CORRELATIONS BETWEEN CHANGES IN MENTAL STATES AND THYROID ACTIVITY AFTER DIFFERENT FORMS OF TREATMENT

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MANY endocrine disturbances have been described as accompanying disturbances in mentation. Single investigations giving a static picture at a certain stage of the disease contribute comparatively little to the understanding of the pathognomonic significance of the biochemical change, even if they are found to be statistically significant.

Longitudinal investigations of the biochemical changes and their suitable chronologic co-ordination to the changes in the mentation should permit more decisive pathogenetic conclusions. Owing to the inherent difficulties connected with biochemical investigations on mental patients, it is a very hard task to accumulate a sufficient number of longitudinal investigation results to decide the degree of their statistical significance. However, such efforts are unavoidable if progress is to be made in psycho-neuro-endocrinologic problems.

In this communication it is proposed to report changes seen in the thyroid function in patients before and after different routine treatment, and in some experimental treatments (not yet in routine use), and to correlate the therapeutic results with the changes seen in the thyroid function. The report comprises observations made in this hospital during the last four years.

Patients

The patients investigated form a fair average of the routine admissions to this hospital. Since it was more interesting for the purpose of this investigation to follow up patients with a thyroid activity outside the normal range on admission, a higher proportion of this group of patients is represented than of those showing an initially normal thyroid activity. The mental state of the patients is recorded in the relevant tables to be found in the following section. The clinical diagnoses were arrived at only after a prolonged period of observation, but were mainly taken from the discharge notes of the patients. The latter contains the diagnosis in the order of the international classification of diseases, 1948. In order to simplify the tables several numbers concerned were often contained in one group. For instance, 301·0, 301·1, 301·2, under the diagnosis "Endogenous depression", or the numbers 303 and 300·3 as "Paranoid schizophrenia". The change in psychiatric state was classified under two headings only; "improved" and "not improved". The criterion for improvement was, whether the patient was well enough to be discharged. It would have been possible to have classified the clinical change under 3 or 4 headings, but for the purposes of statistical evaluation we have found the above method more suitable.

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More detailed results concerning some of the endocrine treatment procedure mentioned in this paper are to be published later.

Methods

In all cases the thyroid activity was assessed with an I^{131} tracer method developed in this hospital especially for use on mental patients, Reiss, Hemphill, Murphy, Halkerston and Badrick (1949), Haigh and Reiss (1950), Reiss, Haigh, Hemphill, Maggs, Reiss and Smith (1952) and Haigh, Reiss and Reiss (1954). Thyroid activity was specified in terms of the following measured quantities.

(1) k, the normalized rate of uptake, by the thyroid, of I^{131} during the hour following intravenous injection of the tracer dose.

(2) E_{48}, the proportion of the I^{131} dose excreted in the urine during the 48 hours following the injection.

(3) U_{24}, the amount of I^{131} present in the thyroid 24 hours after the injection.

E_{48} and U_{24} were expressed as a percentage of the tracer dose. A further index of thyroid activity was defined as $I_t=k/E_{48}$, or $I_t=k/(C-U_{24})$, Haigh, Reiss and Reiss (1954), where C is a constant, numerically equal to 91. It avoids the necessity for urine measurements which are the least reliable, especially with mental patients. The uptake measurements were made with Toroidal counters, Haigh (1951) to reduce the effects of unavoidable movements of the patients with respect to the counter.

It has been found that the increased mental tension of some patients, presumably accompanied by an abnormal mobilization of vaso-constrictor substances, appears to inhibit the rate of uptake of I^{131} during the first hour. An anomalously low thyroid activity is then indicated, Haigh, Reiss and Reiss (1954). This difficulty has been overcome by a system of cross-checking the various parameters, and the complete method permits not only the clinically manifest thyroid disturbance to be detected but also tends to disclose borderline cases not easily diagnosed by present methods.

This tracer method has been standardized by measurements on normal control subjects and several thousand hospital patients. With the latter, there was a normal distribution of the logarithmic values of k and I_t (or I_t) and 70 per cent. of the population fell within fairly sharply defined, and hence assumed normal, limits of k and I_t. None of the normal controls gave values outside these limits, Reiss, Haigh, Hemphill, Maggs, Reiss and Smith (1952). However, for simplicity in the presentation of results which follow the characterization of thyroid activity has been restricted to three categories, namely, normal range, above normal and below normal.

Results

E.C.T.

More than half of all the patients investigated were treated with E.C.T. The number of cases improving mentally was of course very high, as only those likely to benefit from E.C.T. were treated in this manner, the selection being made on the basis of the accumulated experience of many years. The results are compiled in Table I, and it can be seen that independent of whether the thyroid activity was below, inside or above the normal range before treatment, there was a strong tendency for E.C.T. to normalize the thyroid activity and it can also be seen how very much normalization and maintenance of the normal state of the thyroid is connected with improvement of the mental state.

