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DETECTION OF INCOMPLETE ABLATION AFTER YTTRIUM-90 IMPLANTATION OF PITUITARY

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Now that implantation of the pituitary with radioactive material is being widely used, it is of interest and value to have some simple method of determining whether or not pituitary destruction has been complete. Until recently, estimation of urinary gonadotrophins has been considered to be the most reliable test of pituitary destruction (Notter, 1959), but unfortunately it is too sensitive a test of pituitary damage. As little as 50% destruction of the gland can result in failure of significant gonadotrophin secretion.

The experimental work of Ganong and Hume (1956) has demonstrated that secretion of thyrotrophin and corticotrophin continues even although a considerable proportion of the pituitary has been destroyed, and corticotrophin secretion may continue with as little as 5% of the gland left intact. Unfortunately neither of these hormones can be readily assayed direct nor are the methods very sensitive. An indirect estimate of thyrotrophin activity can be obtained by determining the 24- or 48-hour uptake of ^{131}I by the thyroid or by estimating the urinary excretion of ^{131}I and calculating the "T" index. Forrest *et al.* (1960) found that while the values for the T index correlated fairly well with the degree of pituitary destruction, values in the hypothyroid range could be obtained after necrosis of only 50% of the pituitary gland.

Impairment of adrenal function follows deficient secretion of corticotrophin. This may be detected clinically by finding that the patient has become cortisone-dependent, or on cessation of corticosteroids that the patient fails to excrete a water load adequately. The former is not objective enough, the latter non-specific; neither test separates the completely from the incompletely hypophysectomized patient sharply enough, and both put an undue strain on the patient. The latter criticism also applies to the measurement of urinary or plasma steroids after withdrawal of corticosteroid for at least 72 hours. In this test a rise in plasma or urinary steroid level at that time indicates a reserve of corticotrophin. This test can be shortened and the sensitivity possibly increased by administering metyrapone ("metopirone"; SU 4885), the adrenal 11β -hydroxylase inhibitor (Liddle *et al.*, 1959). The purpose of this paper is to show that the metyrapone test

is a satisfactory although indirect method of detecting residual pituitary activity, and that it is much more sensitive in this respect than the best direct means (Loraine, 1962), the estimation of human pituitary gonadotrophin.

Methods

The patients under investigation were admitted one week prior to ^{90}Y implantation of the pituitary. Twenty-four-hour specimens of urine were collected for three days, each collection starting at 6 a.m. On the second day metyrapone was administered every six hours in a dose of 750 mg. Four to six weeks after the implant had been done the patient was readmitted to hospital, 24-hour urine collections being made as before for a period of seven days. On the first day the patient generally continued with cortisone 37.5 mg. and in addition received 80 units of "cortrophin-Zn" intramuscularly in divided doses. Cortisone was discontinued on the second day and a further 80 units of cortrophin-Zn given. Three days were allowed to elapse between the administration of the corticotrophin and the metyrapone, which was given on the sixth day in the same dose as on the previous admission.

A second group of patients, who received no corticotrophin prior to the metyrapone test, were studied. Beta-methasone was given in a dose of 0.5 mg. b.d. for at least two days, then in a dose of 0.5 mg. the day before metyrapone, and stopped completely the day of, and the day after, metyrapone.

The urinary excretion of 17-hydroxycorticosteroids (17-OH-CS) was measured, using a modification of the method described by Appleby *et al.* (1955). In this method urinary 17-OH-CS are finally determined as 17-oxosteroids using the Zimmermann colour reaction. We feel that it is essential to do all the Zimmermann reactions from any one patient at the one time if small changes in steroid excretion are to be detected. Urinary gonadotrophins were measured by the method described by Loraine and Brown (1954).

Results

Patients with breast carcinoma (18), diabetic retinopathy (4), and acromegaly (2) have had pituitary function assessed before and after ^{90}Y implantation of the pituitary.

