 to 16.9 in men (mean, 10.9) and 5.9 to 11.1 (mean, 8.4) in women (normal, 5.5 to 11.7). Serum T4 (or free T4 index) or T3 (or free T3

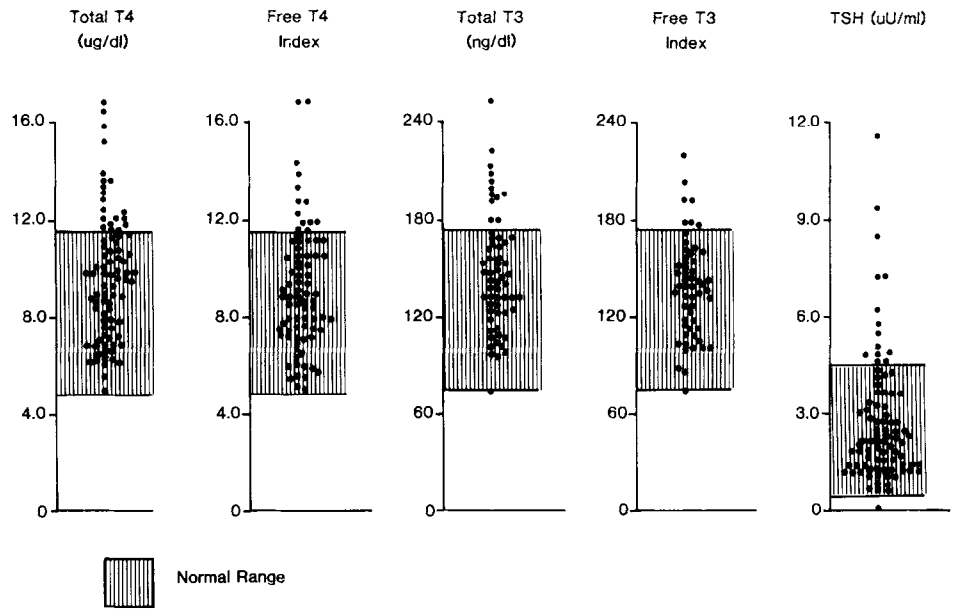

Fig 1. Thyroid function test data in patients hospitalized for psychiatric disorders.

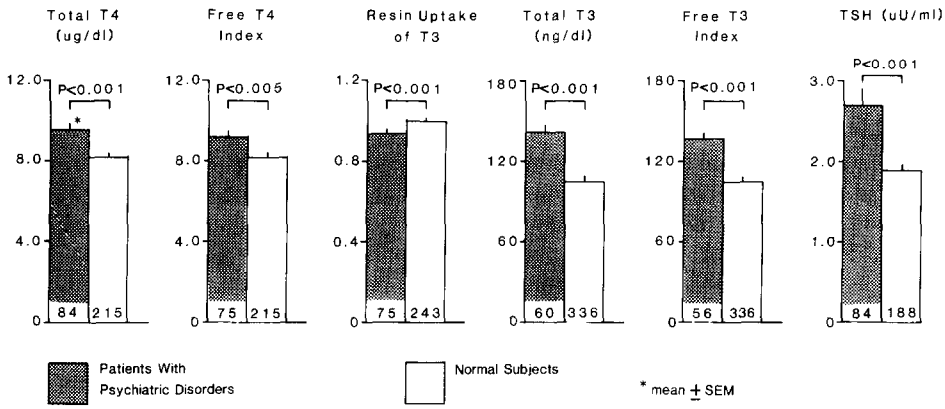

Fig 2. Comparison of thyroid function test data (mean ± SEM) in patients with psychiatric disorders and control subjects.

index) and high serum TSH were not correlated significantly by χ^2 analysis. Figure 4 shows the data on the mean ± SEM for various thyroid function parameters in patients with high serum TSH and those with normal serum TSH. Beside serum TSH, there was no significant difference in various thyroid function tests in the two groups. Psychoactive drugs administered for treatment of patients with high serum TSH were similar to those administered for the treatment of patients with normal serum TSH. Serum TSH was measured again at 7 to 21 days after the first measurement in five patients; it decreased to normal (0.6 to 2.0 μU/mL) in three cases (normal range, 0.4 to 4.4) and was still elevated in the remaining two cases (7.2 and 6.0 μU/mL), respectively. In two patients with persistent elevation of TSH (6.0 to 7.2 μU/mL), serum free T4 index ranged between 10.8 and 16.9 in one case (normal, 5.5 to 11.7) and between 8.8 and 9.4 in the other one. Serum TSH response to TRH was studied in individuals who were still available in the hospital and remained willing for study when initial serum TSH data became available. It was normal in all four cases studied (serum TSH post-TRH, 8 to 28 μU/mL). The baseline serum TSH and T4 were both elevated in two cases, and they were normal in one case; the remaining one patient had normal TSH and elevated T4. One patient whose serum TSH was subnormal (0.1 μU/mL) had elevated free T4 index (16.9) and free T3 index (218). This patient was suffering from depression.