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TABLE I

E.C.T.

Mental Conditions Treated		State of Thyroid Activity before Treatment																			
		Below normal range						Inside normal range					Above normal range								
		Changes after treatment						Changes after treatment					Changes after treatment								
		No. Patients						No. Patients					No. Patients								
		Improvements						Improvements					Improvements								
	Total No.	Unchanged	Further decreased	Increased still below normal range	Increased to normal range	Increased to above normal range		No changes	Changes inside the normal range	Decreased below the normal range	Increased above the normal range		Unchanged	Further increased	Decreased but still above normal	Decreased to normal range	Decreased to below normal range				
Diagnosis	No.						No.					No.									
Endogenous depression	80	16	1 1	1 0	3 3	11 11		36	2 2	31 30	2 0	1 1	28	1 0	2 2	6 6	19 14				
Involutional depression	28	6		1 0		4 4	1 1	16	1 1	15 15	1 1	1 0	6			2 2	3 3	1 1			
Reactive depression	65	11			4 3	6 6	1 1	38	4 3	30 30	1 1	3 0	16			2 1	14 14				
Schizophrenias (various groups)	12	3				3 3		4		3 3	1 0		5		1 0		3 3	1 1			
Paranoic Schizophrenia	6	1				1 1		3		3 3			2		1 0	1 0					
Senile Psychosis	6	1					1 1	3		3 3			2				2 1				
Puerperal Psychosis	4							4		4 4											
Organic Psychosis	4							3	1 0	1 1		1 1	1					1 1			
Obsessional compulsive reaction	5							3	1 0		1 0	1 1	2		1 1		1 1				
Anxiety reaction	11	1					1 1	5	1 1	4 4			5				4 4	1 1			
Psychoneurosis mixed	3							2		1 1	1 0		1				1 1				
Depersonalization	2	1				1 1		1				1 0									
Immature personality	2	1					1 0	1				1 1									

Group No.	State of Thyroid activity at end of E.C.T.	Total No.	Mental state after E.C.T. Improved	Not improved	Groups compared	chi²	p
I	Normal range ..	179	169	10	I–III	55·40	$<<0·001$
II	Changing towards normal range ..	27	23	4	II–III	9·60	$<0·01$
III	Remaining outside normal range or deteriorating ..	25	10	15	—	—	—

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For statistical purposes all results are added together and show very significant correlations between normal thyroid activity after treatment ($chi^2 = 55 \cdot 4$; $P << 0 \cdot 001$) or thyroid activity changing towards normal range ($chi^2 = 9 \cdot 6$; $P < 0 \cdot 01$) and the mental improvement.

C.I.T.

The results of coma insulin treatment are compiled in Table II. Cases treated with C.I.T., in general fall into very different disease entities from those treated with E.C.T.; even so the correlation between mental improvement and normalization of the thyroid occurs after this treatment in the same manner and degree as after E.C.T. Statistical evaluation shows this correlation to be highly significant.

TABLE II

C.I.T.

Mental Conditions Treated	State of Thyroid Activity before Treatment: Below normal range — After treatment: Patients No.	Improvements: Increased to normal range	Inside normal range — After treatment: Patients No.	Improvements: Unchanged	Changed within normal range	Increased to above normal	Above normal range — After treatment: Patients No.	Improvements: Further increased	Decreased but still above normal	Decreased to normal range
Diagnosis	Total No.	No.	No.				No.			
Schizophrenia (mixed forms)	7	1 1	3	1 1	2 2		3	2 0		1 1
Simple schizophrenia	2		1			1 0	1	1 0		
Hebephrenic schizophrenic	5	1 1	1	1 1			3	1 0	1 1	1 1
Catatonic schizophrenic	3	1 1	1		1 1		1		1 1	
Paranoid schizophrenic	7		7	1 0	4 4	2 0				
Schizophrenic, acute reaction	3	2 2					1			1 1
Schizo-affective disorder	1	1 1								

Group No.	Total No.	State of Thyroid activity at end of treatment	Mental state after treatment: Improved	Not improved	Groups compared	chi^2	p
I	19	Within normal range	18	1	I–II	18·90	$< 0 \cdot 001$
	2	Changing towards normal range ..	2	0			
II	7	Remaining outside the normal range or deteriorating ..	0	7			

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Modified Insulin

The indications for modified insulin treatment are not yet so well circumscribed as those for the two previously mentioned treatment procedures. The correlation between mental improvement and normalization of the thyroid is equally obvious at first glance, even when, owing to the small number of patients, no proper statistical evaluation was possible (Table III).

