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Serum Thyroxine Levels in Schizophrenic and Affective Disorder Diagnostic Subgroups

JOHN W. MASON, M.D.,[1,2] JAMES L. KENNEDY, M.D.,[1,2] THOMAS R. KOSTEN, M.D.,[1,3] AND EARL L. GILLER, JR., M.D., PH.D.[1,2]

Serum free thyroxine (FT_4) and total thyroxine (TT_4) levels were measured at 2-week intervals during the course of hospitalization in 29 male inpatients in the following four diagnostic groups: paranoid schizophrenia (PS); undifferentiated schizophrenia; bipolar I disorder, manic; and major depressive disorder, endogenous type. The most striking finding was a difference in the direction of both TT_4 and FT_4 change during clinical recovery in the PS group compared with the other three groups. Analysis of the delta values, representing the change between admission and discharge values, revealed significant differences between the mean rise in the PS group *vs.* the mean decreases in the other three groups for both TT_4 ($p < .0003$) and FT_4 ($p < .003$). For TT_4, 75% of the PS group showed a rise during recovery in contrast to 4% of the remaining groups; for FT_4, 50% of the PS group showed a rise compared with 14% of the other groups. A significant difference was also observed between the FT_4 levels of bipolar I, manic *vs.* PS patients at the time of hospital admission, which may have potential usefulness in the differential diagnosis of these two disorders. This study emphasizes the importance of exploring more fully the psychiatric significance of thyroxine levels within the endocrinological normal range and of doing longitudinal assessments of thyroxine and symptom changes during clinical recovery in psychiatric disorders.

It has long been established that both hypothyroidism and hyperthyroidism are associated with changes in affective and cognitive functioning and with clinical symptoms similar to those of psychiatric disorders (Hayward and Woods, 1931; Whybrow and Hurwitz, 1976). It is understandable, therefore, that the clinical psychoendocrine literature on the hypothalamic-pituitary-thyroid system has developed over the past 60 years largely around a search for clinically significant undiagnosed thyroid glandular disease in psychiatric patients. One early study, for example, found that administration of thyroid extract to schizophrenic patients resulted in an 88% clinical improvement rate in patients showing signs of low thyroid function, as compared with 34% in patients without indications of thyroid deficiency (Hoskins and Sleeper, 1930). Other early observations, such as a low basal metabolic rate in 50% of schizophrenic patients (Bowman et al., 1950), reduced radioiodine uptake response following thyrotropin (TSH) administration in schizophrenic patients (Cranswick, 1956), reduced basal thyroid radioiodine uptake in chronic male schizophrenics (Simpson et al., 1963), and reduced sensitivity to the toxicity of thyroid extract in many schizophrenic patients (Hoskins, 1946), all suggested the possibility of diminished thyroid function as a clinically significant factor in at least a subgroup of schizophrenic patients. These early studies, however, were difficult to interpret because of methodological issues relating to psychiatric diagnostic criteria, nutritional factors, and the relatively indirect thyroid indices used.

More recent studies have focused on relationships between thyroid function and affective disorders. The finding of enhancement of antidepressant medication by either triiodothyronine (T_3; Prange et al., 1969) or thyrotropin-releasing-hormone (TRH; Prange et al., 1970) has raised the question of a possible relative deficiency of thyroid hormone in depression. Subsequently, a study of 270 depressed patients representing diverse geographic regions revealed a 12.2% incidence of clinical or subclinical hypothyroidism (Dackis et al., 1986; Gold et al., 1981). The majority of these patients showed thyroxine levels in the normal range but were classified as grade 3 (subclinical) hypothyroidism because of an enhanced TSH response to TRH infusion, and 60% of them showed evidence of autoimmune thyroiditis. Ten such hypothyroid patients with major depressive disorder were treated with thyroxine administration and eight of these responded within

