The occurrence of psychosis in association with replacement therapy for hypothyroidism was first reported by Ziegler (1931). At that time, he noted the onset of pressure of speech, psychomotor agitation, clang associations and auditory hallucinations within a few days of the initiation of thyroid replacement therapy in one of his patients. Easson (1966) later stated that psychosis, long accepted as a psychiatric presentation of hypothyroidism could occur concomitantly with replacement therapy for hypothyroidism. Lidz (1971) has stated further that this psychosis can occur as an aggravation of an existing myxoedema psychosis or as a novel event. Our observation of a 34-year-old hypothyroid woman who experienced a manic psychosis after replacement therapy (Josephson and Mackenzie, 1979) led us to review the English language literature for evidence of similar occurrences.

Although repeatedly observed (Ziegler, 1931; Easson, 1966; Karnosh and Stout, 1935; Akelaitis, 1936; Means, 1948; Asher, 1949; Calvert et al, 1954; Browning et al, 1954; Josephson and Mackenzie, 1979), characteristics of this phenomenon have not been systematically studied. For at least two reasons such a study would be interesting. First, it might shed light on the elusive, but ineluctable relationship between thyroid activity and affective disturbance. Second, delineation of patients at risk would permit increased attention to their post-treatment course. This might result in earlier recognition and control of severe psychopathological disturbance.

This report, based on our literature review, outlines the characteristic features of this syndrome. Our discussion considers the theoretical underpinnings of the phenomenon and possible clinical application.

Method
A retrospective review of the English language literature describing psychotic reactions associated with thyroid administration was undertaken. To aid this review, a Medlars computer search was used with these code words: ‘hypothyroid’, ‘treatment’, and ‘psychosis’.

Case reports with supporting clinical data were then reviewed with respect to the variables enumerated in Tables I and IV. A reassignment of psychiatric diagnosis was made for each case, using Diagnostic and Statistical Manual of Mental Disorder, Third Edition (1978) (DSM–III). Definitions of diagnoses used,
listed in Table I, reflect recent changes in classifying organic mental disorders. Diagnoses were assigned at two distinct points in the patients’ clinical course. The first diagnosis applies to the clinical presentation immediately prior to the initiation of thyroid replacement therapy. The second applies to the presentation during the psychiatric disturbance following the initiation of replacement therapy. The latter will subsequently be referred to as psychosis following initiation of therapy (PFI).

The use of different thyroid preparations necessitated standardizing the dosage. Micrograms of sodium levo-thyroxine was the standard unit of measurement in this review. Sixty mg (1 grain) of dessicated thyroid equals 100 micrograms of sodium levo-thyroxine (Cobb and Jackson, 1978). Dosages in early reports must be considered approximations because of variability in potency of available preparations.

Results

The literature is replete with references to psychosis following thyroid supplementation in hypothyroidism. For example, Jellinek (1962) has reported on 56 hypothyroid patients with concomitant neurological disorder, 18 of whom had psychiatric disorder. Some of these psychiatric disorders occurred with the initiation of treatment. We found 25 specific cases of this phenomenon but in only 18 were clinical data sufficient for analysis. Table I lists these cases by reporting author.

The characteristic clinical picture of the PFI included the presence of psychopathology prior to the initiation of therapy, the appearance or exacerbation of psychotic symptoms within 4–7 days of treatment initiation and resolution in 1–2 weeks irrespective of therapeutic intervention. The diagnosis of organic affective syndrome, manic type, most often applied to the PFI episodes. The average age at onset was 47 years, the female to male sex ratio was 17 to 1, and the average initial adult dosage was 180 micrograms sodium levo-thyroxine (excluding two cases of life-threatening hypothyroidism). The average duration of hypothyroidism was 28 months, the majority occurring spontaneously. The PFI, though transient, resulted in psychiatric intervention in over half of the cases. These interventions ranged from psychiatric consultation and initiation of neuroleptic medication to the immediate application of restraints and transfer to a psychiatric hospital. All cases, even those not receiving psychiatric intervention, were judged to be severely impaired at the time of the PFI. Complete recovery from PFI occurred in all cases. Resolution of the PFI took place sooner than recovery from medical and psychiatric disturbance evident prior to the treatment.