TABLE III

Modified Insulin Treatment

Mental Conditions Treated	State of Thyroid Activity before Treatment										
	Below normal range				Inside normal range				Above normal range		
	After treatment				After treatment				After treatment		
	No. Patients	Improvements			No. Patients	Improvements			No. Patients	Improvements	
	Total No.	Unchanged	Increased to normal range		Decreased below normal range	Changed within normal range			Further increased	Decreased but still above normal range	Decreased to normal range
Diagnosis	No.				No.				No.		
Involutional depression	2				1		1 1		1	1 1	
Reactive depression	3				1		1 1		2		2 2
Anxiety state	10	3	1 1	2 2	3	1 0	2 2		4	1 0	2 2	1 1
Obsessive compulsive reaction	1								1			1 1

Total No.	State of Thyroid Activity at end of Treatment	Mental State after Treatment: Improved	Mental State after Treatment: Not improved
10	Normal range	10	0
3	Changing towards normal range ..	3	0
3	Remaining outside normal range or deteriorating	1	2

General hospital care and attention, including spontaneous remissions

The thyroid activity of 68 patients was investigated repeatedly during their stay in hospital. These patients received no special treatment during the time of investigation. A number of the patients were not treated as they showed signs of improvement soon after admission, and it was decided to wait in case they showed further signs of spontaneous improvement. They were well cared for, some employed in occupational therapy, others joined the group therapy courses. In twenty-six of the patients ketosteroid excretion was determined several times weekly. In cases where the ketosteroid excretion rate was found outside the normal range, initially, but showed a tendency for normalization during the first ten days, it was decided to withhold any special treatment for a further 10 days, even if there were no immediate signs of mental improvement.

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TABLE IV

General Hospital Care and Attention

Mental Conditions		Initial State of Thyroid Activity																
		Below normal range					Inside normal range					Above normal range						
		Changes after 4–8 weeks					After 4–8 weeks					After 4–8 weeks						
		No. Patients					No. Patients					No. Patients						
		Improvements					Improvements					Improvements						
Diagnosis	Total No.	Unchanged	Decreased further	Increased but still below normal	Increased to normal	Increased to above normal	Unchanged	Changes inside the normal range	Decreased below the normal range	Increased above the normal range		Unchanged	Further increased	Decreased but still above normal	Decreased to normal range	Decreased to below normal range		
	No.						No.					No.						
Endogenous depression	7						3		3 3			4	1 0			3 3		
Involutional depression	2						2	1 0	1 1									
Reactive depression	11	5	2 0		1 0	2 2	5		4 3	1 0		1	1 1					
Schizophrenia (various groups)	9						6	1 0	4 4	1 0		3	2 0		1 0			
Schizophrenia, paranoid	4	2	1 0			1 1						2	1 0	1 0				
Puerperal psychosis	4	1	1 0				1		1 1			2				2 2		
Obsessional compulsive reaction	1						1	1 0										
Unspecified psychosis	3	1		1 0			1		1 1			1				1 1		
Anxiety reaction	19	2	1 0		1 1		12	2 0	9 9		1 0	5	1 1	1 1	1 1	2 2		
Hysterical reaction	2	1				1 1						1				1 1		
Psychoneurosis, mixed	1	1			1 1													
Disturbance of memory	1	1			1 1													
Immature personality	4						1		1 1			3				1 1	2 1	

Group No.	State of Thyroid activity after 4–8 weeks	Total No.	Improved	Not improved	Groups compared	chi²	p
I	Within normal range . .	43	37	6	I–II	24·81	<0·001
	Changing towards normal range . .	8	5	3	—	—	—
II	Remaining outside normal range or deteriorating . .	17	2	15	—	—	—

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It was afterwards seen that these cases showed spontaneous remission, and the thyroid when re-investigated was also in the normal range. The observations are listed in Table IV, the thyroid-normalization: to mental improvement correlation being as highly significant as after E.C.T. or C.I.T.

Leucotomy

Pre-frontal leucotomy was carried out on 16 of the investigated patients, on 5 patients by McKissock's rostral method. Results of investigations are to be found in Table V. There were too few patients investigated for complete statistical evaluation, but the correlation found is equally suggestive as in the previous examples.

TABLE V

Leucotomy

Mental Conditions Treated	State of Thyroid Activity before Treatment: Below normal range — After treatment: Patients No.	Improvements: Unchanged	Improvements: Increased to normal range	Inside normal range — After treatment: Patients No.	Improvements: Unchanged	Improvements: Increased to above normal range	Improvements: Changed within normal range	Improvements: Decreased below normal	Above normal range — After treatment: Patients No.	Improvements: Unchanged	Improvements: Decreased to normal range
Diagnosis	Total No.	No.	No.	No.	No.	No.	No.	No.	No.	No.	No.
Obsessive compulsive reaction	2	1	1 1	1			1 1				
Anxiety reaction	4	1	1 1	2		1 0	1 1		1		1 1
Hysterical reaction	1								1		1 1
Schizophrenia, mixed forms	8	1	1 0	3	1 0		2 2		4	1 0	3 2
Paranoid schizophrenia	6	1	1 0	4		1 0	2 1	1 0	1		1 1