[1] Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut.
[2] West Haven Veterans Administration Medical Center, West Haven, Connecticut. Send reprint requests to Dr. Mason, VA Medical Center/116A, West Haven, CT 06516.
[3] Connecticut Mental Health Center.
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3 weeks with resolution of their depressive symptoms (Dackis et al., 1986). There has also been recent interest in thyroid treatment studies of a subgroup of bipolar disorder patients with a rapid-cycling pattern of illness. There are approximately 20 reported cases of women with this diagnosis successfully treated with thyroid hormone, yet none had evidence of clinical hypothyroidism (Bauer and Whybrow, 1986). Onset of rapid-cycling in a male bipolar patient after subtotal thyroidectomy has been reported, with a TRH response consistent with subclinical hypothyroidism and a good clinical response to thyroxine treatment (Bauer and Whybrow, 1986).

Thus, studies of both bipolar and depressive disorders have indicated that thyroid hormone levels need not be outside the normal or euthyroid range to have clinical significance for psychiatric disorders and the possibility that good psychological functioning for any given individual may be dependent on an optimal level of thyroid function within the normal range may deserve serious consideration (Prange et al., 1970). A longitudinal study of a schizophrenic patient also supports the importance of this perspective, with the finding that thyroid activity was consistently and significantly higher in mute-retarded phases than in hyperactive phases, even though levels were always within normal limits (Libow and Durell, 1965). Brody (1949) also reported long ago that a significant relationship between levels of thyroid activity and a psychiatric symptom, such as tension, can be demonstrated within the normal range of thyroid function without evidence of thyroid disease.

There has been relatively little attention directed to the question of possible differences in thyroid hormone levels between various diagnostic groups or subgroups of psychiatric disorders, perhaps because of the primary concern with a search for clinical thyroid endocrinopathies in psychiatric patients, plus the fact that most psychiatric patients have thyroid hormone levels within the normal range. Even the recent TRH infusion studies of depressive syndromes have been based primarily on a search for endocrine function outside the normal range. The possibility exists, however, that there may be small but consistent differences in levels of thyroid hormones within the normal range between different psychiatric disorders that may have clinical usefulness in patient assessment. Thyroxine levels within a given individual tend to be maintained within a narrow range (Harrop et al., 1985), so that relatively small interindividual differences may be significant with this system. In particular, there have been few reported studies comparing schizophrenic and affective disorder patients and, to our knowledge, none with a longitudinal design and an assessment of severity of clinical symptoms at the time of hormonal measurements. There have been several incidental reports of elevated thyroid activity (Bowman et al., 1950; Morley and Shafer, 1982) and TSH levels (Dewhurst et al., 1969) in patients with paranoid schizophrenia (PS). Other studies by Brody and Man (1950) and Reichlin (1959) showed an increased range of variability of thyroid hormone levels in the paranoid subgroup, perhaps suggesting that consideration should be given to clinical state factors as well as diagnostic category when investigating relationships between thyroid function and psychiatric diagnosis.

The present study is based upon a conceptual approach that differs in several respects from previous psychoendocrine studies of thyroid hormones in psychiatric disorders. First, the criterion for clinical psychiatric significance of thyroxine levels is defined in terms of statistically significant differences between diagnostic groups or subgroups of psychiatric patients, rather than being based upon comparison with normal subjects or normal thyroid hormone limits defined for characterizing glandular pathology of the thyroid system. This approach considers the possibility that significant thyroid hormone level differences between patient subgroups may prove to have usefulness for clinical problems such as differential diagnosis, prognosis, or prediction of treatment response in psychiatric disorders, even though the absolute hormonal levels do not fall in the extreme clinical endocrinological ranges for hypothyroidism or hyperthyroidism. Another feature of the present approach is a longitudinal design with concurrent symptom ratings that is aimed at assessing state as well as trait factors clinically related to thyroid hormone levels and to give preliminary information on the pattern of thyroid hormone change during recovery within patient subgroups. In particular, we have chosen to compare first the broad categories of schizophrenia and affective disorder, and then the four relatively homogeneous diagnostic subgroups, PS, undifferentiated schizophrenia (US), bipolar I disorder, manic (BP), and major depressive disorder, endogenous type (ED).

