

Another possible cause of the hypoglycaemia might be the diversion of blood glucose from the pathway of peripheral utilization to the tumour cells with their increased metabolic demands. This mechanism was well described by McFadzean and Yeung Tse Tse (1956) in their report on primary hepatomas.

Failure to recognize the exact cause of the low blood-sugar before death, the severity of the patient's illness, and the short period of survival in hospital prevented the completion of investigations which might have helped in elucidating some of the metabolic abnormalities in this case.

I am deeply indebted to Professor B. Malamos for permission to report this case and for his helpful criticism, and to Professor D. Eleftheriou for the histological report.

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## RADIOACTIVE IODINE STUDIES IN THE DIAGNOSIS OF HASHIMOTO'S THYROIDITIS

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Hashimoto's thyroiditis has recently been the subject of extensive investigation. Most workers have studied the immunological and biochemical abnormalities associated with this disorder, but relatively little attention has been paid to radioactive iodine ( $^{131}\text{I}$ ) tests. Though it is recognized that these may produce abnormal results, attempts to evaluate their use in the diagnosis of the condition have been infrequent. This paper reports our findings in 41 patients with Hashimoto's thyroiditis using routine  $^{131}\text{I}$  tests. Our experience with some of the special tests that have been suggested to be useful in establishing the diagnosis is recorded.

### Subjects and Methods

Of the 41 patients investigated, 18 were euthyroid and 23 hypothyroid. The thyroid status of the patients was assessed on the basis of the clinical findings. The presence of hypothyroidism was confirmed by estimations of basal metabolic rate and serum cholesterol, electrocardiography, and the measurement of reaction time (Murray, 1958). A tentative diagnosis of Hashimoto's thyroiditis was made in the first place in each of the patients because of firm or hard generalized

thyroid enlargement. It was confirmed either by histological examination or by the finding of biochemical abnormalities (Luxton and Cooke, 1956) and positive precipitin tests (Goudie *et al.*, 1957).

Routine  $^{131}\text{I}$  studies were carried out in all patients. The gland uptake of  $^{131}\text{I}$  was measured by a shielded scintillation counter at 24 or 48 hours after the oral administration of 25  $\mu\text{c}$  of  $^{131}\text{I}$ . The serum protein-bound  $^{131}\text{I}$  (P.B. $^{131}\text{I}$ ) was measured by the resin-extraction method of Zieve *et al.* (1956) on a blood sample withdrawn at 48 hours. The butanol-extractable fraction was estimated after four washes of a serum sample by twice its volume of butanol after the pH had been adjusted to 2. Scanning of the neck was carried out by placing a shielded end-window Geiger counter in direct contact with the neck, expressing the results as counts/ $\frac{1}{2}$  min./10  $\mu\text{c}$ .

In seven patients with Hashimoto's thyroiditis and in 14 control patients with thyrotoxicosis or non-toxic goitres, studies were carried out after an intravenous tracer dose of  $^{131}\text{I}$  (Berson *et al.*, 1952). 25  $\mu\text{c}$  of  $^{131}\text{I}$