Total No.	State of Thyroid Activity after Leucotomy	Mental State after Leucotomy: Improved	Mental State after Leucotomy: Not improved
16	Within normal range	12	4
5	Remaining outside normal range or deteriorating	0	5

Treatment with Thyrotrophic Hormone

It is instructive to compare the results as seen after E.C.T. in patients with hypothyroidism, with the results of treatment with thyrotrophic hormone. This substance was originally used for diagnostic purposes in order to decide whether the hypothyroidism was a primary thyroid underfunction or a secondary one due to pituitary anterior lobe underfunction (see Reiss *et al.*, 1949). The daily dose injected consisted of 200-600 guinea-pig units (Junkman and Scholler or Heyl and Laqueur) which equal 20-60 USP units. Treatment lasted 2-4 weeks.

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Examples of primary hypothyrotic patients are apparently the three patients, the thyroid activity of whom remained outside the normal range, as shown in Table VIII. Such patients were usually treated afterwards with a suitable thyroid preparation and will be reported about in another paper.

Patient material treated and the results are compiled in Table VI. The statistical analysis shows a significant correlation between improvement of thyroid activity and mental state which is in the same grade of significance ($\chi^2=11\cdot01$; $P=0\cdot001$) as seen in the hypothyrotic patients treated with E.C.T.

TABLE VI

Treatment with Thyrotrophic Hormone. (All Patients Hypothyrotic before Treatment.)

Mental Conditions Treated		Changes after Treatment: No. of Patients: Improvements				
Diagnosis	No.	Unchanged	Further decreased	Increased but still below normal range	Increased to normal range	Increased to above normal range
Endogenous depression	4		1 0		3 3	
Involutional depression	1	1 0				
Reactive depression	7			1 0	4 4	2 1
Schizophrenia	2				2 2	
Senile Psychosis	1				1 1	
Anxiety reaction	4				4 4	
Obsessive compulsive reaction	1				1 1	
Hysterical reaction	1					1 0
Unspecified Psychosis	2		1 0		1 0	

Group No.	Total No.	State of Thyroid Activity at end of Treatment	Mental State after Thyrotrophic Hormone: Improved	Not improved	Groups compared	chi²	p
I	16	Normal range	15	1	I–II	11·01	0·001
II	4	Changing towards normal change ..	1	3	—	—	—
	3	Remaining outside normal range or deteriorating ..	0	3	—	—	—

Sex steroid hormone therapy

Treatment with sex hormones was carried out from the following viewpoints:

(*a*) In hypothyrotic patients who also showed signs of other glandular underfunctions, for instance, low 17-ketosteroid or cortin excretion; or failure of the pituitary anterior lobe to produce A.C.T.H. after adequate stimulation.

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It was intended in these cases to stimulate the pituitary anterior lobe function by implanting Testosterone crystals (400-600 mgs.) guaranteeing the steady absorption of small amounts of Testosterone which should be sufficient for the purpose.

(*b*) In patients with normal thyroid activity, who showed a decreased 17-ketosteroid or cortin excretion and a negative A.C.T.H. response by the

TABLE VII

Treatment with Steroid Sex Hormones

Mental Conditions Treated	State of Thyroid Activity before Treatment													
	Below normal range				Inside normal range					Above normal range				
	After treatment				Changes after treatment					Changes after treatment				
	No.	Patients			No.	Patients				No.	Patients			
		Improvements				Improvements					Improvements			
Diagnosis	Total No.	Unchanged	Increased to normal range		Unchanged	Changes inside the normal range	Decreased below the normal range	Increased above the normal range		Further increased	Decreased but still above normal	Decreased to normal range	Decreased to below normal range	
	No.				No.					No.				
Endogenous depression	12	3	1	2	5		4		1	4	1		2	1
			0	2			3		0		0		2	1
Involutional depression	3				1			1		2		1	1	
								0				1	1	
Reactive depression	11				6	2	3	1		5			5	
						1	2	1					5	
Schizophrenias (various groups)	9	1	1		3		1	1	1	5	1	1	3	
			0				1	0	0		0	0	2	
Paranoic Schizophrenia	5				2		2			3			3	
							2						3	
Anxiety Reaction	6				3		2	1		3	1			2
							2	0			1			2
Depersonalization	1				1		1							
							0							
Puerperal Psychosis	1				1		1							
							1							
Organic Psychosis	1									1		1		
												0		
Immature Personality	1				1		1							
							1							

Group No.	State of Thyroid activity at end of treatment	Total No.	Mental state after sex hormones: Improved	Mental state after sex hormones: Not improved	Groups compared	chi²	p
I	Within normal range ..	33	28	5	I–II	13·28	<0·001
	Changing towards normal range ..	6	4	2	—	—	—
II	Remaining outside normal range or deteriorating ..	11	2	9	—	—	—

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adrenal cortex, the general treatment was Testosterone Propionate 25 mgs. injected daily. In female patients, however, who also showed a prolan I+ reaction in the morning urine, it was found advantageous to combine the injection of Testosterone with 1 mg. Oestradiol daily.

