IODINE-132 UPTAKES BY THE THYROID IN PSYCHOTICS

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THE study of thyroid function as the uptake of radioiodine (I^{131}) is a well-established test. Since the half-life of the isotope is long (8 days) it is unreasonable to make frequent repeated tests in the same person because of the cumulative radiation risk and the complexity of interpretation when residual radioactive iodine is still present in the body. However, in psychiatry daily or twice daily measurements of thyroid function might be very useful in studying patients who show sudden or rapid mental changes (Sands, 1958), and a radioiodine isotope with a half-life of only 2·26 hours which has become more readily available (I^{132}), deserves trial. The primary aim of the present work was to make daily measurements on one man through several short (6-day) cycles of behavioural change. He was predominantly manic-depressive in type and has already been described in detail (Crammer, 1959). To discover how variable the measurement could be, repeated observations were also made on a group of 20 chronic male patients living together and showing an unchanging clinical picture. Observations were repeated on them after three months of chlorpromazine treatment to see whether this would have altered the values obtained for thyroid uptake.

METHODS

Preparation of Radioactive Iodine Solution. Alkaline tellurium^{132} sulphate solution obtained from Harwell was treated with acid hydroxylamine and hydrogen peroxide solution. This mixture was distilled in an all-glass micro-distillation apparatus and condensed into alkaline 0·02 normal thio-sulphate solution. About 10 ml. of distillate was used each time and the resultant solution was made isotonic by the addition of a calculated quantity of strong saline solution. Additional physiological saline was added to give the correct activity for the required dose in 1 ml. of saline. The bulk material was distributed in 1 ml. sealed ampoules. These were sterilized for 30 minutes in a boiling water-bath and were used within 1–2 hours of preparation. The dose was drawn from the ampoule into a tuberculin syringe and given into an arm vein.

Counting Techniques. The dose delivered to the patient was taken as the difference between counting rates obtained from the full syringe and from the same syringe after injection. All the counting in these determinations was carried out by means of a ratemeter working from four G 10 Pb Geiger Counters (20th Century) arranged in a square pattern. This arrangement of counters gave a large area in the centre of the square in which the counting rate of the

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sample was almost independent of its position. The counters were held in a frame which could be opened and fitted quickly round the patient's neck, at the level of the thyroid, the gland being positioned in the area of uniform sensitivity by bringing the neck forward against a simple cuff fixed to the frame. As a routine it was found convenient to measure the activity in the thyroid (neck) 90 minutes after injection. The count so obtained was corrected for background count and the decay of the radioisotope.

In all cases a standard ampoule was set up at the beginning of the experiment and the decay rate followed throughout the period of the experiment using the counter assembly.

Significance of Results. It was found that the uptake figures obtained in this fashion followed the same pattern as those obtained with Iodine^{131}, e.g. 20–50 per cent. uptake normal, 60 per cent. and over hyperthyroidism, below 15 per cent. hypothyroidism. The estimated error in the determination is of the order of 3 per cent.

Cases Studied. The 20 men, all between the ages of 30 and 60 and all having been at least 10 years in hospital, were mostly chronic schizophrenics living together in the same open ward. For at least a fortnight before each test all cooking and table salt was "analar" sodium chloride, but no other dietary restriction was enforced. Apart from the period of drug trial, when half of them received chlorpromazine capsules, 300 mg. daily, and the other half identical capsules containing lactose, they received no drugs of any kind, not even the laxatives or cough cures usually provided by the nurses. The intention was to maintain a constant low iodine intake. The cyclical patient was not on any drugs, was in a different ward, and his intake was uncontrolled. All patients were familiarized with the procedure by rehearsals before the actual tests were begun. All tests were carried out between 2 p.m. and 5 p.m. on each test day.

Results

(*a*) *The Group*

Table I shows the measurements of thyroid activity on four days before the drug trial, and on three days after chlorpromazine treatment had been continued for at least three months. Agreement between the values for 25 and 26 July is in general quite good, except for 7, 9, and 16, 17, 18, who show differences of at least 20 per cent. between the two days. When 29 July is also considered, 6 shows an aberrant value, while 24 October yields at least 8, 10, 14, 16 with values differing from their previous three. These individual variations are unlikely to be due to diet since food was nominally the same for all, while the variation on the same day is an increase for some, a decrease for others (the uniform depression of all values on 21 March is likely to be a dietary effect). Individual variations of this sort have been noted by other workers (Fellinger, Höfer, and Vetter, 1955; Hanbury *et al.*, 1954; Hare and Haigh, 1955; Francois *et al.*, 1958), and require further exploration since their cause is undetermined. For our present purpose, therefore, a finding of no change in iodine uptake during a mental change or chemotherapy would be much more significant than the reverse, which might merely be "spontaneous" variation.