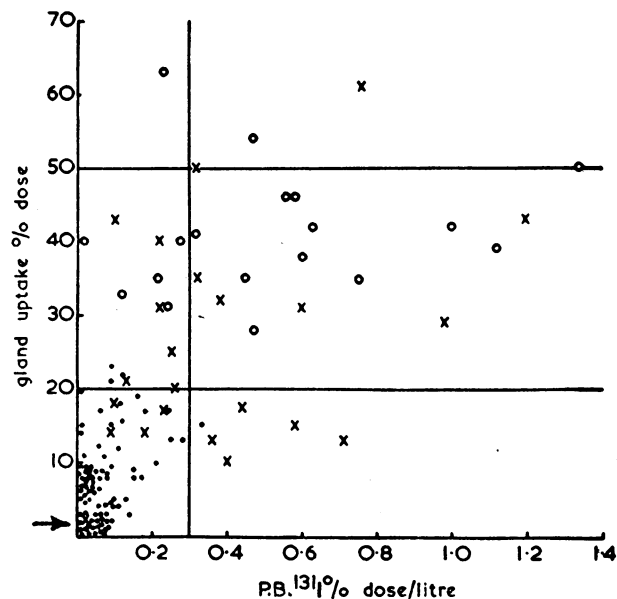


FIG. 1.—Relationship of gland uptake of  $^{131}\text{I}$  and 48-hour P.B. $^{131}\text{I}$  in patients with primary myxoedema and Hashimoto's thyroiditis. The arrow shows the position of the fifth patient with uptake below 20%. ● = Primary myxoedema. × = Myxoedematous Hashimoto. ○ = Euthyroid Hashimoto.

was injected intravenously and the rate of uptake by the thyroid gland was measured at regular intervals for 30 minutes. After the administration of 600 mg. of potassium perchlorate orally, the uptake was measured for a further 30 minutes. The uptake at the end of this period was expressed as a percentage of the uptake just before the administration of perchlorate. In six euthyroid subjects with Hashimoto's thyroiditis, the routine  $^{131}\text{I}$  studies were repeated after the administration of L-thyroxine sodium in daily doses of 0.2–0.3 mg. for periods varying from 10 days to 20 weeks.

### Results

The results of the routine estimations of gland uptake and serum P.B. $^{131}\text{I}$  are shown in Fig. 1, together with the findings in 85 proved cases of primary myxoedema. It was found that there was no significant difference in the results between the uptakes at 24 hours and 48 hours, and they have been included together. Only

three of the 85 cases of primary myxoedema had gland uptakes greater than 19% of the dose, compared with 13 of the 23 hypothyroid patients with Hashimoto's thyroiditis. Of the 18 euthyroid cases of Hashimoto's thyroiditis, 16 had uptakes in the normal range of 20% to 50% of the dose; two of them had an uptake greater than 50%.

In 24 of the Hashimoto patients the 48-hour serum P.B.<sup>131</sup>I was greater than 0.3% of the dose per litre. This comprised 12 each of the hypothyroid and euthyroid groups. Only one of the patients with primary myxoedema had a P.B.<sup>131</sup>I above 0.3% of the dose per litre. This subject had a positive precipitin test and a palpable thyroid isthmus, and might therefore be considered to be a case of Hashimoto's thyroiditis.

TABLE  
Distribution of Gland Uptake and 48-hour P.B.<sup>131</sup>I

	Gland Uptake of <sup>131</sup> I (% of Dose)			Serum P.B. <sup>131</sup> I (% of Dose/Litre)	
	<20	20-50	>50	<0.3	>0.3
Primary myxoedema (85 cases)	82	3	—	81	1
Hashimoto's thyroiditis:					
Hypothyroid (23 cases)	10	—	—	5	5
	—	12	—	6	6
	—	—	1	—	1
Euthyroid (18 cases)	—	16	—	5	11
	—	—	2	1	1

When the results of the gland uptake and serum P.B.<sup>131</sup>I tests are compared in the patients with Hashimoto's thyroiditis (see Table) it can be seen that all of the 18 euthyroid patients had a thyroid uptake of more than 20%—in six the P.B.<sup>131</sup>I was normal and in 12 it was above 0.3% of the dose per litre. The P.B.<sup>131</sup>I was normal in five and elevated in five of the 10 hypothyroid patients in whom the thyroid uptake of <sup>131</sup>I was less than 20%. It was normal in six and elevated in seven of the 13 hypothyroid patients in whom the thyroid uptake of <sup>131</sup>I was above 20%.

In the three patients studied the butanol-extractable fraction of the total serum <sup>131</sup>I was 57.6% (0.26% of

the dose per litre), 51.0% (0.87%), and 45.0% (0.14%) These values showed that a significant proportion of the total P.B.<sup>131</sup>I was butanol-insoluble, as the respective results for P.B.<sup>131</sup>I were 0.47%, 1.56%, and 0.31% of the dose per litre.

