ABBREVIATION OF BERSON TECHNIC FOR ESTIMATION OF THYROIDAL CLEARANCE OF PLASMA RADIOIODIDE: USE OF BERSON TEST TO RECOGNIZE THYROIDAL PROTEIN-BINDING DEFECTS

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METHOD

Berson, Yalow, Sorrentino and Roswit (1) designed a simplified technic for estimating the rate at which the thyroid gland clears the plasma of intravenously administered radioiodide (I¹⁸¹). The amount of I¹⁸¹ taken up by the thyroid in 30 minutes is correlated with the average concentration of I¹³¹ in the plasma during the half hour. Plasma I¹³¹ is not actually measured, but is determined on the assumption that its concentration is a function of the weight of the body. Regardless of this and other assumptions involved, the method is one of the most precise in evaluation of thyroidal function in our experience (2, 3).

Calculation of clearances at periods of time less than 30 minutes has been found necessary on those infrequent occasions when there was an electronic or mechanical failure of the radiation detector, or when the patient was so restless that the uptake tracing became erratic before the 30 minute time was concluded.

In an attempt to determine whether the Berson procedure might be shortened, 1,250 of our records were reviewed. One hundred particularly uniform tracings, with clearance values of not less than 10 to more than 300 ml of plasma cleared of I¹³¹ per minute, were analyzed at various intervals between 5 and 30 minutes to establish new mathematical constants for practical application of the test.

During the course of our review, 11 tracings were found in which an initial uptake of I^{131} was succeeded, after about 10 or 20 minutes usually, by a reversal of the curve. Not only do these cases present a problem in the calculation of clearance of plasma I^{131} , but their rarity (about 1 per cent) seems to warrant their presentation. The Berson technic (1) was followed closely, with the only modification consisting of adaptation to our *in vivo* equipment: a 2 inch (5.1 cm) sodium iodide (thallium-activated) scintillation crystal situated at a distance of 20 cm between the surface of the crystal and the skin overlying the thyroid. The radioactivity was registered continuously on a counting rate-meter and in turn on an Esterline-Angus recorder (for example, Figure 1). Pulse-height discrimination was so set that 100 counts per second were recorded per microcurie of I¹³¹ in the neck.

The equation for calculating the thyroidal clearance (Cl in milliliters cleared per minute), based on the observations of Berson and colleagues, is $Cl = \frac{Th \cdot 200 \cdot W}{\overline{D} \cdot 30}$, where Th is the calculated uptake of I³³¹ during the test, W is the body weight in kilograms, \overline{D} is the calculated average fraction of the retained dose of I¹³¹, and 30 is the length of test in minutes. Berson's group found a fairly constant ratio between body weight and the fraction of the retained dose of I¹³¹ in the plasma, a plasma/body weight constant expressed by the number 200 in the above equation.

From the 100 tracings under analysis, the uptake (Th) was calculated at 5, 7.5, 10, 15, 20 and 25 minutes; the time in the denominator was changed accordingly. Assuming Cl from the standard 30 minute test, the only unknown became the plasma/body weight constant; this was then simply calculated.

RESULTS

Calculation of the plasma radioiodide/body weight constant for various intervals of time between 5 and 30 minutes, instead of the conventional 30 minutes, is presented in Table I. The standard deviation is seen to increase as the duration of the test diminishes. However, the error at 20 minutes is sufficiently small that it seems warranted to abbreviate the test routinely to this time from the standpoint of comfort to the patient.

Data on 11 patients with a reversing uptake pat-

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tern are included in Table II, and the actual uptake curves are reproduced in Figure 2.

It is clear from inspection of the curves that the standard Berson procedure is inappropriate for the calculation of thyroidal clearance of plasma I¹³¹ in these cases. This may be shown numerically by calculating the "clearance" at 5 minutes as well as at 30 minutes (Table II). In Patient 5, the one with iodide goiter, "clearances" were found to be 149 ml per minute at 5 minutes, 126 at 10, 108 at 15, 94 at 20, 82 at 25, and only 74 at 30 minutes. Since the diminishing "clearance" values reflect a loss of I¹³¹ from the thyroid during the test, none of these values truly represents the clearance. The closest approximation was reached by extrapolating the values to time zero, which yielded, in this instance, about 170 ml per minute.

DISCUSSION

The usual pattern of uptake of I^{131} by the thyroid gland is a continuously rising one until secretion of hormonal I^{131} reverses the curve. In normal persons this usually takes place about a day after the dose of I^{131} is given; in an occasional



FIG. 1. ERRATIC RECORD OF THYROIDAL UPTAKE OF I¹³¹. The patient was restless the last 15 minutes of the test. N, neck background before test started; E, extrathyroidal I¹³¹ in the neck before significant I¹³¹ was taken up by thyroid; O, observed uptake of I¹³¹ during half hour test (actually the difference between value at 30 minutes and value E); W, weight of patient; D, intravenously administered dose of NaI¹³¹; U, urinary excretion of I¹³¹ during test; Cl, thyroidal clearance of plasma I¹³¹ calculated from these data.