Many of these reports did not include systematic mental state examinations. Further, psychiatric personnel were not always present during the psychosis. Consequently, certain symptoms may be underestimated. With this limitation, the frequency of symptomatology reported during the PFI is recorded in Table II. Increased psychomotor activity, persecutory delusions and elevated or irritable mood were the most frequent manifestations. Several categories need further delineation. The behaviour noted in patients with poor judgement included engaging in assaultive behaviour toward medical staff (7 occurrences), attempting to leave the hospital (2 occurrences) and attempting to correct thyroid deficiency by ingesting a container of pills (1 occurrence). The depressed patients included three with suicidal ideation, two of whom made attempts. These attempts were judged to be potentially lethal. The first patient tried to jump out a window. The second attempted to ingest buttons, smelling salts, a comb and bed sheets and, when restrained, tried to suffocate herself. Those patients with anxiety experienced considerable distress best described as panic with a sense of impending danger. Comment on the quality of sleep was frequently omitted. In the case observed by ourselves, however, insomnia was a prominent feature.

The DSM–III diagnoses assigned are listed in Table III. The use of the word organic indicates that a specific organic factor was judged to be aetiologically related to the disturbance. It is not meant to imply that disturbances in memory, orientation or attention were prominent. The category of organic affective disorder, mixed type, deserves note. Although not a sub-group in DSM–III, this best describes the
### Table I

**DSM-III diagnoses**

<table>
<thead>
<tr>
<th>Case (Age-Sex)</th>
<th>Aetiology/duration of hypothyroidism</th>
<th>Prior to initiation of thyroid replacement therapy</th>
<th>PFI</th>
<th>Onset of PFI</th>
<th>Duration of PFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>58—F (Ziegler, 1931)</td>
<td>Spontaneous/1 yr</td>
<td>O.P.</td>
<td>O.A.* (manic)</td>
<td>a few days</td>
<td>gradually improved</td>
</tr>
<tr>
<td>43—F (Karnosh and Stout, 1935)</td>
<td>Spontaneous</td>
<td>O.A. (depressed)</td>
<td>O.A. (manic)</td>
<td>4 days</td>
<td>1 month</td>
</tr>
<tr>
<td>58—F (Karnosh and Stout, 1935)</td>
<td>Spontaneous?</td>
<td>O.D.*</td>
<td>O.D.*</td>
<td>early</td>
<td>temporary manifestation</td>
</tr>
<tr>
<td>58—F (Akelaitis, 1936)</td>
<td>Spontaneous/4 yrs</td>
<td>O.A.* (depressed)</td>
<td>O.D.*</td>
<td>2 days</td>
<td>7 days</td>
</tr>
<tr>
<td>66—F (Akelaitis, 1936)</td>
<td>Spontaneous/6 yrs</td>
<td>O.A. (depressed)</td>
<td>O.A.* (manic)</td>
<td>4 days</td>
<td>10 days</td>
</tr>
<tr>
<td>10—F (Means, 1948)</td>
<td>Spontaneous/4 yrs</td>
<td>None</td>
<td>O.A.* (manic)</td>
<td>7 days</td>
<td>9 days</td>
</tr>
<tr>
<td>53—F (Asher, 1949)</td>
<td>Spontaneous/6 mths</td>
<td>O.D.</td>
<td>O.D.*</td>
<td>at first</td>
<td>2 weeks</td>
</tr>
<tr>
<td>64—F (Asher, 1949)</td>
<td>Spontaneous/1 yr</td>
<td>O.D.</td>
<td>O.A. (manic)</td>
<td>3 days</td>
<td>2 weeks</td>
</tr>
<tr>
<td>54—F (Asher, 1949)</td>
<td>Spontaneous/1 yr</td>
<td>O.A. (mixed)</td>
<td>O.A.*</td>
<td>6 days</td>
<td>5 weeks</td>
</tr>
<tr>
<td>73—F (Asher, 1949)</td>
<td>Spontaneous?</td>
<td>Dementia</td>
<td>O.A.</td>
<td>5 days</td>
<td>1 day (death due to myocardial infarction)</td>
</tr>
<tr>
<td>48—F (Calvert et al., 1954)</td>
<td>Spontaneous?</td>
<td>Other OBS</td>
<td>O.A.* (manic)</td>
<td>21 days</td>
<td>1 week</td>
</tr>
<tr>
<td>55—F (Browning et al., 1954)</td>
<td>Spontaneous/1 yr</td>
<td>O.A. (manic)</td>
<td>O.A. (manic)</td>
<td>13 days</td>
<td>gradual diminution</td>
</tr>
<tr>
<td>34—F (Eason, 1966)</td>
<td>Spontaneous/2 yr</td>
<td>O.P.</td>
<td>O.D.</td>
<td>4 days</td>
<td>2 weeks</td>
</tr>
<tr>
<td>44—M (Eason, 1966)</td>
<td>Post thyroidectomy 2 mths</td>
<td>O.D.*</td>
<td>O.A.* (manic)</td>
<td>4 days</td>
<td>6 days</td>
</tr>
<tr>
<td>41—F (Eason, 1966)</td>
<td>Spontaneous/1 yr</td>
<td>O.A.* (depressed)</td>
<td>O.A.* (manic)</td>
<td>6 days</td>
<td>gradually subsided</td>
</tr>
<tr>
<td>31—F (Eason, 1966)</td>
<td>Post thyroidectomy 18 mths</td>
<td>O.D.</td>
<td>O.A.* (manic)</td>
<td>5 days</td>
<td>7 days</td>
</tr>
<tr>
<td>34—F (Josephson and MacKenzie, 1979)</td>
<td>Post 1st ablation</td>
<td>O.A.* (manic)</td>
<td>O.A.* (manic)</td>
<td>3 days</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