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Metyrapone Tests after Corticotrophin Stimulation

The results in these patients (14) are given in Table I, and in the Chart are shown four patterns of response or absence of response to metyrapone following the implant. Case 2 had only a fair response to metyrapone before the operation, but after the implant the excretion of 17-OH-CS fell when metyrapone was administered, indicating failure

TABLE I.—Changes in Endocrine Function After ^{90}Y Implant

Case No.	Condition	Urinary Gonadotrophins (HMG Units 24 hr.)		Metyrapone Test	
		Pre- ^{90}Y	Post- ^{90}Y	Pre- ^{90}Y	Post- ^{90}Y
1	Ca.	60	2	++	—
2	Ca.	24	2	++	—
3	Ca.	22	3	++	—
4	Ca.	90	4	++	++
5	Ca.	75	11	++	—
6	Ca.	23	5	++	—
7	Ca.	19	3	++	++
8	Ca.	5	—	++	++
9	Ca.	25	3	++	—
10	Ca.	37	9	+	—
11	Ca.	100	3	+	—
12	D.R.	5	3	++	±
13	D.R.	—	—	++	—
14	D.R.	49	16	++	++

Ca = Mammary carcinoma. D.R. = Diabetic retinopathy. ++ indicates a good response to metyrapone; + indicates a fair but significant response.

Effect of metyrapone before and after ^{90}Y implantation of the pituitary in four patients with breast carcinoma or diabetic retinopathy.

of corticotrophin secretion by the pituitary. In contrast to this is the result in Case 5, in which a significant rise of 17-OH-CS occurred when metyrapone was administered after the pituitary implantation, although the response was less than it had been before the operation. This result is evidence of incomplete destruction of the pituitary, as corticotrophin is still being secreted.

Interpretation of the results is much more difficult if there is still a high 17-OH-CS excretion on the third day after A.C.T.H., as with Case 12. The steroid excretion remained about the basal level during the metyrapone test, but nevertheless continued to fall. It is not possible in such a case to be certain whether the continuing raised steroid excretion is due to the continuing effect of exogenous A.C.T.H. or to the secretion of corticotrophin by the pituitary. The latter possibility seems unlikely in this instance, for on histological examination of the pituitary 99% was seen to be destroyed. A delayed A.C.T.H. response was obtained in Case 13, but there was a marked reduction in 17-OH-CS excretion after metyrapone, so that probably corticotrophin secretion did not occur.

Two other cases had a high 17-OH-CS excretion on the third day after receiving A.C.T.H. In one (Case 14) there was undoubtedly a response to metyrapone, but in the other (Case 10) the 17-OH-CS excretion was only slightly above the basal level during the test period. However, incomplete pituitary destruction was confirmed by finding a significant excretion of gonadotrophins. The other cases studied showed a definite response to metyrapone in four instances, and a failure to respond in another four.

Metyrapone Test without Previous Corticotrophin Stimulation

It may not be essential to stimulate the adrenal with corticotrophin before doing the second metyrapone test. Adrenal atrophy is probably not gross after four to six weeks of maintenance doses of cortisone, especially if there is still some residual pituitary activity. We therefore tested the pituitary-adrenal function in 10 patients without stimulating the adrenal prior to the second metyrapone test, to see whether residual pituitary activity could be detected under these conditions (Table II). Five of these patients

TABLE II.—Metyrapone Tests Without Previous Corticotrophin Stimulation

Case No.		Time of Test	Urinary Gonadotrophins (HMG Units/ 24 hr.)	Metyrapone Test (17-OH-CS mg./24 hr.)						Response
				Basal	Metyrapone					
					1st Day	2nd Day	1st Day After	2nd Day After		
15	Ac.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y	150 3	5.3 5.2	20.3 11.6	76.3	36.4 28.1	22.5 17.9	++ ++	
16	Ac.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y	35 3	13.1 6.8	18.1 3.7	22.1	13.7 4.9	7.8 8.2	+ ±	
17	Ca.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y	19 3	11.0 3.6	28.8 9.9		49.4 12.5	38.8 8.7	++ +	
18	Ca.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y	130 3	4.2 15.3	9.9 8.5		19.7 7.4	14.8 5.4	++ —	
19	Ca.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y	26 3	10.6 6.9	17.3 3.7		18.0 3.5	14.2 2.7	+ —	
20*	D.R.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y		7.0 9.1	7.4 10.0		14.9 19.3	9.4 10.3	+ +	
21*	Ca.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y		21.1 <1	30.6 3.3		53.3 7.1	32.1 16.7	++ +	
22*	Ca.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y		6.4 2.8	9.7 3.5		23.4 6.4	15.8 7.0	++ +	
23*	Ca.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y		21.3 1.2	39.7 2.4		111.4 4.0	84.1	+++ ±	
24*	Ca.	{ Pre- ⁹⁰ Y Post- ⁹⁰ Y		11.3 4.2	41.9 1.9		53.0 1.4	20.1 1.2	++ —	

Ac = Acromegaly.