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Plasma radioiodide constants (k) in the Berson test of thyroidal clearance of plasma I¹³¹, at intervals of 5 to 25 minutes after equilibration in the neck of intravenous doses of I¹³¹

Minutes		_ ±1	SD	k* Values proposed
after equili- bration	k*		As % of k	for routine use
25	191.1	6.9	3.6	190
20	180.0	9.6	5.3	180
15	168.9	13.6	8.1	170
10	157.2	18.4	11.7	160
7.5	147.6	20.3	13.8	150
5	137.3	23.2	16.9	135

* k = Mean value for the constant of plasma I¹³¹/body weight. The mean values for k are based on 100 studies of uptake. The value for k at 30 minutes was taken as 200. Berson and associates experimentally determined that in the 30 minute period of their test the average fraction of a dose of I¹³¹ retained (that is, not in the thyroid or urine) per milliliter of plasma when multiplied by the body weight in kilograms was 5×10^{-3} . In the development of the clearance equation, this value, transposed from the denominator to the numerator, becomes 0.2×10^{-3} .

patient with hyperthyroidism, hormonal secretion may begin to reduce thyroidal I¹³¹ as early as two hours after the dose, although the peak uptake in Graves' disease usually occurs several hours later.

In contradistinction to this conventional pattern, 11 patients were observed in whom thyroidal release of I¹³¹ became evident within the first onehalf hour to one hour; it was recognized only because the Berson clearance test was being performed.

Details on the patient with "iodide goiter" have been reported (4). Paris and associates, studying this patient and other patients with "iodide goiter," found that after a rapid initial uptake of I¹³¹ by the goitrous thyroid, there was a reversal of the uptake curve (4). The rate of disappearance of I¹³¹ from the thyroid gland exactly matched the rate of disappearance of I¹³¹ from the blood stream. Since no hormonal I¹³¹ was recoverable, it would appear that these patients had an adequate or exaggerated iodide-trapping mechanism, but an inability to bind any of the halide to pro-In consequence, an equilibrium between tein. thyroidal iodide and plasma iodide was reached Such an equilibrium presumand maintained. ably occurs even when the binding rate of the thyroid is normal (5). Subsequently, the patient was taken off iodide drugs and a fully normal

Age, Patient sex	A		Apparent thyroidal clear- ance of I ¹³¹ at:		BMR	Serum PBI	Drugs	
	Diagnosis	5 min	30 min					
				ml/	min	%	µg/100 ml	
	1	24	Hashimoto's	47	16	-23	1.7	Before TSH
		F	disease†	64	13			After TSH
	2	33 F	Hashimoto's disease†	33	18	0	4.6	
	3	31 F	Hashimoto's disease†	85	49	+5		
	4	49 F	Probable Hashimoto's disease	8	3	+6	5.1	
	5	33 F	Iodide goiter†	149	74	-11		Iodides‡
	6	13 M	Goitrous cretinism†	190	55		2.5	
	7	44 F	Mild Graves' disease	93	25	-3	3.9	PTU§
	8	58 M	Tension state	17	4	+6	5.0	Tapazole
	9	39 M	Osteoporosis; hypogonadism	21	4	-14	2.5	PTU¶ TSH
	10	66 F	Previous I ¹³¹ therapy for Graves' diseaset	13	5			
	11	47 F	Smooth, diffuse goiter of uncer- tain type†	71	22	+18	8.7	

 TABLE II

 Eleven patients whose thyroids took up I¹³¹ initially but tended to release it during period of observation (Figure 2) *

* Abbreviations: BMR = basal metabolic rate; PBI = protein-bound iodine; PTU = propylthiouracil; TSH = thyroid-stimulating hormone.

† Tissue obtained at operation.

‡ For asthma.

& Received 200 mg 3 times a day for about a year.

Received 10 mg 3 times a day for 3 weeks.

Received 100 mg 3 times a day for 8 days; received also bovine thyrotropin, 5 units daily, for 5 days before test.

function returned to the thyroid gland, including disappearance of the reversing uptake curve.

In the extensive literature on the effect of propylthiouracil, it is agreed that this drug primarily blocks protein binding of thyroidal iodine (6). A reversing uptake curve might, therefore, be expected to occur in patients receiving this drug. Ingbar (7) has proposed an explanation for the rarity of the phenomenon on the basis of the exorbitant doses required to halt the thyroidal binding rate effectively, especially in Graves' disease. He has, however, observed the reversing pattern in patients, as have Taurog, Chaikoff and Feller (8) in animals. Three of our patients were receiving propylthiouracil or methimazole.

