technical help, and supplies of ethizone and calcium B.P.A.S.; and we are especially indebted to Miss A. Osborne, who has undertaken all the urine analyses, for allowing us the use of her notes. A fuller report will be published by her at a later date.

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THE SIGNIFICANCE OF THE THYROID IN PSYCHIATRIC ILLNESS AND TREATMENT

ROUTINE EXAMINATION WITH A RADIOACTIVE TRACER METHOD

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In previous communications we reported that abnormal indices of thyroid activity occur in a fair proportion of psychiatric patients (Reiss *et al.*, 1951b). Changes in the thyroid activity of such patients after E.C.T. and treatment with pituitary anterior lobe hormones were described (Reiss *et al.*, 1951a).

The thyroid activity is now investigated as a routine in the majority of patients admitted to our hospital, so that we have extended the studies further, and here report on some of the results of this work in more than 1,000 patients in 1949–50 and 1950–1. The question of whether there is a real causal interrelationship between ascertained thyroid disturbance and mental illness is examined in the light of these research results.

Methods.—The radioactive tracer methods used have already been described (Haigh and Reiss, 1950; Reiss *et al.*, 1952). The normal ranges are seen in Fig. 3. For the determination of the basal metabolism rate the usual spirometric method was used. Where complete relaxation of the patient could not be obtained the investigation was carried out under thiopentone. Methods of treatment are referred to in the description of each case.

Results

Distribution of Thyroid Indices

Figs. 1 and 2 are histograms of the distribution of the I₁ values in 302 male and 244 female psychiatric patients in 1949–50, and of 222 male and 271 female similar cases in 1950–1. Fig. 3 shows the histograms of the patients in

1949–50 superimposed on the histograms of 1950–1. The distribution of thyroid indices in about 1,000 unselected psychiatric patients in two successive years is seen to be almost exactly the same. For comparison, the limits for normal controls are plotted above the histograms of Fig. 3, and the arithmetic mean values are in good agreement for the corresponding values of the normal controls. These normal control values never overlapped the values recorded in patients who had clinical evidence of hypothyrosis or hyperthyrosis. It is clear that the spread of the patient material is much wider than the spread of the normals, and that among the patients there are a number in whom thyroid function lies outside the normal range but in whom clinical evidence of thyroid abnormality is lacking. The number of these borderline cases is appreciable, amounting to about 20%. The mean values of the thyroid indices in males are lower than in females, both in patients and in normal controls. In male borderline cases thyroid function tends towards hypothyroidism, and in females to hyperthyroidism.

Distribution of Thyroid Indices According to Certain Psychiatric Disease Categories

The cases were classified in a number of fairly well defined psychiatric categories, and the relation between these psychiatric disorders and their associated thyroid values is shown in Fig. 4. For this purpose the thyroid values were classified in four standards, as follows: the normal range was divided equally into upper and lower normal; outside these limits are the regions of underfunction and overfunction, which comprise mainly borderline cases.

In most groups there seems to be no significant relationship between the disease and the standard of thyroid function. There are, however, the following exceptions. In the female anxiety group there is a tendency to thyroid hyperfunction, more than 60% of the cases being in the upper normal or overfunctional range. In contrast, in the male anxiety group there is a tendency to thyroid underfunction, about 36% being lower normal and 38% underfunctional.

In 40% of female patients with recent schizophrenia the thyroid index was above the upper range of normality, but in female chronic schizophrenia this was seldom observed. In male recent schizophrenia, by contrast, underfunction of the thyroid was more usual.

Changes in Thyroid Function Accompanying Changes in the Psychiatric Illness Occurring Spontaneously or after Treatment

We have previously reported (Reiss *et al.*, 1951a) the effect of E.C.T. on thyroid function. The cases investigated were mainly depressives, which usually recover with E.C.T., and the series was small (34 cases). We have extended the investigation to include a more representative group of 183 cases of most common forms of psychiatric disorder treated in various ways or remitting spontaneously. Thyroid function was assessed before and after treatment, and compared with the clinical result. The forms of treatment included E.C.T., modified insulin, coma insulin, carbon dioxide, leucotomy, psychotherapy, and various combinations. A number of cases in which there was a spontaneous remission were also investigated.