While the primary purpose of this study is to investigate the possible usefulness of thyroid hormone criteria in the differential diagnosis of affective *vs.* schizophrenic disorders, a secondary purpose relates to the possible role of thyroid hormone in clinical recovery from such disorders. We have recently reported a strong relationship between thyroxine change and clinical recovery in a group of male inpatients with a broad variety of psychiatric diagnoses. The group of patients that improved the most included not only those with low initial levels that then rose substantially, but also those with high initial levels that fell substantially (Southwick et al., 1989). This earlier finding raises a question concerning the possibility that certain diag-

agnostic subgroups might differ with regard to a characteristic direction of thyroxine change during clinical recovery. The present report examines, then, not only possible links between thyroxine and psychiatric diagnoses at the time of hospital admission, but also possible links between direction of thyroxine change during recovery and psychiatric diagnoses.

Methods

A series of 29 male inpatients, 20 to 58 years old, with diagnoses of PS (N = 8), US (N = 6), BP (N = 7), and ED (N = 8) were studied longitudinally during hospitalization at the Veterans Administration Medical Center. Informed consent was obtained after full explanation of our purpose and procedures. Research Diagnostic Criteria were used (Spitzer et al., 1978) following the Schedule for Affective Disorders and Schizophrenia (SADS) interview (Endicott and Spitzer, 1978). None of the patients was experiencing the first episode of psychiatric illness so that our sample represents patients with a chronic or subchronic course. Patients with drug or alcohol abuse in the past 2 months, major medical illness, or organic brain syndromes were excluded. Following hospital admission and at 2-week intervals thereafter, 9 a.m. serum samples were obtained and Brief Psychiatric Rating Scale (BPRS) assessments were performed (Overall and Gorham, 1962). The number of samples averaged four per patient. No sampling was done in periods of unusual physical activity nor in periods when unusual procedures, such as endocrine challenge tests, were being performed. Serum samples were promptly frozen at −70°C until analysis for free and total thyroxine concentration using the radioimmunoassay kit provided by Clinical Assays, Cambridge, Massachusetts. In our laboratory, the coefficients of intraassay and interassay variation for total thyroxine assay are 2.2% and 3.7%, respectively, and for free thyroxine assay are 3.2% and 4.2%, respectively, within the concentration range of our study samples.

Results

The first stage of data analysis compares observations in all schizophrenic with those for all affective disorder patients. Figure 1 shows that the affective disorder patients (N = 15) have higher initial values after hospital admission than do schizophrenic patients (N = 14) for both total thyroxine (TT_4) and free thyroxine (FT_4), with a marked decline in both hormonal levels during clinical recovery in the affective disorder patients but not in the schizophrenic patients. Using the first and last TT_4 values for both diagnostic groups, a two-way repeated measures analysis of variance showed significant effects for change over time, $F(1,28)$ = 8.39, $p < .007$, and for diagnosis-time interaction, $F(1,28) = 7.60$, $p < .01$, but not for diagnosis, $F(1,28) = .01$, $p < .9$, indicating that the difference in direction of hormonal change during recovery is the crucial parameter discriminating the two patient groups. In the case of FT_4, a similar analysis shows significant effects for diagnosis, $F(1,28) = 4.65$, $p < .04$, and for change over time, $F(1,28) = 12.66$, $p < .001$, but the diagnosis-time interaction effect does not reach significance, $F(1,28) = 2.40$, $p < .1$, indicating that the higher FT_4 values, especially early in hospitalization, in the affective disorder patients are the main discriminating feature. Using the BPRS sum values as an index of overall severity of illness, no significant difference was observed between the schizophrenic and affective disorder groups in the first sample (25.1 ± 3.4 *vs.* 28.0 ± 2.8), the mean sample (17.6 ± 2.2 *vs.* 18.0 ± 2.4), or the last sample (13.1 ± 2.4 *vs.* 12.5 ± 3.1), nor were significant effects for either diagnosis or diagnosis-time interaction found, using the first and last values in a two-way repeated measures analysis of variance. Thus, the hormonal differences between the