*These patients had their pituitaries implanted with ^{90}Y by Mr. J. F. Philip or Mr. D. W. Blair, Aberdeen Royal Infirmary. The dose of metyrapone used in their tests was 750 mg. four-hourly, whereas for the others it was 750 mg. six-hourly.

showed definite responses to metyrapone after pituitary implantation.

Urinary Gonadotrophins

Seventeen of the 24 patients had urinary gonadotrophins estimated before and after pituitary implantation (Tables I and II). Another patient (Case 8) had an initial level so low as not to warrant a repeat estimation post- ^{90}Y . Only three showed significant levels after the implant—that is, more than 6 human menopausal gonadotrophin units per 24 hours—and these three patients all responded to metyrapone. Another six patients, while showing a response to metyrapone, did not excrete significant amounts of gonadotrophins. These results indicate that the metyrapone test is superior to an estimation of urinary gonadotrophins for detecting residual pituitary activity.

Histology

Pituitaries from four patients investigated in the present series were examined histologically, as described by Forrest *et al.* (1959). Two patients (Cases 8 and 9) had 80% destruction of the gland and both had a definite response to metyrapone. A third patient (Case 1) with 80% destruction showed no response to metyrapone. The findings in the fourth patient (Case 12) are discussed above.

Discussion

In our series of patients subjected to pituitary irradiation, only 3 out of 17 showed significant levels of urinary gonadotrophins after treatment, although of these 17 9 showed definite, and 2 (Cases 12 and 16) possible, evidence of corticotrophin secretion. It would appear from these results that the metyrapone test is the more sensitive test in detecting incomplete pituitary destruction.

It has been difficult to decide which is the best scheme for the metyrapone test. Originally Liddle *et al.* (1959) suggested that in cases of hypopituitarism corticotrophin should be given prior to the test. In cases of recent pituitary destruction this is probably unnecessary and undesirable, since previous corticotrophin stimulation impairs the subsequent responsiveness of the pituitary-adrenal axis to metyrapone (Solem and Brinck-Johnsen, 1961; Plager and Cushman, 1962; Brownie and Sprunt, 1962) and might make detection of minimal residual pituitary activity more difficult. Other advantages are the shorter duration of the test, and the easier recognition of a response to metyrapone. It is important that betamethasone be given for several days before the test, otherwise continuing excretion of the metabolites of cortisone may mask the response, in the same way as did a continuing response to corticotrophin.

Although the schemes for testing pituitary reserve of corticotrophin outlined in this paper may not be ideal, there is no doubt that they are superior as a test of residual

pituitary function to the measurement of urinary gonadotrophins. Our results would indicate that the proportion of completely destroyed pituitaries in our series is lower than that reported by Forest *et al.* (1959). One reason for this may be the smaller dose of ^{90}Y (9.0 mc.) used in most of our cases. Forrest *et al.* (1959) found virtually complete destruction with a dose of 14 mc., although their tests were probably not as sensitive as the metyrapone test. However, with the lower dose the incidence of diabetes insipidus is greatly reduced and there is no appreciable visual upset.

Summary

Until recently the measurement of urinary gonadotrophins was the most reliable test for the detection of residual pituitary activity, especially in post-menopausal women. We have found it to be less sensitive than the metyrapone test.

In the present series metyrapone was given in a dose of 750 mg. either four-hourly or six-hourly for 24 hours, both before and after implantation of the pituitary with 9 mc. of yttrium-90, and the pituitary-adrenal response assessed by measuring urinary 17-OH-CS. On testing with metyrapone, 9 out of 17 patients showed definite evidence of residual pituitary activity after implantation, but only three of these showed significant levels of urinary gonadotrophins.

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