1. O.P. = Organic Personality Syndrome: A marked change in personality occurs involving one of emotional lability, poor impulse control, apathy, or suspiciousness.
2. O.A. = Organic Affective Syndrome: The predominant clinical feature is a disturbance in mood, with evidence for at least two associated symptoms of mania or depression.
3. O.D. = Organic Delusional Syndrome: Delusions are the predominant clinical feature, although hallucinations and language disorder may be present. Delusions occur in a state of wakefulness.
4. ** = Received psychiatric intervention, including medication, restraints, consultation or transfer.
daily cycling of elation and excitability, alternating with depression, observed in these two patients. The patient receiving other organic brain syndrome diagnosis was described as mentally dull but rational with no affective aberration described.

The data summarized in Table IV indicates that almost all patients had demonstrable psychopathology prior to treatment. Although the degree of impairment varied, 15 of 18 patients were judged to be psychotic at the time of thyroid replacement. The duration of hypothyroidism was longer in those in whom the condition occurred spontaneously rather than iatrogenically (121 ablation or surgery). The initial dose in a majority of cases was above 150 micrograms, the average initial dose according to contemporary standards (Ridgway et al., 1976). Although incomplete, the historical data suggests a relatively high incidence of past personal and family psychiatric disorder in these patients.

Discussion

Our survey indicates that when thyroid replacement is complicated by the emergence of psychosis, a characteristic clinical picture unfolds. The syndrome, referred to as the PFI, appears 4–7 days after aggressive initiation of thyroid replacement, the average initial daily dosage being greater than 150 micrograms of thyroxine. The psychosis lasts one to two weeks and resolves without sequelae, irrespective of therapeutic intervention.
This syndrome appears to be distinct from the mental changes associated with hypothyroidism. First, the peak of psychopathologic disturbance is coincident with the occurrence of peak activity after thyroxine administration (Astwood, 1975). The time course of recovery, one to two weeks, is distinct from the gradual resolution of mental sequelae secondary to hypothyroidism. Second, the psychopathological features meet DSM-III criteria for an organic affective syndrome, manic type. Increased psychomotor activity, persecutory delusions, elation and irritability are particularly prominent. This homogeneity is in contrast with the protean manifestations of the psychosis associated with hypothyroidism (Olivarius and Röder, 1970).

This syndrome appears to be uncommon. While hypothyroidism has a prevalence of 1 per cent, we could locate only 25 cases of PFI in the literature. This frequency, however, may be spuriously low due to underreporting of the phenomenon. The psychopathology following initiation, usually unobserved by psychiatric personnel, may be dismissed as a continuation of mental dysfunction secondary to hypothyroidism. Alternatively, it may be viewed as an unrelated mental disorder or a variant of the common side effects of headache, palpitations and anxiety (Refetoff, 1975). Irrespective of its incidence, the syndrome carries a considerable risk of morbidity. Attempted ingestion, self-mutilation, externally directed aggression and elopement are documented complications. The excellent prognosis associated with PFI emphasizes the need to protect these patients during the period of their psychosis.