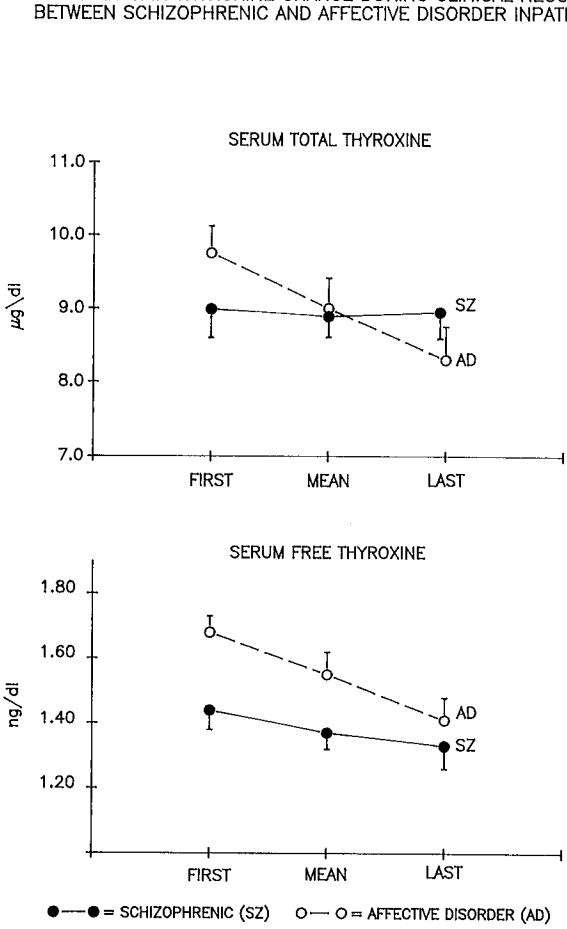

FIG. 1. Serum thyroxine levels in schizophrenic and affective disorder diagnostic groups

two groups cannot be linked to differences in severity of illness or degree of clinical recovery during hospitalization. With regard to other possible confounding factors, no significant correlations were observed between FT_4 or TT_4 and age, weight, height, or antipsychotic or antidepressant medication at the time of hospital admission. None of the patients was on lithium medication at the time of admission. There were also no significant differences between the two diagnostic groups on admission in either antipsychotic medication ($t = .60$, $p < .6$) or in antidepressant medication ($t = .23$, $p < .8$).

The second stage of data analysis explores the differences between four more homogeneous diagnostic subgroups comprising the above two major groups. Figure 2 shows that it is the BP subgroup that primarily accounts for the significant FT_4 difference between the affective disorder and schizophrenic groups, and also reveals that the PS subgroup is responsible for the difference between the schizophrenic and affective disorder groups in the slope of the TT_4 and FT_4 curves during clinical recovery. Figure 2 makes clear the close similarity in the downward slopes of both TT_4 and FT_4 in the other three diagnostic subgroups, in contrast to the tendency for a rising slope during clinical recovery in the PS subgroup, especially in TT_4. A two-way repeated measures analysis of variance, using the first and last FT_4 values, revealed effects for diagnosis, $F(3,28) = 2.84$, $p < .058$; for change over time, $F(1,28) = 22.45$, $p < .0001$; and for diagnosis-time interaction, $F(3,28) = 6.21$, $p < .003$, indicating clearly the significance of the difference in the rise of FT_4 levels during clinical recovery in the PS subgroup compared with the declining FT_4 levels in the other three subgroups. A similar analysis of TT_4 values reveals effects for change over time, $F(1,28) = 15.55$, $p < .0006$, and for diagnosis-time interaction, $F(3,28) = 9.11$, $p < .0003$, but not for diagnosis alone, $F(3,28) = .22$, $p < .9$, indicating the rise in TT_4 levels during recovery in the PS group to be highly significant in comparison with the declining TT_4 levels in the other three groups.