The administration of potassium perchlorate to the 14 patients with non-toxic goitres or untreated thyrotoxicosis resulted in a block of further uptake in 10. A typical example is shown in Fig. 2a. In three the perchlorate had no effect, and in one there was a slight decrease in the uptake signifying discharge of radioiodine. In this patient the uptake 30 minutes after the drug was 94% of the value just before its administration. In all the seven patients with Hashimoto's thyroiditis the discharge of <sup>131</sup>I from the thyroid gland was pronounced (Fig. 2b), ranging from 12% to 21%.

The onset of the effect of perchlorate varied from within two to three minutes (recorded as "early") to 16 minutes, being more rapid in the Hashimoto group. The variation in this period may be related to absorption, as no precautions as regards fasting were taken.

It can be seen from Fig. 3 that the administration of thyroxine resulted in marked suppression both of the gland uptake of <sup>131</sup>I and serum P.B.<sup>131</sup>I in all of the six patients studied. This effect was achieved with doses of thyroxine varying from 0.2 mg. to 0.3 mg. daily given during periods of 10 days to 20 weeks.

Discussion

In previous reports of radioactive iodine studies in Hashimoto's thyroiditis more attention has been paid to the results of the gland uptake of <sup>131</sup>I than to the serum P.B.<sup>131</sup>I. There seems to be general agreement that the gland uptake may vary greatly (Skillern *et al.*, 1956; Doniach and Hudson, 1957; Furr and Crile, 1954; and Beare, 1958). In the present series the uptakes ranged from 2% to 64%, lying within our normal range of 20% to 50% in 16 of the 18 euthyroid patients and in 12 of the 23 hypothyroid patients. In three patients (two euthyroid and one hypothyroid) the uptake exceeded the upper limit of normal. Both Skillern *et al.* (1956) and Doniach and Hudson (1957) noted that there was poor correlation between the

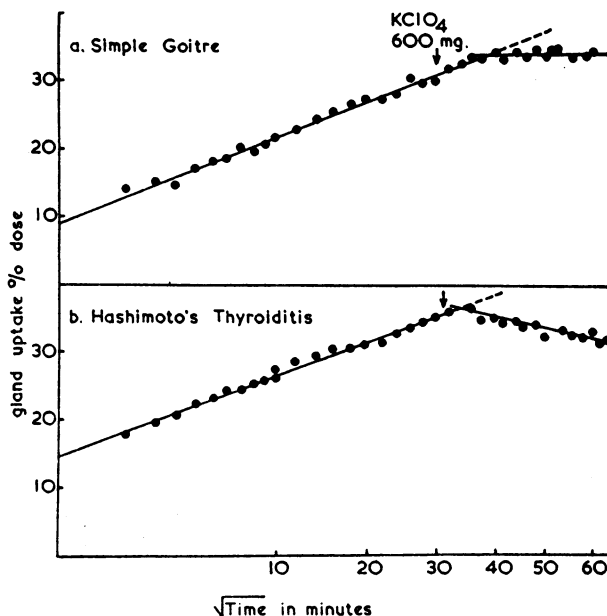


FIG. 2.—Effect of potassium perchlorate on gland uptake after intravenous injection of <sup>131</sup>I.