DISCUSSION

Complex interrelationships exist between thyroid dysfunction and psychiatric illnesses. Both hyperthyroidism and hypothyroidism may be associated with psychiatric disturbances.[5,7] On the other hand, abnormalities in thyroid function are quite common in a wide variety of psychiatric illnesses.[1,2,12-14] Some have suggested that psychiatric disturbances may precipitate hyperthyroidism. However, thyroid function abnormalities in psychiatric illnesses are often transient and tend to disappear in the course of a few weeks without treatment directed at the thyroid. The abnormalities previously reported in acute psychiatric disorders include elevated serum T4 (1% to 33%), elevated free T4 index (9% to 18%), elevated T3 (~6.5%), subnormal serum T3 (~2%); and suppressed serum TSH response to TRH.[1,2,9-14] Some have even reported subnormal free T4 index,[2] but this experience has not been consistent[1] (present study). High serum TSH serum values have been recorded previously in about 1% patients with psychiatric disorders.[13] However, these patients were hypothyroid as evidenced by subnormal serum T4 and/or free T4 index.[13] The finding of clearly elevated serum TSH in a substantial portion (~17%) of clinically euthyroid patients with psychiatric disorders, whose serum T4 was clearly normal or even high, is a novel finding of the present study. It is conceivable that this abnormality was not recognized previously because the radioimmunoas-

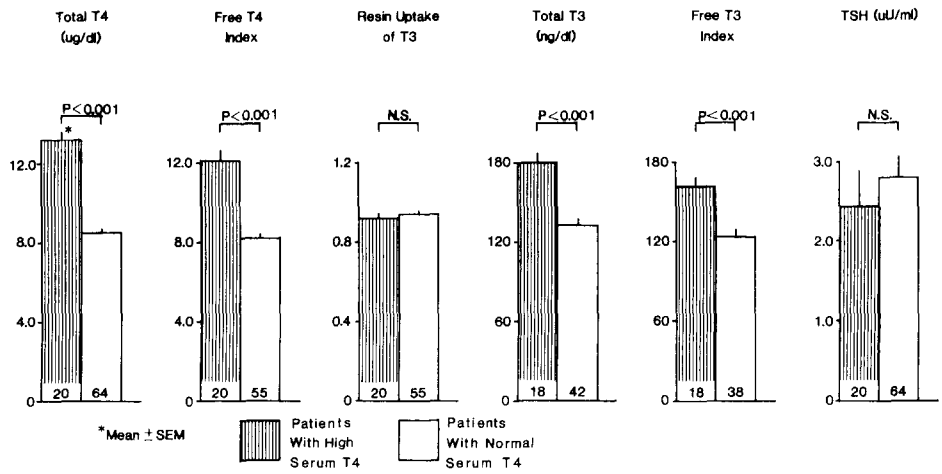

Fig 3. Thyroid function tests in psychiatric disorders: comparison of patients with high serum T4 and those with normal serum T4.

Table 1. Thyroid Function Tests in HPP With Elevated Free T3 Index

Patient No.	Age (yr)/Sex	Psychiatric Diagnosis	Serum Total T4 (μg/dL)	Serum Total T3 (ng/dL)	Free T4 Index	Free T3 Index	TSH (μU/mL)	Drugs Ingested
1	28/F	Personality disorder, depression	15.8	284	9.8	176	12	Tylox, Estinyl
2	41/F	Atypical depression, personality disorder	13.4	253	9.4	177	7.2	Cogentin, Xanax, Trofranil, phenobarbital, history of recent estrogen use
3	36/M	Obsessive compulsive, behavior, depression anxiety	11.9	205	11.8	203	3.6	Desyrel
4	34/M	Bipolar disorder, history of substance abuse	12.0	195	11.8	191	1.2	Xanax, Doriden, Tylenol, Codeine
5	72/F	Depression	16.4	212	16.9	218	<0.1	—
6	74/M	Depression, suicidal, history of ethanol abuse	12.2	191	12.2	191	1.2	Librium
7	48/F	Bipolar disorder, mania	11.6	195	10.7	179	2.5	Haldol, Cogentin
Normal range			4.8-11.5	75-175	4.8-11.5	75-175	0.4-4.4	