(*b*) *Effect of Chlorpromazine*

The clinical therapeutic effects will be reported elsewhere (Letemendia and Harris).

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TABLE I

Percentage I^{132} Uptakes on Different Days

Patient	25 July	26 July	29 July	24 Oct.	17 Jan.	23 Jan.	21 Mar.
1	29	30	(32)	30	35	41	26
2	33	32	33	33	32	32	23
3	27	28	30	(27)	26	28	24
4	30	32	34	32	30	35	26
5	23	26	25	21	(29)	27	(23)
6	33	33	39	30	33	33	27
7	43	33	43	40	26	32	27
8	27	25	28	34	34	28	25
9	35	28	35	32	35	32	23
10	29	30	34	42	33	25	23
11	31	32	31	24	30	39	23
12	26	26	30	(26)	29	30	23
13	31	28	33	(29)	32	32	23
14	32	27	30	19	30	30	28
15	34	30	35	21	34	27	23
16	32	25	30	16	26	32	23
17	38	29	35	38	44	47	33
18	29	36	35	29	43	38	27
19	23	29	34	31	41	48	31
20	37	34	30	27	40	52	26

Treatment began after 24 October, the first ten receiving placebo, the second ten (below double line) chlorpromazine 300 mg. daily. Figures in brackets are values calculated as described in the text.

TABLE II

Comparison of Average Percentage Uptakes

Date	First Ten	Second Ten	Difference	Standard Error of Difference
25 July	30·8	31·1	+ 0·3	2·27
26 July	29·6	29·4	− 0·2	
29 July	33·4	32·3	− 1·1	
24 October	32·6	25·6	− 7·0	3·26
17 January	31·6	34·7	+ 3·1	
23 January	31·3	37·2	+ 5·9	3·24
21 March	24·7	26·0	+ 1·3	1·25

The second ten received chlorpromazine after 24 October.

Table II compares the observed uptakes of control and treated groups both before and after treatment. The difference between the averages of the two groups must be more than twice the standard error of their difference for the result to be statistically significant. Before treatment the groups compare well, except on 24 October, when, however, the "first ten" comprise nine and the "second ten" only eight observations. After treatment the chlorpromazine group tends to give a slightly greater thyroid activity reading than the controls, but the difference fails to reach significance. However, statistical analysis is handicapped by the unavoidable absence of a few observations. These can be estimated (values in brackets, Table I), by calculating the mean daily percentage uptake for a patient from the available readings and weighting this by a factor derived from the variation between days. Thus the missing observation on 29 July (patient 1) is estimated as:

$$\text{mean of observation on 25, 26 July and 24 October, for the Patient} \times \frac{\text{Overall mean for first 10 patients on 29 July}}{\text{Overall mean for first 10 patients on 25, 26, 29 July, and 24 October}}$$

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Table III shows a comparison of mean differences between the experimental and control groups. In the pre-treatment period the readings are reasonably homogeneous, the control group having a mean daily uptake of 31·5 per cent., compared with the experimental group's 29·9 per cent. (see A). This difference is still well below a reasonable level of significance (t=·91, p=·35).

TABLE III

Comparisons of the Two Groups

	Comparison	n	Mean	D.	t.	P.
A.	Control Group (Pre-treatment) ..	10	31·5			
	v.			1·6	0·91	<0·4 >0·3
	Experimental Group (Pre-treatment)	10	29·9			
B.	Control Group (Post-treatment) ..	10	29·1			
	v.			3·7	1·89	<0·1 >0·05
	Experimental Group (Post-treatment)	10	32·8			
C.	Control Group (Mean differences between pre-treatment and post-treatment values)	10	2·4			Significant at
	v.			5·3	2·77	<0·02>0·01
	Experimental Group (ditto)	10	− 2·9			
D.	Control Group (Pre-treatment) ..	10	31·5			
	v.			2·4	1·87	<0·1 >0·05
	Control Group (Post-treatment) ..	10	29·1			
E.	Experimental Group (Pre-treatment)	10	29·9			Significant at
	v.			2·9	2·17	<0·05>0·02
	Experimental Group (post-treatment)	10	32·8			

After treatment a straight comparison (B) of the two groups also shows a non-significant difference between means (t=1·89) which suggests that the chlorpromazine treatment has had no effect on iodine uptake. This may be misleading, however, as the trend of the changes in each group has been in opposite directions. The mean uptake for the controls has fallen from 31·5 to 29·1 per cent. (possibly a seasonal change?), whereas for the chlorpromazine-treated it has increased from 29·9 to 32·8 per cent. On the assumption that the two groups would have behaved similarly in the absence of chlorpromazine, the difference might be due to treatment. The mean change for the control group (D) is a loss of 2·4 (t=1·87, p<·1). The mean change for the chlorpromazine group (E) is a gain of 2·9 (t=2·17, p<·05). If a direct comparison of the behaviour of the two groups is made (C), then the difference of the means of the individual changes is 5·3 (t=2·77, p<·02), which is quite highly significant.