Gardner, Hayles, Woolner and Owen (9), in a study of goitrous cretins, found that those patients incapable of converting thyroidal iodine to the protein-bound form were characterized by a reversing uptake curve. The release rate from the thyroid and the renal excretion rate of I^{131} were the same. Our patient with goitrous cretinism would seem to fit into this category.

By analogy with the various types of patients described above (goitrous, cretins, iodide goiter, propylthiouracil goiter), the same defect characterized the patient (Table II) who had had I¹³¹ therapy for hyperthyroidism, the four patients with Hashimoto's disease and the one with an undiagnosed goiter.

From Ingbar's data it is difficult to explain the findings in Hashimoto's disease; he estimated that the thyroidal binding rate had to be inhibited 90 per cent to obtain a "negative slope accumulation curve" (7). The level of hormonal iodine, i.e., butanol-extractable iodine and butanol-insoluble

iodine (10) in the plasma of these patients often totals a normal value for protein-bound iodine (for example, Patients 2 and 4), suggesting a binding rate considerably greater than 10 per cent of normal. Although our experience with the Berson test in Hashimoto's disease is limited to these four patients, the unanimity of the finding of a reversing uptake curve suggests a new diagnostic clue.

The eleventh patient is difficult to classify, because we are not certain what type of goiter she had. She was 47 years old, with mitral stenosis and insufficiency, and was found to have a small, diffuse, non-nodular goiter. She was euthyroid clinically. The basal metabolic rate was plus 18 per cent. The protein-bound iodine was increased (8.7 μ g per 100 ml) but the uptake of I¹³¹ was not commensurate (13 per cent in one-half hour and 6 per cent in six hours, with only about 1 per cent remaining after 24 hours). No explanation for this discrepancy between protein-bound iodine and I¹³¹ uptake was found. No history of ingestion of interfering medication could be obtained. Needle biopsy of the thyroid showed microfollicles and macrofollicles, but no thyroiditis or parenchymatous hypertrophy.

SUMMARY AND CONCLUSIONS

One hundred tracings of thyroid uptake were analyzed at intervals of 5, 7.5, 10, 15, 20 and 25 minutes after extrathyroidal equilibration of intravenously administered I^{131} , to establish constants for calculations of thyroidal clearance of plasma I^{131} by the method of Berson and colleagues.

In the Berson calculation, a constant of 200 for the plasma I¹³¹/body weight relationship was proposed for the usual 30 minute interval. Our calculated constants for shorter intervals were: 137.3 ± 23.2 (1 SD) at 5 minutes; 147.6 ± 20.3 at 7.5 minutes; 157.2 ± 18.4 at 10 minutes; 168.9 ± 13.6 at 15 minutes; 180.0 ± 9.6 at 20 minutes; and 191.1 ± 6.9 at 25 minutes. For clinical purposes the accuracy is sufficient at 20 minutes, so that we recommend shortening the test on a routine basis to 20 minutes, since the test is most useful in those patients least able to lie quietly, that is, those with Graves' disease.



FIG. 2. THYROIDAL UPTAKE OF I¹³¹ IN 11 PATIENTS WHO CONCENTRATED I¹³¹ IN THEIR THYROIDS INITIALLY BUT SUBSEQUENTLY RELEASED PART OF IT (TABLE II). Uptake is recorded in microcuries of I¹³¹. The abscissa is time in minutes after equilibration of the I¹³¹ in the neck, that is, before actual thyroidal uptake has begun. The test was performed twice on Patient 1: 1a, before giving thyroid-stimulating hormone, and 1b, 24 hours after intramuscular injection of 10 units of bovine thyroid-stimulating hormone. Doses of I¹³¹ given Patient 1a and 1b were 50.0 and 25.0 μ c respectively. Patients 2 through 11 received 23.8, 23.5, 50.5, 52.0, 14.7, 23.8, 22.3, 50.4, 51.5, and 22.4 μ c., respectively.

With short-time constants available, the Berson clearance test may be abbreviated as needed for the convenience of the patient, or as required if the equipment should fail before the standard test is concluded, or as needed for evaluation of the rare patient who traps I^{131} but releases it promptly, presumably still in its inorganic form.

Eleven patients, from among 1,250 studied, exhibited the phenomenon of normal or accelerated thyroidal uptake of I^{131} followed, within the half hour of the Berson test, by reversal of the uptake curve. One patient was a goitrous cretin, one had an iodide goiter, three were receiving propyl-thiouracil or methimazole (Tapazole), and one had been treated with a therapeutic dose of I^{131} . In these six patients, apparently complete block in thyroidal protein-binding of iodine existed; the loss of thyroidal radioiodide reflected the equilibrium between thyroidal and plasma iodide, an equilibrium dominated by the renal excretion of iodide.

The remaining five patients, four with Hashimoto's disease and one with a goiter of undiagnosed type, also exhibited a reversal of I^{131} uptake during the Berson test. Here the explanation is less clear; serum values for protein-bound iodine do not warrant the assumption of a prominent defect of protein-binding of iodine in the thyroid.

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