In 76 of these patients there was evidence of disturbed thyroid function before treatment, and normal values in 107. Changes in the thyroid values of all the patients after treatment are shown in Tables I–III. In 82 of the 107 euthyroid cases (Table I) treatment produced no change or

TABLE I.—Changes in the Thyroid Activity During Treatment of Euthyroid Patients

Direction of Change	Changes in Mentation	
	Improved	Not Improved
No change	7	3
Changes inside the normal range	57	15
Change to hypofunctional range	12	7
Change to hyperfunctional range	5	1

FIG. 1.—Distribution of $\log_{10} I_t$ values in male patients, 1949-50 and 1950-1. FIG. 2.—Distribution of $\log_{10} I_t$ values in female patients, 1949-50 and 1950-1.

changes only within the normal range; there was some slight change beyond the normal limits in the remaining 25 cases, 17 of whom made a clinical recovery. It is interesting that of the 82 patients who showed no change or change within the normal range only 22% failed to improve after treatment; while 39% of the patients whose thyroid levels became subnormal did not improve. Although suggestive, this difference is not statistically significant ($\chi^2 = 1.124$, with a corresponding P value of >0.20).

TABLE II

Thyroid Activity		Psychiatric Changes	
State Before Therapy	Change During Therapy	Improved	Not Improved
Underfunction	Normalized	20	0
	Not normalized	12*	5
Overfunction	Normalized	25	3
	Not normalized	7*	4

* The I_t in 12 of these 19 cases was improving, but the normal range was not yet reached at the time the mental improvement was detected. In one of the hyperthyrotic patients of this group the I_t was also decreased but below the normal range, and only 6 of the cases showed no change of the I_t in the right direction.

From inspection of the results in Tables II and III it is clear that there is no significant difference in the proportions of "normalized thyroid" improved and not-improved patients in the underfunction and overfunction categories,

TABLE III

Treatment	No.	Psychiatric Change		Thyroid Activity		Correlation Between Change in Thyroid and Psychiatric Change	
		Im-proved	Not Im-proved	Normalized	Not Normalized		
E.C.T. . .	43	38	5	27	16	31	12
Psychotherapy . .	11	7	4	6	5	6	5
Spontaneous remission . .	9	9	—	7	2	7	2
Coma insulin therapy . .	3	3	—	3	—	3	—
Mod. insulin therapy . .	5	3	2	2	3	4	1
Other (CO ₂ , leucotomy) . .	5	4	1	3	2	4	1
Total . .	76	64	12	48	28	55	21

MALE PATIENTS

DISTRIBUTION OF $\log_{10} I_T$ VALUES

524 MEASUREMENTS 1949/51

FEMALE PATIENTS

DISTRIBUTION OF $\log_{10} I_T$ VALUES

515 MEASUREMENTS 1949/51

FIG. 3.—Distribution of $\log_{10} I_t$ values in male and female patients, 1949–51.

and that the proportions of "not normalized thyroid" improved and not-improved patients in these categories are also very similar. For statistical purposes, therefore, the underfunction and overfunction categories are combined, the proportion of "normalized thyroid" improved to not improved being compared with the proportion of "not normalized thyroid" improved to not improved, regardless of whether thyroid activity had shown underfunction or overfunction before treatment. This comparison indicates that there is a highly significant relationship between psychiatric improvement (as opposed to no change or deterioration) and normalization of thyroid activity. (The value of χ^2 is 7.076, using Yates's correction for continuity. This corresponds to a P value of <0.01 , thus indicating that this relationship could occur by chance only once in 100 times.)

Treatment According to Thyroid Indications

It appeared reasonable to treat ascertained thyroid disturbances and observe the effects on the mental state. A number of patients suffering from various psychiatric illnesses were therefore given specific treatment on thyroid indications only.

We are well aware how controversial and sometimes conflicting have been the results of endocrine therapy in psychiatry reported by various authors, and how difficult it is to allow for the usual degree of apparent improvement after patients have settled down in hospital environment. We have therefore endeavoured to relate treatment and its results to suitable laboratory investigations and to have all patients followed up after discharge by doctors or social workers. We are still checking and revising our results in the light of what we know about the subsequent history of our patients. The thyroid disturbances were usually treated as follows.

Thyroid Underfunction.—Most patients were treated initially with thyrotrophic hormone for two weeks. If thyroid activity had been increased on reassessment with I^{131} at the end of this period it was assumed that the thyroid underfunction was secondary to primary pituitary underfunction, and treatment with thyrotrophic hormone was continued until the thyroid index became normal. If thyrotrophic hormone was ineffective primary thyroid underfunction was assumed, and the patients were then treated with dry thyroid tablets, or thyroxine or "thyranon" injections, until the B.M.R. became normal, as the tracer method cannot be reliably used during administration of thyroid hormones.