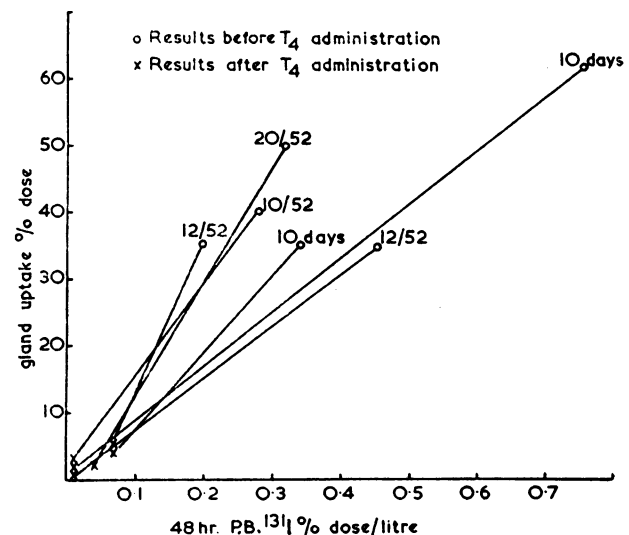


FIG. 3.—Effect of L-thyroxine sodium on the gland uptake and P.B.<sup>131</sup>I. Numbers indicate duration of treatment.

uptake and basal metabolism. We have found a similar lack of correlation between the uptake and both basal metabolism and the serum cholesterol. It is clear that a number of anomalous results are to be expected when  $^{131}\text{I}$  tests are used in the investigation of hypothyroidism. A normal thyroid uptake, or more rarely even an elevated uptake, does not eliminate the diagnosis of myxoedema. Indeed, its occurrence in a patient who presents the clinical picture of myxoedema and who has received no antithyroid drug therapy must suggest the possible diagnosis of Hashimoto's thyroiditis. In euthyroid patients with a firm goitre in whom there is a diagnostic difficulty in distinguishing between Hashimoto's thyroiditis and subacute thyroiditis, a normal uptake of  $^{131}\text{I}$  favours the former condition and a low uptake favours the latter.

The presence of relatively high levels of serum P.B. $^{131}\text{I}$  has been noted previously—for example, by Owen and McConeahy (1956) in 13 out of 37 cases, by Doniach and Hudson (1957) in four cases, and by Beare (1958) in one case. In the present series elevated levels of P.B. $^{131}\text{I}$ , such as are usually accepted as suggestive of thyrotoxicosis, were found in 58% of the cases. It is clear, therefore, that the P.B. $^{131}\text{I}$  value must, especially if it is not supported by the results of other tests, be interpreted with caution and in the light of the clinical picture.

When the results of the  $^{131}\text{I}$  uptake studies and the serum P.B. $^{131}\text{I}$  are considered in conjunction more useful information is obtained. It is clear that unusual combinations of results, such as a low or normal uptake of  $^{131}\text{I}$  in association with an elevated serum P.B. $^{131}\text{I}$ , deserve careful thought, and when they are found, a

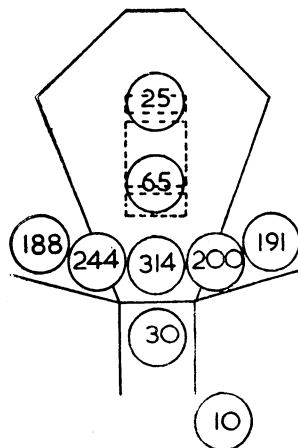


FIG. 4.—Half-minute counts recorded per 10  $\mu\text{c}$   $^{131}\text{I}$  over neck, sternum, and heart, with G.-M. counter in contact with skin.

diagnosis of Hashimoto's thyroiditis should always be considered. Likewise, Hashimoto's thyroiditis is a possibility when an elevated uptake of  $^{131}\text{I}$  and a raised serum P.B. $^{131}\text{I}$  are found in a patient who is being investigated as a likely case of myxoedema. Similar unusual combinations of results may, of course, also occur in patients who have received previous antithyroid therapy, in carcinoma of the thyroid, in sporadic goitrous cretinism, and in some cases of sporadic goitre. Scanning of the thyroid may help to differentiate between Hashimoto's thyroiditis

and neoplasm. We have found, like Doniach and Hudson (1957), that in the former the isotope distribution is uniform, a typical result being illustrated in Fig. 4. This is unlike the unequal distribution usually found in carcinoma. The elevated levels of serum P.B. $^{131}\text{I}$  would appear to be the result of at least two different mechanisms. Owen and McConeahy (1956) found in the serum of patients with Hashimoto's thyroiditis an unusual iodinated protein which, being butanol-insoluble, they considered to resemble thyroglobulin. They found that in about one-third of the patients the proportion of