(*c*) In hyperthyrotic patients, in order to find out initially if the overfunction of the thyroid was due to an overproduction of thyrotrophic hormone, high doses of Oestradiol (50,000 to 100,000 units daily) were injected, and if the thyroid activity seemed reduced after a fortnight, secondary hyperthyroidism was assumed and the treatment continued till the thyroid activity was within or below normal range. In cases where complete normalization of the thyroid activity was not achieved the treatment was combined with NaI (100 mgs. daily). In cases showing low ketosteroid excretion at the same time, treatment was combined with 25 mgs. Testosterone Propionate daily.

The disease entities treated, as can be seen from Table VII, were more varied than in either C.I.T. or E.C.T. but the established correlation between thyroid and treatment result was not less significant.

A.C.T.H. Treatment

A.C.T.H. was not given to any cases showing a decreased thyroid activity.

In cases with normal thyroid activity A.C.T.H. was given only when the ketosteroid excretion was very low, the adrenal cortex responsitivity in mobilizing ketosteroid normal, but the ability of the pituitary anterior lobe to mobilize increased amounts of A.C.T.H. after stimulation reduced. Very small doses of A.C.T.H. 2-10 mgs. daily were sufficient to raise the daily ketosteroid excretion of such patients.

In hyperthyrotic patients who showed low ketosteroid excretion rate a positive adrenal cortex response and a negative response of the pituitary anterior

TABLE VIII

A.C.T.H. Treatment

Mental Conditions Treated	State of Thyroid Activity before Treatment						
	Normal range			Above normal range			
	After treatment			After treatment			
	Patients			Patients			
	No.	Improvements		No.	Improvements		
Diagnosis	Total No.	No.	Changed within the normal range	No.	Unchanged	Decreased but still above normal	Decreased to normal range
Involutional depression	2	1	1 1				1 1
Reactive depression	4	1	1 1	3	1 1	1 0	1 1
Endogenous depression	3			3			3 3
Anxiety reaction	1			1			1 1

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lobe to produce A.C.T.H. endogenously after stimulation, a larger dose of A.C.T.H. (25 mgs. 3-4 times daily) was injected in order to suppress thyrotrophic activity and increase adrenal cortex activity.

Too few patients were investigated in this series to permit any definite evaluation of A.C.T.H. treatment. However, the few investigation results given in Table VIII, suggest the existence of similar thyroid-mental correlations as in the other treatments.

Discussion

1. *The general correlation of changes in mentation and in thyroid activity*

As shown in the preceding section a very significant correlation exists between changes in mentation and the thyroid function. This correlation has been shown to be independent from the psychiatric disease entity or the method of treatment.

Table IX

Survey of all Patients

Group No.	Total No.	State of Thyroid Activity at the end of Treatment	Mental State at end of Treatment: Improved	Mental State at end of Treatment: Not improved	Groups compared	chi²	p
I	324	Within normal range ..	297	27	I–III	162·0	$<<0·001$
II	54	Changing towards normal range ..	40	14	II–III	29·70	$<0·001$
III	72	Remaining outside normal range or deteriorating ..	17	55	—	—	—

The results gained from all the investigations are compiled in Table IX and statistically analysed. It would appear from this analysis that the correlationship mentioned is highly significant indeed ($chi^2=162·0$; $P<<0·001$).

This relationship is also apparent when the patients are grouped according to the initial thyroid function level. In Table X, the results obtained from primary hypothyrotic cases are listed. In 96 per cent. of the patients showing decreased thyroid activity before treatment, the mentation was improved after treatment if the thyroid activity increased to normal range. On comparing this group with the 88 per cent. not improved patients whose thyroid activity remained unchanged or deteriorated, the correlation proved highly significant ($chi^2=48·16$; $P<0·001$). Also, in cases where the thyroid activity was improving after treatment or was already improved, and over-shot (temporarily) the normal range, a significant correlation ($chi^2=9·70$; $P<0·01$) between improvement of thyroid activity and mental improvement can be seen.

Table X

Patients with Initially Decreased Thyroid Function

Group No.	Total No.	Thyroid Activity after Treatment	Mental State after Treatment: Improved	Mental State after Treatment: Not improved	Groups compared	chi²	p
I	11	Unchanged	2	9			
	5	Decreased further ..	0	5			
II	10	Increased, but still below normal range	7	3	II–I	9·70	$<0·01$
	10	Increased to above normal range ..	7	3			
III	59	Increased to normal range	57	2	III–I	48·16	$<0·001$

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Table XI shows the changes seen in patients who had an increased thyroid activity before treatment. Here again thyroid changes and mental changes are correlated. A significantly higher proportion of cases improves when the thyroid is decreased to normal range than when the thyroid activity remains unchanged or further increases ($\chi^2=34\cdot66$; $P<0\cdot001$). If the thyroid activity is changed into the normal direction, but has not yet reached the normal range, the relationship still holds but is less significant.