Thyroid Overfunction.—It may be assumed that in many cases hyperfunction of the thyroid is due to increased production of thyrotrophic hormone by the pituitary anterior lobe. Attempts to determine thyrotrophic hormone in blood to settle this question are being made in our department, but the method is not yet in clinical use. Nevertheless, in thyroid hyperfunction the direction of treatment at first is to suppress the production of thyrotrophic hormone with oestrone or A.C.T.H. Generally, 50,000 units of oestradiol were administered daily. In some cases the thyroid level fell to normal or below normal in the course of ten days. If there was no result treat-

ment was continued with methylthiouracil (0.2 g. thrice daily) and 100 mg. of sodium iodide daily.

In some cases the thyroid value measured by I^{131} may be normal or subnormal, but the B.M.R. increased. Measured under strictly controlled conditions this seems to be due to hypersensitivity to thyroid hormone (see Reiss *et al.*, 1952), and these cases have been treated with ergotamine tartrate.

Although, for reasons mentioned before, we are not prepared at present to give statistics of the results of treatment, the following four cases are reported in some detail by way of illustration of the methods of treatment.

Case 1

A female university student aged 18 was admitted on November 26, 1950. Diagnosis: hebephrenic schizophrenia of gradual onset; duration about a year. There was considerable thought disorder, with hallucinations. She was deteriorating. November 28: thyroid index, $I_t=18.8$ (considerably increased); B.M.R. (under thiopentone) +27%; no clinical signs of hyperthyroidism. Treatment: methylthiouracil, 0.2 g. t.d.s., combined after a week with 100 mg. NaI daily. The B.M.R. (under thiopentone) on January 8, 1951, was -5% and on February 2 was -1%. The B.M.R. (without thiopentone) was +0% on February 13, +3% on February 28, and -3% on March 20.

Clinical Progress.—January 8, 1951: marked improvement in thinking; disappearance of hallucinations; good insight; gained 12 lb. (5.4 kg.) in weight. March 10: discharged symptom-free. June 15: social worker reported that patient was teaching at a small school; mentally normal. October 27: normal; had resumed work at the university. February 1, 1952: attending regularly as an out-patient; began to relapse; much thought disorder with delusions and completely incongruous emotion. February 16: readmitted; I_t at time of admission 15.0 (again increased); psychiatric state as before. March 6: "oestrogen," 3,000 units daily, with NaI, 100 mg. daily. March 20: state unchanged; B.M.R. now reduced to -13%. April 7: thought disorder as before. June 9: much improved and mentally clear; rational but a little dull; B.M.R. -3%. July 9: remained improved; $I_t=0.4$, B.M.R. -8%. August 26: remission; awaiting discharge; contemplating taking up a teaching post.

Case 2

A married woman aged 31 was admitted on December 8, 1950. Diagnosis: anxiety state, moderately severe, with

FIG. 4.—Thyroid values in psychiatric disorders.

panic attacks, palpitations, much somatic discomfort, and disturbance of sleep. Immature personality. Acute onset five months before admission. December 1: $I_t=16.8$ (increased value). December 20: B.M.R. +25%. Treatment: patient showed positive prolactin reaction, and general hyperfunction of the pituitary anterior lobe was assumed. Treatment was therefore with oestrone instead of thiouracil. January 4, 1951: 50,000 units oestroform and 100 mg. NaI daily. January 29: oestrone dose reduced to 9,000 units daily. February 1: $I_t=0.3$.

Clinical Progress.—She began to improve more quickly than is usual with thiouracil treatment, and ten days after treatment started she was eating and sleeping well and the panic attacks had disappeared. February 18: discharged, recovered; still remains well.

Case 3

A labourer aged 20 was admitted on February 10, 1949. Diagnosis: chronic hebephrenic schizophrenia; duration two years; marked thought disorder, with delusions and hallucinations. Unemployment. May 9: $K=0.37 \times 10^{-2}$ (very reduced value); 17-ketosteroid excretion, 12.2 (normal); cortin excretion, 2.6 (normal). Treatment with thyroid, 1 gr. (65 mg.) twice daily, for hypothyroidism. May 23: if anything, worse. May 30: marked subjective and objective improvement. Discharged on July 2. Although symptom-free, probably a little slow. Instructed to continue taking thyroid, 1 gr. (65 mg.) twice daily. Remained so well that in February, 1950, he stopped taking tablets, and two weeks later he relapsed and was readmitted in much the same state as previously.