Thus the effect of chlorpromazine may have been to increase the percentage uptake of I^{132} by a small amount, but if so, the change was of an altogether smaller order than that observed in thyroid disease.

(*c*) *Cyclical Patient*

Table IV shows the values obtained through two consecutive and one further cycles. The uptake on 24 October was measured thirty minutes late because on this one occasion the patient was in strange surroundings, became very

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TABLE IV

Percentage I^{132} Uptakes in a Cyclical Patient

Mental State	Date	Uptake %	Date	Uptake %	Date	Uptake %
Late semi-stupor	23 Oct.	36	29 Oct.	33	22 Nov.	41
Hypomanic	24	51*	30	40	23	40
Manic	25	33	31	42	24	44
Manic	26	30	1 Nov.	32	25	37
Transitional	27	35	20	33		
Depressive stupor	28	36	21	40		

* Two-hour reading: see text.

restless and escaped from the hospital. The result is, therefore, not fully comparable with all the others in environmental circumstances. Bearing in mind the absence of dietary control we may say that the other results agree fairly well with one another and show no consistent change between stupor and the height of manic activity, though there is perhaps a suggestion that activity is greater at the onset of manic phase than at its end. If there is a change in thyroid activity with change in mental state, it must be small and of an altogether different order from the change to myxoedema or hyperthyroidism. The manic, like the anxious person, may be expected to give an essentially normal radio-iodine uptake.

DISCUSSION

Although there have been many studies of thyroid gland function in mental illness, the consensus of opinion is that it is normal in the functional psychoses (Bowman *et al.*, 1950; Altschule, 1953), and the present results agree with this. Likewise, the therapeutic use of thyroid gland extracts has proved disappointing except in the uncommon case of periodic catatonic schizophrenia, where it may produce symptomatic cure (Gjessing, 1938), and thyroxine or tri-iodothyronine are equally effective (Gornall *et al.*, 1952). Periodic catatonia is one of the conditions where chlorpromazine also produces symptomatic cure (Kaiser, 1954; Labhardt, 1954; L. Gjessing, personal communication; Crammer, 1957). It is evident from our results, which agree with those recently reported by Reichlin *et al.* (1959), and Newman and Fish (1958), using different methods, that chlorpromazine has no particular stimulant effect on thyroid function in a daily dose usually considered therapeutically effective. In consequence it is likely that in the periodic catatonia patient it acts directly on brain metabolism, and not unlikely that thyroxine also has a direct central pharmacological effect rather than working therapeutically through peripheral metabolic action.

The variability of iodine uptake by the thyroid of the same individual on different days under seemingly standard conditions has been noted by all workers who have made serial determinations with I^{131} or I^{132}. Francois *et al.* (1958), using I^{132} on 23 normal men obtained values ranging from 20 to 31 per cent., and 30 to 43 per cent., and showed that these were quite outside experimental error and must be a sign of some physiological change. Earlier, Hare and Haigh (1955), using I^{131} in both normals and psychotics, attempted to define the cause of the variation and were left with the suspicion that a rise might sometimes be due to a period of heightened alertness to environment, as in a patient's pleasurable awareness of unusual surroundings on a motor-coach outing. The single high reading of 50 per cent. in our cyclical patient is consistent with this. In animal work Harris (1957) has been able to demonstrate changes in the rate of thyroid secretion in response to brief environmental

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changes of emotional significance. It is possible, then, that in man also the thyroid is responsive to significant external events, whereas it is unaffected by those internal events which manifest themselves as psychiatric syndromes, for in anxiety states, manic excitement, stupor, active paranoid schizophrenia, and so on, it appears to continue normal function.

However this may be, until the variability in thyroid uptake readings can be understood and controlled, attempts to correlate mental change with change in iodine uptake ("ring count"), for instance during insulin coma treatment (Batt *et al.*, 1957), are bound to be invalid. Only lack of change can at present be considered significant.

Summary

1. Thyroid function has been measured by the use of a short-life iodine isotope, which allows daily repetition of observations, in a group of 20 chronically psychotic men, and in a man with a 6-day manic-depressive cycle.

2. By this test thyroid function was essentially normal in all.

3. In any individual most of the measurements agreed well, but there were always a few which deviated widely. This has been noted also by others and its explanation is unknown. It invalidates attempts to relate changes in iodine uptake to changes in mental state.

4. Administration of chlorpromazine (300 mg. daily) for at least three months produced a very small increase in thyroid function (radio-iodine uptake), which failed to reach statistical significance unless it was assumed to be superimposed on a mild, possibly seasonal, functional depression of activity.

5. In the cyclical patient no significant difference was found in thyroid activity between manic and stuporose days.

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