TABLE XI

Patients with Initially Increased Thyroid Activity

Group No.	Total No.	Thyroid Activity after Treatment	Mental State after Treatment: Improved	Mental State after Treatment: Not improved	Groups compared	chi²	p
I	9	Unchanged	3	6			
	15	Further increased ..	5	10			
II	25	Decreased but still above normal range	18	7	II–I	9·09	<0·01
	9	Decreased to below normal range ..	8	1			
III	90	Decreased to normal range	82	8	III–I	34·66	<<0·001

In Table XII results are compiled from patients who had a normal thyroid activity before treatment. It is interesting to note that a deterioration of the thyroid activity of these patients during, or caused by, the treatment does not seem irrelevant for the treatment result. While only 4 per cent. of the patients,

TABLE XII

Patients with Initially Normal Thyroid Function

Group No.	Total No.	Thyroid Activity after Treatment	Mental State: Improved	Mental State: Not improved	Groups compared	chi²	p
I	154	Changed within the normal range ..	148	6	—	—	—
II	21	Unchanged	10	11	II–I	44·16	<<0·001
III	15	Increased to above normal range ..	3	12	III–I	99·83	<<0·001
	17	Decreased to below normal range ..	4	13			

the thyroid activity of whom changed inside the normal range, did not improve, 78 per cent. of the patients, the thyroid activity of whom went outside the normal range during the treatment, remained unimproved. This correlation between the changes in the thyroid activity and the mental state is statistically significant ($chi^2=99\cdot83$; $P<<0\cdot001$). One particularly interesting fact only revealed itself when these tables were compiled: there exists a significant difference in the probability for mental recovery between the patients in whom the thyroid activity showed changes inside the normal range and the patients whose thyroid activity remained completely unchanged. The latter group of patients shows significantly fewer mental improvements than the former. It will be explained further, below, that the changes in the thyroid activity during treatment are only an *indicator* of changes in the hormone equilibrium, which are apparently

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correlated to changes in mentation. The fact that changes in the thyroid activity are taking place, even if these changes remain inside the normal range, apparently indicates that changes in total hormone equilibrium are taking place. If, however, no change whatsoever occurs in the thyroid activity, that might indicate that the treatment in question does not influence the hormone equilibrium at all in these particular cases.

2. *Comparison of the effect of different psychiatric routine treatments*

Three years ago, when reviewing the influence of E.C.T. on the thyroid activity (Reiss, Hemphill, Maggs, Haigh and Reiss, 1951) it was surprising to find that the *same treatment* could increase the thyroid activity in patients showing an initially decreased thyroid function, and also reduce a previously increased activity towards the normal range. The explanation was put forward that E.C.T. does not influence the thyroid directly, but interferes with the function of the pituitary anterior lobe and its production or release of the various hormones, thyrotrophic, corticotrophic, gonadotrophic hormones, etc., all these hormones being antagonistic among each other. Thus, in some cases of thyroid underfunction the endocrinologically relevant sequel of E.C.T. consists in an increased production of thyrotrophic hormone which might act either by direct stimulation of the thyroid or by suppression of thyroid antagonistic hormones; while in cases of increased thyroid activity, secretion of more antagonists, such as corticotrophic or gonadotrophic hormone are decisive for the reduction in the thyroid activity observed. In other words: there is no specific influence on the thyroid function by E.C.T.; E.C.T. influences the total hormone equilibrium; changes in the thyroid activity are only an *indicator* for a multitude of changes in the endocrine system taking place after E.C.T. Investigations of changes in other endocrine functions after E.C.T. or other routine treatments, have corroborated this view (Reiss, 1952; 1953; 1954).

A new interesting feature is introduced by the fact that other routine treatments, such as coma insulin and modified insulin therapy show a similar correlation in their effects on the mental activity with changes in thyroid activity as in E.C.T. Quite different psychiatric disease entities, however, are treated with E.C.T. and the other methods of treatment mentioned. The results concerning the change in thyroid activity do not give any clue towards these differences. It cannot be over-emphasized in this connection that the changes in thyroid activity accompanying changes in the mentation are as already mentioned above only *one* indicator that changes in the endocrine equilibrium are taking place. Apart from thyroid activity, the changes in adrenal cortex function and some changes in the function of the sex glands were investigated, but one can fairly say that a considerable part of the endocrine changes taking place are still unknown. Many more investigations will be needed in order to assess the differences between the total action on the hormone equilibrium between E.C.T. and C.I.T.