March 24, 1950: $I_t=1.3$ (subnormal); treated with thyrotrophic hormone. April 12: $I_t=2.9$ (normal range); rapid improvement. Discharged on May 6. Thyroid, 1 gr. (65 mg.) twice daily, continued. Remained well while continuing treatment for the next 10 months. Relapsed on July 4, 1951, and readmitted as before. July 5: $I_t=0.5$ (very subnormal); treatment as before with thyrotrophic hormone. August 17: $I_t=2.1$ (normal). Considerable psychiatric improvement. Maintenance therapy begun by replacing thyrotrophic hormone by thyroid sicc. twice daily. Discharged on November 12. At this time there was still some flattening of effect and dullness, but no florid symptoms. He has remained symptom-free and at work, and is still taking thyroid, 1 gr. (65 mg.) twice daily. August 26, 1952: patient has remained well on thyroid, 1 gr. (65 mg.) twice daily.

Case 4

A male clerk aged 46 was admitted on April 18, 1951. Diagnosis: chronic anxiety neurosis of 17 years' duration, with panic states, various phobias, lack of confidence, and inability to sleep, most pronounced for six months before admission. He had given up work. April 26: $K=0.52$; $I_t=0.8$ (very subnormal). May 17: condition rather worse; treatment begun with 400 units thyrotrophic hormone daily. May 22: $K=1.05$; $I_t=1.7$ (still subnormal). June 14: $K=2.2$ (lower normal range).

Clinical Progress.—From about May 31 some improvement. A fortnight later, more confidence and less anxiety. Discharged on June 29. Still mildly anxious, but phobias had disappeared. More confident and capable of handling business.

Discussion

The distribution of values of thyroid activity in the psychiatric hospital population presented here agrees in general with our previous reports dealing with much smaller numbers of patients.

It seems fairly clear, as we have discussed before, that there are a great many intermediate states and borderline cases of thyroid disturbance in psychiatric patients as compared with normals. This might be regarded as a reflection of a general constitutional abnormality or weakness in some psychiatric subjects and not of aetiological importance. We think this is not the case, for when the case material

is broken down into groups it will be seen that hypofunction and hyperfunction are more commonly found in some disorders than in others; and, further, that thyroid function is usually corrected in patients who recover, and in some cases it corrects itself as psychiatric recovery takes place.

On the basis that there is a neuro-endocrine interrelationship, the disturbances of the thyroid may be a consequence or a cause, primary or contributory, of mental disorder. However, in most cases the whole disorder has progressed so far that there is a vicious circle, so that we can only speculate on the primary pathological factor.

The statistical evaluation of a large group of patients in whom there was disturbed thyroid activity before treatment, and who showed mental improvement parallel with normalization of the thyroid function, points significantly to a close correlation between the processes of mental and thyroid restoration. We do not think it likely that the changes in the thyroid and mental disorder could have occurred independently without causal interrelationship. It is obvious that in some cases mental improvement may have been responsible for the thyroid normalization, but in others—especially where the improvement in thyroid state preceded mental improvement—it is possible that the thyroid disorder was primary, or was part of a complex endocrine disturbance responsible for mental abnormality.

The most convincing proof that abnormal thyroid activity in some cases is responsible for mental disturbance is the remission of symptoms in patients treated for the thyroid disorder alone. Although we have reported here in some detail four satisfactory cases, a very large series would have to be produced to prove this point and to provide case material for further research in causation.

The purely empirical treatment of psychiatric disorders with hormones and drugs alike is rightly in discredit. We are of the opinion that reporting small numbers of cases who have improved, apparently as the result of hormone treatment, only adds to the confusion unless in each case there have been systematic and continued laboratory investigations. With the methods at present at our disposal this is an ideal very hard to achieve, but—in the case of the thyroid—not outside the possibilities of many of the larger psychiatric research units.

Summary

The indices of thyroid activity in 1,000 psychiatric patients, using the I^{131} tracer method, have been studied in two successive years.

About 20% were outside normal limits.

The histograms of the distribution of indices in 1949–50 and in 1950–1 are almost identical.

Thyroid function in relationship to various psychiatric disorders, treatments, and spontaneous remissions have been studied and discussed.

In a significant number of cases in which the thyroid indices were abnormal before treatment normalization of the thyroid accompanied mental improvement.

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Last year the Pharmaceutical Society initiated legal proceedings in 43 cases under the Pharmacy Acts (1852–1941), the Penicillin Act (1947), and the Summary Jurisdiction Act (1848); only five of these cases proved unsuccessful. This fact is among information contained in the Registrar's Report of the Pharmaceutical Society for 1952, which was published recently.