says (RIA) then available were not adequately sensitive. Thus, Spratt et al had employed a TSH RIA that had a detection threshold of 5 μU/mL, and serum TSH in most of the HPP (and all normal subjects) is indeed less than this threshold.[1] The TSH assay used in our study had a detection threshold of 0.05 μU/mL (or less) and allowed a clear separation of normal TSH from both subnormal and supranormal values. However, we observed TSH values of up to 12 μU/mL in our patients (Fig 1). It is unclear why Spratt et al did not observe such TSH values, which are clearly above their detection limit of 5 μU/mL.

High serum TSH in our patients could not be ascribed to concomitant chronic thyroiditis, ages of the patients, or the presence of a specific psychiatric illness. None of our patients had a goiter and antithyroid antibodies were undetectable. Antithyroid antibodies have been described in more than 25% of patients with chronic thyroiditis even when they are over 60 years of age and serum TSH is minimally elevated (5 to 10 μU/mL).[15] Ages or the pattern of drugs ingested by patients with elevated TSH did not differ from those ingested by patients with normal TSH. Additionally, elevated TSH values were observed in some patients at the time of their first hospitalization for a psychiatric illness when they had not yet ingested psychoactive drugs. Therefore, it is unlikely that ingestion of drugs played a causative role in high serum TSH of all our patients, although they may have contributed to some, albeit a minor degree in some of them. Elevation of serum TSH similar to that seen here in psychiatric illnesses has also been described in patients with systemic nonthyroid illness.[16]

Interestingly, Levy et al[12] have suggested that elevated serum T4 (or free T4 index) is observed commonly in patients with characteristic anxiety components such that they reported decreased autonomic systems. This issue was not evaluated in relation to TSH or other parameters in our study.

Just as is true of T4 (or free T4 index),[1,2] elevation of serum TSH is often transient in HPP. We documented normalization of elevated TSH within 3 weeks in three of five patients so studied; this finding argues against an unusual effect of the patients serum in the assay as the explanation of a high TSH in HPP, an inference further strenghtened by the finding of normal serum TSH response to TRH in our patients.

The mechanism of elevated serum T4 (and free T4 or free T4 index) in HPP remains unclear. It has not been possible to relate this abnormality to ingestion of a specific drug[1] and no data are available to support the possibility of altered

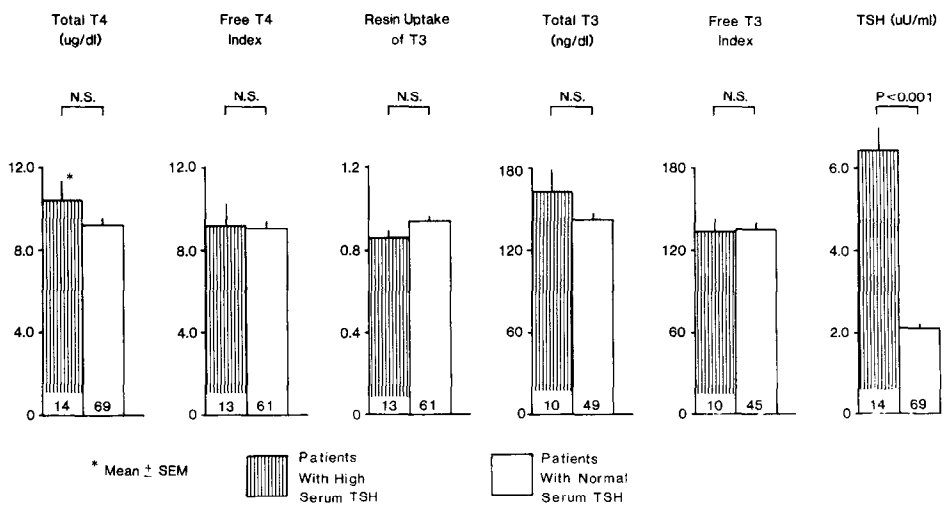

Fig 4. Thyroid function tests in patients with psychiatric disorders: comparison of patients with high serum TSH and those with normal TSH.