3. *General hospital care and attention*

The incidence of mental improvement seen in patients who do not receive any special treatment, is of course smaller than in patients who do. It is all the more interesting that in this group of patients as well, there is a very significant correlation between improvement in mentation and thyroid activity. It is well known that very often hyper-thyroidism starts after a psychic trauma. Conrad (1934) has claimed that as many as 94 per cent. of his hyperthyrotic patients revealed a psycho traumatic case history. The epidemic rise of thyrotoxicosis in

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Denmark during the last war may also have some connection with possible psycho-traumatic causes (Averson, 1949). It is also generally known how hyperthyroidism and exophthalmos can develop in a very short time after sudden fright. It may be recalled that in the past patients suffering from the less severe hyperthyrotic symptoms were often sent to nursing homes situated perhaps in a mild climate on low mountain sides, where changed environment and nutrition were mainly responsible for the patients return to health. Some of the psychiatric patients too, soon show mental improvement after hospitalization only. The significance of the changes seen in the thyroid function and the improvement of the patients, is still being analysed. It is interesting that in some members of this group of patients, it was possible to predict the coming spontaneous remission by investigating another component essential for the maintenance of the endocrine equilibrium. This was particularly the case in patients who showed increased thyroid activity and very low ketosteroid excretion, the ketosteroid excretion rate starting to rise spontaneously, soon after admission to the hospital (see also Reiss, 1953).

4. *Leucotomies*

Easily recognized endocrine changes after leucotomy are no rarity, particularly in women who after previous amenorrhoea start to menstruate regularly. Some time ago the author observed that a woman who was regarded as eunuchoidal, and was one of the first pre-frontal leucotomies carried out at the Burden Institute, started to menstruate soon after the operation. Hemphill (1944) described enlargement of the testicles in a hypogonadal man after prefrontal leucotomy. The general body weight increase which is also frequently seen after leucotomy is yet another indication that endocrine changes are taking place, the nature of which are not yet completely analysed.

Leucotomy apparently interferes with the supraoptico-hypothalamic, and -pituitary anterior lobe connections. The operation influences, in this way, the pituitary anterior lobe function.

It is therefore, not surprising to find changes in the thyroid activity after leucotomy, these changes being of course, indicators for much more complex changes taking place within the total hormone equilibrium. The psycho-neuro-endocrine correlation seen in leucotomy is the same as in the other treatments in spite of the very different mechanisms of action.

5. *Endocrine treatments*

The rationale of the different endocrine treatments has already been discussed in this paper, together with the evaluation of the results. They were carried out mainly in order to narrow down the range of the possible decisive elements participating in the disturbed hormone equilibrium of the patients.

The various shock treatments are still purely empirical and act via a multitude of components, few of them really essential for the mental improvement. In contrast, endocrine treatment appears to be more specific with a narrower range of possible influences on the endocrine equilibrium and mentation. Needless to say, if changes similar to those seen after shock treatments could be brought about by some other, less dramatic, means it might be a great improvement in our therapeutic possibilities. As far as the changes in the thyroid activity as an indicator of the situation in the endocrine equilibrium are concerned, the effect of the various endocrine treatments described in this paper compares favourably, on a statistical basis, with the shock treatments.

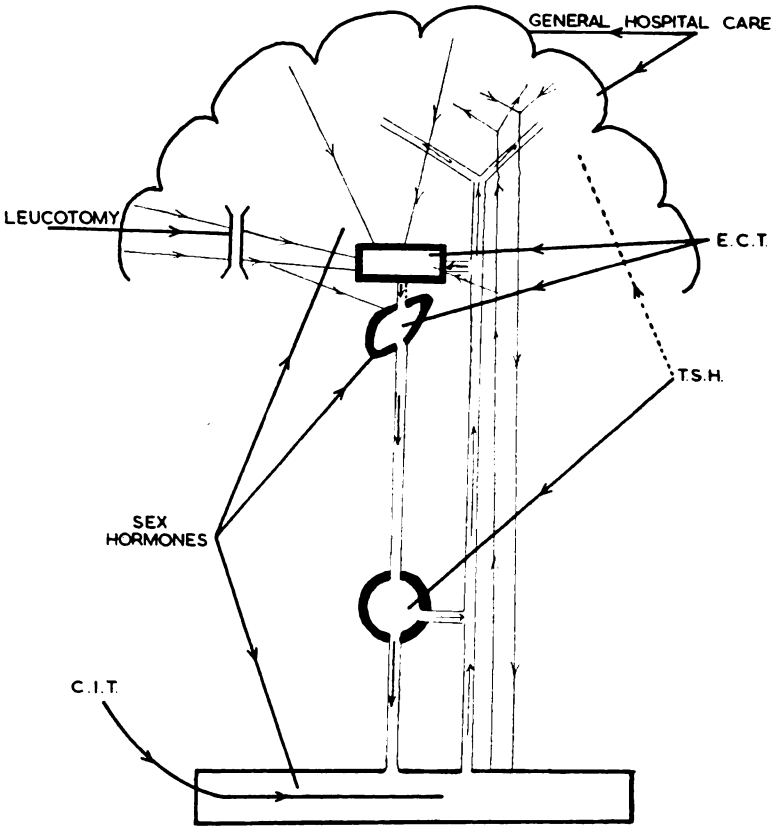
It would, of course, be erroneous to arrive at any conclusions regarding

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endocrine causes of disturbed mentation, on the basis of these treatment results. Owing to the well known neuro-endocrine interrelationship, most of the endocrine disturbances found during mental disorder, can be either the consequence or the cause of the disease. In the majority of the cases admitted to a mental hospital the disease has already progressed so far that a vicious circle exists, and it is difficult to determine the primary pathological event. From this viewpoint, it will be useful to compare the actions of the different treatments discussed in this paper on the neuro-endocrine axis.