The strength of this tendency for the PS subgroup to differ in the direction of thyroxine change during recovery is evident in the scatter plot of delta (last minus first value) data on all individual patients presented in Figure 3. In the case of TT_4, 75% of the PS subgroup, in contrast to only 4% of the patients in the other three subgroups, show a rise during recovery (χ^2 with Yates correction = 12.0, $df = 1$, $p < .001$), while 50% of the PS subgroup show an FT_4 rise, compared with 14% in the other subgroups (χ^2 with Yates correction = 3.58, $df = 1$, $p < .058$). Table 1 summarizes the actual first, mean, last, and delta values

DIFFERENCE IN DIRECTION OF THYROXINE CHANGE DURING RECOVERY BETWEEN PARANOID SCHIZOPHRENICS AND OTHER DIAGNOSTIC SUBGROUPS

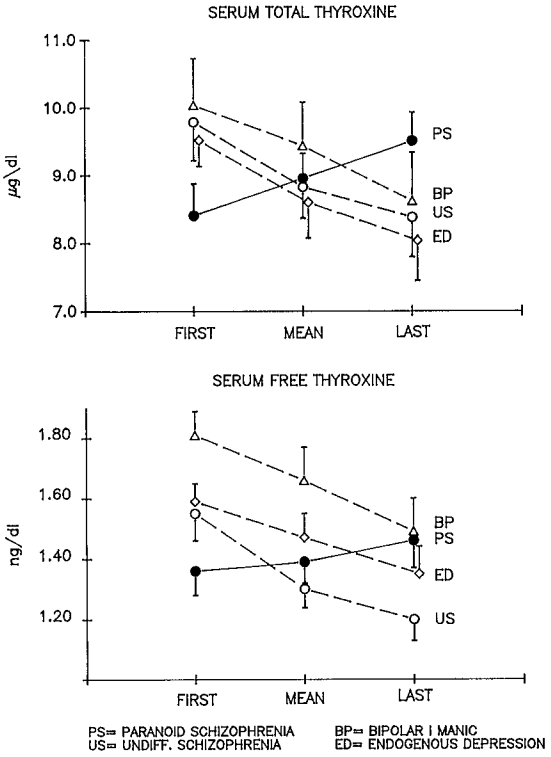

FIG. 2. Serum thyroxine levels in schizophrenic and affective disorder diagnostic subgroups

for TT_4, FT_4, and the BPRS sum in all four diagnostic subgroups.

With regard to possible confounding variables, an analysis of variance revealed no significant differences among the four diagnostic groups in our sample in age, weight, or height or in antipsychotic or antidepressant medication dosage at the time of the first sample. It also appears that the difference in direction of change between the PS and other groups is not likely to be related primarily to medication differences. Elimination of all BP patients treated with lithium from our sample, for example, does not affect the significance of the difference between the PS and BP groups. It is also noteworthy that the US and PS groups had very similar mean doses of antipsychotic medication yet showed opposite direction of TT_4 change during recovery. Finally, severity of illness does not appear to play a role in our findings, since there are no significant differences in BPRS sum values among the four diagnostic groups at the times of the first, mean, or last serum samples.