The preponderance of manic symptomatology is consistent with the role thyroid hormone is known to play in modulating catechol receptor sensitivity (Prange, 1969). Animal research has demonstrated a decreased receptor sensitivity to CNS catecholamines in hypothyroidism accompanied by a compensatory increase in catechol concentration (Klawans et al., 1974; Stolk and Whybrow, 1975). In the presence of increased catechol concentrations, rapid administration of thyroxine could abruptly augment catechol receptor sensitivity, thereby precipitating a hypercatecholaminergic state.

Such a state is thought to be the neurochemical basis for mania (Akiskal and McKinney, 1975). This hypothesis is consistent with Bunney's speculation that the switch process is mediated by alterations in receptor site sensitivity (Bunney et al., 1972). In order to elucidate the role of pathological fluctuations in thyroid activity in the onset of mania, Checkley (1978) reviewed the course of 267 patients with a history of affective disorder. Five of these patients had well documented episodes of thyrotoxicosis. He found no correlation between the onset of excessive thyroid activity and the appearance of mania. However, in Checkley's series, the hyperthyroid state developed gradually in euthyroid patients. In contrast our patients were shifted from a chronic hypothyroid state to a fully replaced state in several days.

We speculate that it is rapidity of change in thyroid activity relative to neurotransmitter receptor balance which is important in the switch process rather than the absolute level of thyroid activity.

Concurrent psychosis appears to be the most useful predictor of the occurrence of a PFI. Seventeen of the 18 patients demonstrated significant pre-replacement psychopathology. Of these, fifteen were psychotic with evidence of poor reality testing. How powerful is this predictor in view of Jain's finding that 75 per cent of hypothyroid patients have psychiatric symptoms (1972)? An analysis of these symptoms reveals neurotic symptomatology, anxiety and depression, predominating. In only two of his 30 subjects were psychotic symptoms observed secondary to hypothyroidism—one subject was paranoid, the other experiencing hallucinations. The rarity of psychosis in his series agrees with recent observations of hypothyroid patients (Lidz, 1971). In view of this low incidence, the high frequency of pre-treatment psychosis in our patients supports its usefulness as a predictor.

Women, and persons with a personal or family history of mental disorder, appear to be at increased risk for PFI. Over 90 per cent of our patients were female. This striking predominance may reflect an interaction between the increased incidence of affective disorder (2:1) and thyroid disease (4:1) in women. Our data
point to a relatively high incidence of personal or family psychiatric history in persons who develop the PFI. In those case reports which provided sufficient data, 50 per cent of subjects gave a positive history of mental disorder in themselves or first degree relatives. Investigation of these aspects of the medical history prior to initiation of treatment would seem indicated.

The ratio of spontaneous to induced in our sample is not sufficiently different from the ratio of their overall incidence to support aetiology as a risk factor. However, the fact that in 81 per cent of our patients, the duration of hypothyroidism was greater than six months, suggests that duration of the preceding hypothyroid state may be related to the risk of PFI, irrespective of aetiology.

Lidz (1971) has suggested a lower initial replacement dosage be given to hypothyroid patients who are psychiatrically disturbed. Our data support this strategy. In 80 per cent of our subjects, replacement therapy was initiated with a maintenance dosage of at least 150 micrograms of thyroxine. Use of a lower dose has a precedent in cardiac patients where aggressive introduction of therapy can precipitate angina pectoris. This can be avoided or mitigated with a reduced initial dose. Could the PFI have been averted with a lower initial dosage and slower incremental adjustments? A case report of a young hypothyroid woman addresses this question (Means, 1948). Means noted the onset of mania seven days after the initiation of thyroid replacement which cleared after the cessation of treatment. The psychosis recurred when thyroid was re-initiated and again remitted after discontinuation of therapy. The third attempt at treatment, begun at 20 per cent of the previous initial dosage, resulted in an uneventful course of therapy. We believe that individuals who fit the high risk profile, namely middle-aged women with psychotic symptoms who have a positive personal or family psychiatric history, should be given a lower initial dosage and closely observed for the onset of mania early in the course of their treatment.

Our conclusions must be tempered by the acknowledgement that retrospective studies have significant limitations (Kerlinger, 1973). A literature search relies on the observations of multiple commentators varying in their thoroughness and acumen. In addition sample bias may occur if some psychopathological states are preferentially reported. While these limitations qualify our findings, they do not obscure the clinical and theoretical implications of our study.

References


THYROID INDUCED MANIA IN HYPOTHYROID PATIENTS


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