6. *The influence of the various treatments on a psycho-neuro-endocrine circle*

Neuro-endocrine interrelation was extensively described and discussed by the author in this journal (Reiss, 1939; 1944). A scheme illustrating this interrelation, with the pituitary anterior lobe as centre-piece (omitting the posterior lobe) is to be seen in Fig. 1; it is worth considering in order to compare the role



of the different treatments concerned. The scheme shows the physiological interconnection between: Higher Brain Centres—Hypothalamus—Pituitary Anterior Lobe—Peripheral Ductless Glands and Body-periphery, including the relevant centrifugal or centripetal nervous paths, and the humoral connections between the different glands, body-periphery and brain. The physiological interconnection which has been found between these components makes it understandable that a disturbance taking place in any level must upset the whole

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neuro-endocrine equilibrium. Increased stimuli of the higher brain centres, as for instance severe emotions or psychic traumata, lead via the hypothalamus to increased production of pituitary anterior lobe hormones (i.e. thyrotrophic hormone) which stimulates the peripheral glands to the secretion of higher amounts of hormones. The latter now act back on the hypothalamus and higher brain centres causing a change in all their activities, among them their regulatory influence on the pituitary anterior lobe. Thus, a pathogenetic cycle of events is set up, becoming progressively worse. Obviously, such vicious circles with a similar pathologic outcome can start in the peripheral ductless gland or the body periphery by most variable stimuli, leading finally to analogous pathologic manifestations as disturbances started after psychic traumata.

It is clear that therapeutic efforts should be directed towards interruption of such pathogenetic vicious circles. This is being achieved by the different treatment procedures discussed above. They interfere, as can be seen in Fig. 1 with the neuro-endocrine circle on quite different planes.

E.C.T. stimulates the brain directly and interferes with the hormone equilibrium by direct stimulation of the pituitary anterior lobe or via the hypothalamus, the latter way being more probable if the experimental deductions of Markee, Sawyer and Hollinshead (1946) and Harris (1952) are correct.

The changes that can occur after change of environment and emotional involvements after hospitalization start on a higher level, in the higher brain centres.

Leucotomy interferes with the supraoptico-hypothalamo-hypophysial nervous connections, influencing the pituitary anterior lobe secretion in this way.

Coma-insulin therapy acts primarily in the periphery, depleting the carbohydrate stores, resulting in a diminution of the blood-sugar concentration. Certain parts of the brain are very sensitive to a reduction in the blood-sugar level, and convulsions occur by a mechanism not yet fully elucidated. The results of this kind of stimulation on the hormone equilibrium are, as far as the regulation of thyrotrophic hormone production is concerned, similar to that achieved by E.C.T.

Treatment with hormones is more circumscribed and direct. Thyrotrophic hormone acts directly on the thyroid, but an additional direct action on the brain or certain brain-parts cannot be excluded if one takes into account the role played by thyrotrophic hormone in the production of exophthalmos.

The sex hormones act on different levels. Small doses stimulate, high doses inhibit, the pituitary anterior lobe secretion. These actions are apparently decisive for the thyroid changes as described above. The action of the sex hormones on the genital tract and their vasodilatory action on the brain capillaries, Reiss and Golla (1940) contribute obviously to appropriate changes in other components of the hormone equilibrium.

Surveying the varying spheres of their interaction with the psycho-neuro-endocrine circle, it is not surprising that the different treatment procedures all act in a similar way in their influence on the thyroid function.

SUMMARY

The thyroid activity of over 400 psychiatric patients was investigated before and after treatment.

A highly significant correlation was found between a normal thyroid activity after treatment and mental improvement, or, thyroid activity outside the normal range and non-improvement.

This correlation held good in all the disease entities investigated and was independent of the treatment applied.

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Changes in the thyroid activity measured are regarded mainly as indicating more extensive changes in the total hormone equilibrium of the patient.

The action of electroconvulsive shock therapy, coma insulin therapy, treatment with thyrotrophic hormone, treatment with steroid sex hormones, of leucotomy and of general hospital care and attention, on the psycho-neuro-endocrine circle are discussed. The various forms of treatment act in different levels of the neuro-endocrine regulatory system, but their final result appears to be the same as far as the hormone equilibrium is concerned.

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