From a clinical standpoint, perhaps a particularly interesting finding is the significant difference in FT_4

TABLE 1
Comparison of Hormonal and Clinical Data Among Different Diagnostic Subgroups

	N	First	Mean	Last	Delta[a]
Free thyroxine (ng/dl)					
US	6	1.55 ± .09[b]	1.34 ± .06	1.17 ± .07	−.38 ± .11
PS	8	1.36 ± .08	1.39 ± .07	1.46 ± .09	.10
BP	7	1.81 ± .08	1.66 ± .11	1.47 ± .11	−.34 ± .06
ED	8	1.57 ± .06	1.47 ± .08	1.35 ± .09	−.22 ± .09
Total thyroxine (μg/dl)					
US	6	9.78 ± .56	8.82 ± .46	8.37 ± .58	−1.42 ± .61
PS	8	8.40 ± .47	8.95 ± .37	9.40 ± .42	1.00 ± .45
BP	7	10.03 ± .69	9.43 ± .64	8.61 ± .72	−1.41 ± .22
ED	8	9.51 ± .38	8.59 ± .52	8.03 ± .59	−1.49 ± .35
BPRS sum					
US	6	23.8 ± 6.1	15.8 ± 3.9	11.8 ± 3.5	−12.0 ± 4.0
PS	8	26.1 ± 4.3	18.9 ± 2.8	14.1 ± 3.5	−12.0 ± 3.5
BP	7	30.6 ± 5.3	17.9 ± 4.1	9.1 ± 3.2	−21.4 ± 4.5
ED	8	25.8 ± 2.7	18.1 ± 3.0	15.4 ± 5.1	−10.4 ± 5.4

[a] Delta = last minus first sample value.
[b] $\bar{X}$ ± SE.

levels between the PS and BP groups in the first sample ($t = 3.91$, $p < .002$). Since these two diagnostic categories can sometimes be difficult to discriminate at admission on purely clinical grounds, the possible usefulness of FT_4 measurement as an adjunct in this differential diagnosis may deserve further exploration.

Discussion

Our study does not indicate any major differences in thyroxine parameters between the broad general categories of schizophrenia and affective disorder, but does show some significant findings in PS and BP patients that involve both direction of change and absolute levels of thyroxine, which may have clinical implications with regard to both diagnosis and the recovery process. Our data emphasize the methodological importance of a longitudinal design in studies of hormonal markers for psychiatric diagnosis, as substantial changes in thyroxine levels were commonly observed during recovery in most of the diagnostic groups.

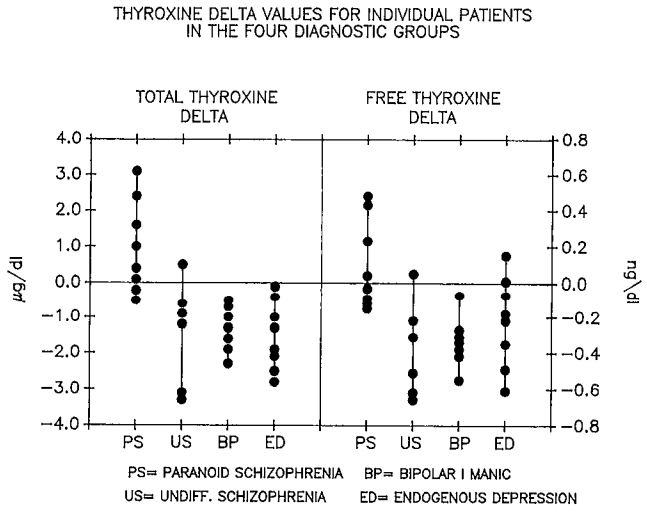

FIG. 3. Serum thyroxine delta values in schizophrenic and affective disorder diagnostic subgroups

Perhaps the most intriguing finding in the present study is the striking difference in the direction of thyroxine change during recovery between the PS group and the other three diagnostic groups. In the US, BP, and ED groups, thyroxine levels were highest at the time of hospital admission when symptoms were most severe, following which both thyroxine and symptom levels decreased substantially. In the PS group, however, thyroxine levels were lowest at the time of hospital admission when symptoms were most severe, and this inverse relationship continued during recovery, with the BPRS sum decreasing as thyroxine levels increased. This finding emphasizes the importance of assessing state or stage of illness as well as diagnosis at the time of hormonal sampling in clinical psychoendocrine studies of this type.