serum P.B. $^{131}\text{I}$  that was butanol-insoluble exceeded the butanol-soluble P.B. $^{131}\text{I}$ . We have also found, in three patients studied, that an appreciable proportion of the total P.B. $^{131}\text{I}$  is butanol-insoluble—namely, 44% to 54.9%. The suggestion by Owen and McConeahy (1956), that this abnormal protein might represent a leak from damaged thyroid cells, may be of significance in view of the more recent studies of auto-immunization in this condition. Nevertheless, it should be noted that in one of our patients, as in four cases described by Owen and McConeahy (1956), the butanol-soluble fraction is also significantly elevated. This suggests that the high levels of P.B. $^{131}\text{I}$  do, in part, reflect a rapid production and discharge of hormone with an unusually large number of its molecules labelled with  $^{131}\text{I}$  because of a diminished thyroidal iodine pool (Riggs, 1952; Blom and Terpstra, 1953; Wayne, 1954).

Morgans and Trotter (1957) showed that in Hashimoto's thyroiditis there was a fairly rapid discharge of radioiodine from the gland after an oral dose of potassium perchlorate. Using a modified technique, our experience with this test has been similar. We have found it especially useful in those patients in whom the consistency of the gland suggested Hashimoto's thyroiditis but in whom routine  $^{131}\text{I}$  tests were normal. In all of the seven patients with Hashimoto's thyroiditis there was an appreciable discharge of  $^{131}\text{I}$  from the thyroid. Such a result demonstrates defective organic binding of iodine. This defect in hormone synthesis is only rarely encountered in untreated patients with simple goitres.

Skilern *et al.* (1956) showed that the administration of thyrotrophic hormone (T.S.H.) to patients with Hashimoto's thyroiditis failed to produce any increase in the uptake of  $^{131}\text{I}$ . They considered that the thyroid gland was under maximal stimulation by T.S.H. We were unable to estimate the T.S.H. levels in blood or urine, so we could not make direct observations of anterior pituitary thyrotrophic activity in our patients. We therefore used thyroxine to study it indirectly. Thyroxine depresses the anterior pituitary and the output of thyrotrophic hormone falls. Reduction of thyroid activity as shown by suppression both of the gland uptake of  $^{131}\text{I}$  and of the serum P.B. $^{131}\text{I}$  may be taken as indirect evidence that prior to the thyroxine the thyroid has been under the influence of T.S.H. Suppression occurred in all the patients tested. It is, of course, well recognized that in thyrotoxicosis such treatment produces no change in the  $^{131}\text{I}$  findings (Werner *et al.*, 1952). This suppression test is therefore of practical value in those patients suspected of Hashimoto's thyroiditis in whom the radioiodine studies show values in the toxic range, as a result of which confusion with thyrotoxicosis might arise.

### Summary

The results of  $^{131}\text{I}$  tests are reported in 41 proved cases of Hashimoto's thyroiditis, of which 23 were hypothyroid and 18 euthyroid.

The results of the thyroid uptake of  $^{131}\text{I}$  and the serum P.B. $^{131}\text{I}$  tests are often anomalous. They provide more useful information when they are considered in conjunction than when they are considered singly.

An elevated P.B. $^{131}\text{I}$  occurred with a low uptake of  $^{131}\text{I}$  in five cases, and with a normal uptake in 17 cases. Such a combination of results should suggest the possibility of Hashimoto's thyroiditis.

When both the serum P.B.<sup>131</sup>I and the thyroid uptake of <sup>131</sup>I are raised, as in two of our cases, distinction from thyrotoxicosis may be achieved by the thyroxine suppression test.

The raised serum P.B.<sup>131</sup>I may be due in part to the presence of an abnormal iodinated protein in the blood and in part to the unusually rapid production and discharge of hormone from a gland with a low iodine pool.