distribution of extrathyroidal T4 as an important factor contributing to high serum T4 of psychiatric illnesses. Spratt et al[1] suggested that high circulating phenylethylamine (or a similar factor) in chronic paranoid schizophrenia[17] and possibly other psychiatric illnesses as well may be a factor responsible for high T4 in HPP. This was so considered because phenylenthylamine is related structurally to amphetamines, which have been shown to cause an elevation of serum T4 (without increased serum TSH).[18]

If the above-mentioned factors were the major determinants of elevated serum T4 (and/or T3) of psychiatric illnesses, we would expect to find suppressed serum TSH in HPP. This was rarely (~1%) the case. Serum TSH and serum TSH response to TRH were typically either clearly normal and supranormal in our patients. These data suggest that the elevation of serum TSH results from a central hypothalamo-pituitary dysfunction and that this may be the primary event responsible for elevated serum T4, free index and T3 in HPP. This consideration may lead some to expect an elevated serum TSH in all instances of elevated T4 (and free T4 index), which was clearly not the case. However, the difference between the expectation and the finding may conceivably be resolved if one considers the marked difference in plasma clearance rates of TSH (≈62 L/d, half-life 54 minutes[19]) and T4 (≈1.3 L/d, half-life 6 days[20,21]). Thus, there would be periods when serum TSH has returned to normal but serum T4 is still elevated. Our data indicating serum TSH to be either clearly normal or elevated strongly suggest the hypothesis that increased central tone in the hypothalamo-thyrotropic axis resulting in transient elevations of TSH may be responsible for the high T4. Interestingly, we did find high normal (10.8) or high (16.9) free index T4 index in one of our two cases with persistently elevated TSH; However, it was clearly normal (8.8, 9.4) in the other case. It is possible that there is altered glycosylation and reduced bioactivity of TSH in some psychiatric illnesses in a manner similar to that recently described in systemic nonthyroidal illnesses.[22] The combination of high serum T4 and normal serum TSH may also signify reduced metabolic clearance rate of T4 in some psychiatric illnesses. Clearly, study of kinetics of thyroid hormones and frequent, around the clock measurement of TSH, T4 and T3 and the evaluation of bioactivity of TSH would be necessary to further evaluate the possibility of altered pituitary-thyroid axis in psychiatric disorders. A poor correlation between TSH and free T4 index (Figs 3 and 4), comparable mean TSH levels in patients with elevated T4 and normal T4 and comparable mean T4 levels in patients with elevated TSH and normal TSH are some findings that do not support the issue of a supranormal setting of pituitary-thyroid in psychiatric disorders. It is hoped that future studies will provide more clear and comprehensive information on the basis for alterations in thyroid hormone and TSH levels in psychiatric disorders than has been possible in this study. In the meantime, it is critical to be aware of these abnormalities so as to avoid errors in diagnosis and/or management of thyroid disease.

APPENDIX: Detail of Registered Trademarks

Commercial Name	Generic Name	Manufacturer	Location
Cogentin®	Benztropine, mesylate	Merck, Sharpe & Dohme	West Point, PA
Desyrel®	Trazadone Hcl	Mead Johnson Pharmaceuticals	Evansville IN
Doxepin HCl®		Lederle Labs	Wayne, NJ
Halcion®	Triazolam	Upjohn Co	Kalamazoo, MI
Haldol®	Haloperidol	McNeil Pharmaceuticals	Springhouse, PA
Mellaril®	Thioridazine HCl	Sandoz Pharmaceuticals	East Hanover, NJ
Navane®	Thiothixene HCl	Roerig	New York, NY
Norpramin®	Desipramine HCl	Merrell Dow	Cincinnati, OH
Prolixin®	Fluphenazine Decanoate	Princeton Pharmaceuticals	Princeton, NJ
Ritalin®	Methylphenindate HCl	CIBA Pharmaceuticals	Summit, NJ
Serax®	Oxazepam	Wyeth-Ayerst	Philadelphia, PA
Stelazine®	Trifluoperazine HCl	Smith, Kline & French	Philadelphia, PA
Tylenol®	Acetominophen	McNeil Consumer Products	Fort Washington, PA
Tylox®	Oxycodone and acetaminophen	McNeil Pharmaceuticals	Springhouse, PA
Estinyl®	Ethinyl Estradiol	Schering	Kenilworth, NJ
Tofranil®	Imipramine HCl	Geigy	Ardsley, NY
Doriden®	Glutethimide	Rorer Pharmaceuticals	Fort Washington, PA
Librium®	Chlordiazepoxide HCl	Roche Laboratories	Nutley, NJ

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