In the interpretation of these results, several issues need to be considered. From an endocrinological point of view, the fact that both free and total thyroxine show a generally similar pattern within each diagnostic group, *e.g.*, both are initially low and then rise in the PS group, would favor the interpretation that the hormonal changes observed probably involve largely secretory rather than binding mechanisms. Further studies along these lines might well include measurement of thyroid-binding globulin, thyrotropin, T_3, and TRH testing for more detailed characterization of thyroid function. From a clinical point of view, the bidirectional nature of brain-hormone relationships raises a question as to whether the thyroxine rise in the PS group is a secondary reflection of psychological reor-

ganization during recovery, or is rather a primary event that precedes and contributes to the improvement in clinical state. Perhaps if the sampling intervals for thyroxine and symptom assessment were frequent enough, some indication might be seen of whether hormonal or clinical change clearly occurs first, but the 2-week sampling interval of the present study does not permit even tentative conclusions in this regard. Our findings do indicate, however, that the symptom and thyroxine changes are correlated within given diagnostic groups. In the PS group, for example, there is a significant negative correlation between TT_4 and the hostility BPRS factor using all time points ($r = -.42$, $p < .03$, $N = 27$), whereas in the BP group there is a positive correlation between TT_4 and the thought disorder BPRS factor ($r = .49$, $p < .03$, $N = 20$). These correlational findings are in the directions that would be expected on the basis of the configuration of the recovery curves observed in this study.

Historically, the study of thyroxine effects upon psychological mechanisms has been limited largely to symptom assessment in hypothyroid and hyperthyroid patients and little is known of normative effects of thyroxine upon specific cognitive and affective functions. In general, it has been found that hypothyroidism is often associated with depressive symptoms and hyperthyroidism with anxiety, tension, and irritability, but these disturbances in affect are not consistent in all patients. Psychometric studies indicate that the most apparent impairment in thyroid disorders is in cognitive mechanisms involving the processes of attention, abstraction, memory, and intellectual function, sometimes with delusional and hallucinatory phenomena (Whybrow et al., 1969). An experimental study of vigilance levels in hypothyroid patients before and after substitution therapy revealed that relatively complex vigilance performance, as measured by critical flicker-fusion and vernier visual acuity, was markedly and promptly improved by thyroxine treatment. This study indicated that even a slight and easily unrecognized reduction in thyroxine production might seriously impair the function of the everyday life of the individual (Levander and Rosenquist, 1979). The larger question of how the basic and rather protean effects of thyroxine upon cognitive and affective mechanisms may contribute to the development of different symptom patterns in different psychiatric disorders remains to be more fully investigated.

The question of the psychiatric significance of thyroxine levels within the normal range appears to be a very important and neglected issue. Table 1 shows that the mean thyroxine values for all groups at all points lie within the endocrinologically defined normal limits (TT_4 = 4.5 to 11.5 μg/dl, FT_4 = .7 to 2.0 ng/dl). In our sample of 29 patients, only two BP patients slightly exceeded the upper limit for TT_4, and one of these exceeded the upper limit for FT_4 also. No patient had thyroxine values in the hypothyroid range. Yet significant relationships were observed in the present study between thyroxine levels in the euthyroid range and clinically significant psychiatric parameters such as diagnostic category, symptomatology, and recovery. It is true that we cannot rule out the possibility of subclinical endocrine disorders such as grade 3 hypothyroidism that might be detected with TRH testing, but our data militate against dismissal of thyroxine levels in the normal range as being of no clinical psychiatric significance, and in this regard support some recent studies of affective disorders (Bauer and Whybrow, 1986; Gold et al., 1981) as well as some earlier psychoendocrine studies of the thyroid system (Brody, 1949; Libow and Durell, 1965). It seems reasonable to test further the hypothesis that thyroxine levels and changes within the euthyroid range may exert modulatory influences upon cognitive and affective mechanisms and upon symptom development which may play a clinically significant role in the pathogenesis or course of various psychiatric disorders.