The observation of the effect of potassium perchlorate, which discharges an appreciable amount of the thyroid <sup>131</sup>I content in cases of Hashimoto's thyroiditis, is a useful additional diagnostic aid.

Part of this work was carried out during the tenure of an appointment by one of us (I. P. C. M.) in the Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, and we thank Professor E. J. Wayne for permission to publish the results obtained in patients who were under his care. We also thank Dr. E. G. Oastler for his helpful advice and criticism. Part of the expenses of the investigation were met by the Rankin Fund of Glasgow University. This research programme has been supported by a grant to one of us (E. M. McG.) from the Scottish Hospital Endowments Research Trust.

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The International Atomic Energy Agency has decided to undertake the measurement and analysis of samples of air, water, soil, and food to help in determining the degree of radioactivity in man's environment. This work, which will be done in the Agency's laboratory, now being built near Vienna, will be undertaken at the request of member states and of international organizations which have relations with the Agency and in collaboration with the United Nations Scientific Committee on the Effects of Atomic Radiation. Arrangements will also be made in the laboratory for a limited amount of training of scientists from interested member states in the relevant techniques. Collection of samples and their analysis would indicate the amount of radioactivity, and help in taking measures to reduce the radiation hazards of peaceful atomic energy work. Several member governments have asked the Agency how it can assist them in the collection of samples and in subsequent analysis and measurements. The Agency's assistance may also take the form of provision of experts and equipment to interested member states for carrying out measurements on the spot and helping national programmes of work in this field. It is expected that, apart from direct and specific assistance, the Agency's work will help in establishing international standards of sampling, measurement, and analysis. (International Atomic Energy Agency. PR 60/9.)

## RENAL AGENESIS AND SEVERE URINARY TRACT DYSPLASIA\*

A REVIEW OF 50 CASES, WITH PARTICULAR REFERENCE TO THE ASSOCIATED ANOMALIES

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Babies born with renal agenesis, and other forms of severe urinary tract dysplasia, show certain characteristic clinical and pathological features. In 50 cases encountered by us the abnormalities of the urinary tract were as follows: bilateral renal agenesis in 28, severe bilateral cystic dysplasia in 17, and congenital urethral atresia in 5 cases. The fact that intrauterine foetal micturition could not have been present was a feature common to all the cases.

### Clinical Features

#### Quantity of Liquor Amnii

In the 50 cases reviewed the following clinical observations on liquor volume had been recorded: deficiency or absence of liquor specifically recorded in 7, notes suggestive of liquor deficiency in 28, relevant information not recorded in 14 cases, liquor present in 1 case.

The one case in which liquor was definitely present was of particular interest, the foetus being an iniencephalic with bilateral renal agenesis. The possible significance of the iniencephaly in relation to the fact that liquor was not only present but in excess is discussed later.

The following features were regarded as "suggestive" of oligohydramnios: (1) The finding at examinations in late pregnancy of a uterus smaller than expected from the duration of amenorrhoea. (2) Failure to record rupture of the membranes or escape of liquor at any time before or during labour. The space on the case sheet for the insertion of the time of rupture of the membranes was frequently left blank; in the hourly or half-hourly labour records the membranes were often stated to be intact within 10 or 15 minutes of the time of delivery, but there was no record of their having ruptured, or having been ruptured, between this time and the delivery.

To test the reliability of these criteria a series of 100 case records of patients who were delivered of normal babies was sampled. By the above criteria, only 3 out of the 100 suggested a deficiency of liquor. The finding of these features in 28 of the 50 cases of renal dysplasia is therefore extremely significant.

Nevertheless, the most convincing cases are the first small group in which a specific record was made of the liquor deficiency. In three of these a provisional diagnosis of renal agenesis was made at antenatal examination, and the virtual absence of liquor confirmed by particular observation during labour and delivery.

\*Based on a communication to the Pathological Society of Great Britain and Ireland, July, 1958.