Although a difference in direction of thyroxine change during recovery between the PS group and the other diagnostic groups was observed, the PS, US, and ED groups all fluctuated within a very similar range of absolute thyroxine values during hospitalization. Only the admission FT_4 value in the BP group appears to be sufficiently higher than the other groups' to have potential usefulness as a diagnostic criterion. Of the four groups studied, the greatest clinical interest from the standpoint of differential diagnosis might be in discriminating between the PS and BP groups, because of overlapping symptomatology and the major differences in pharmacotherapy of the two disorders. Interestingly, these two groups happen to represent the two extremes in both FT_4 and TT_4 levels at the time of hospital admission, thereby suggesting that the use of thyroxine measurements as biological criteria for discriminating PS from BP patients may deserve further exploration. In such an approach, subtypes of BP patients would need to be considered, since it is well known, for example, that occasional BP patients, especially women, may have hypothyroid thyroxine levels, probably secondary to lithium medication over a long period (Cho et al., 1979). Our present sample does not include a patient in this category.

Several limitations of our data should be specified for guidance in further work along these lines. Our sample includes only men with a chronic or subchronic course of psychiatric illness, so that our generalizations may not extend to women or to first episode or severe, acute stages of illness. A larger sample size is needed so that additional diagnostic subgroups can be

evaluated. Demographic or medication variables do not appear to confound our results, but there is a need to study more fully possible interactions between psychotropic medication and thyroxine function in the recovery process. The enhancement of antidepressant activity by thyroid hormone has been recognized for some time (Prange et al., 1969) but more recently evidence that the effects of the antipsychotic, haloperidol, are also enhanced by thyroxine administration has been presented from animal studies (Crocker and Overstreet, 1984), supporting earlier work indicating that thyroid status can modify the sensitivity of dopamine receptors (Klawans et al., 1974). An influence of thyroid status on dopamine receptor regulation could provide a potential route of interaction between thyroid hormones and psychosis which may warrant further study. Whether such a relationship can be demonstrated in the recovery of psychotic patients remains to be investigated and our data suggest that the PS group might be particularly appropriate for inclusion in such a study.

Finally, the history of clinical psychoendocrine research strongly suggests that it may be productive to conceptualize the role of hormones in psychiatric disorders, not in terms of single neuroendocrine systems in isolation, but in terms of the balance or overall pattern organization of multiple hormonal systems that exert interdependent effects at the cellular level (Mason, 1968; Reiss, 1958). We have previously reported findings in schizophrenic and affective disorder patients for several other hormonal systems, including cortisol (Mason et al., 1986), epinephrine and norepinephrine (Kosten et al., 1987), and testosterone (Mason et al., 1988). Each of these hormones, like thyroxine, appears to provide some power for discriminating between diagnostic groups of psychiatric patients. However, there is always some overlap in hormonal values between any two given diagnostic groups and no single system alone, therefore, provides a diagnostic criterion with sufficient sensitivity or predictive accuracy so that it may be usefully applied to the individual patient in a routine clinical way. Because of this limitation, it appears desirable to explore the possibility that multivariate approaches that can combine the discriminating power of a profile of hormonal measurements might provide a substantially higher degree of predictive accuracy than single markers and be of great practical value in developing improved biological criteria as adjuncts to psychiatric diagnosis.

Conclusions

This study indicates a significant difference in the direction of both total and free thyroxine change during clinical recovery in PS patients *vs.* three other diagnostic groups. The clinical significance of the elevation of thyroxine levels in the PS group *vs.* the decreasing levels in the other groups during the course of clinical improvement is not yet clear, but it appears to be worthy of further study for possible relevance to diagnostic or treatment issues. The finding of relatively high FT_4 levels in BP patients, significantly higher than PS patients at the time of hospital admission, may also deserve further study for possible diagnostic usefulness. More generally, this study emphasizes the need for a fuller exploration of the potential psychiatric significance of thyroxine levels within the endocrinologically defined normal range and for longitudinal assessment of thyroxine change during clinical recovery.

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