Summary

A case of post-operative hypotension due to paroxysmal atrial tachycardia with block is described. It was due to digitalis intoxication in the presence of potassium deficiency, and the possible aetiological factors include the normal metabolic response to trauma.

We wish to thank Dr. J. A. Strong and Mr. C. W. A. Falconer for permission to describe this case.

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PITUITARY-ADRENAL FUNCTION IN CASES OF PITUITARY TUMOUR

BY

VINCENT MARKS,* M.A., B.M., M.R.C.P.Ed.

MARGARET SUMMERS, B.Sc.

Department of Chemical Pathology, National Hospital, Queen Square, London

The technical difficulty of measuring adrenocorticotrophin (A.C.T.H.) accounts to a large extent for the paucity of reliable information on the incidence of impaired pituitary-adrenal function in patients with pituitary "chromophobe" adenoma† despite its obvious clinical importance. Clinical and biochemical differences between primary and secondary adrenal insufficiency, possibly complicated by abnormalities of gonad, thyroid, and somatotrophic function, make interpretation of standard laboratory procedures for adrenal function difficult or impossible.

Adrenal insufficiency may develop as part of the syndrome of panhypopituitarism, but this is uncommon with pituitary chromophobe adenoma. Most patients with pituitary adenoma first present with visual failure; clinical evidence of endocrine dysfunction, either objective or symptomatic, is seldom pronounced (Younghusband *et al.*, 1952; Nurnberger and Korey, 1953; Troen and Rynearson, 1956). More particularly, the classical features of Addison's disease—that is, cutaneous pigmentation, muscular weakness and wasting, anorexia, gastro-intestinal upsets, cramps, asthenia, hypotension, hypoglycaemia, and abnormalities of electrolyte balance—are rare. Tests of carbohydrate metabolism and measurement of urinary steroids are often normal, but water diuresis, a more sensitive but non-specific index of pituitary-adrenal function, is frequently impaired (Jefferson, 1957b; Heimbach, 1959). At post-mortem examinations the adrenals more often appear normal in size or large than small and atrophied (Russfield *et al.*, 1956).

In an attempt to obtain more specific information concerning pituitary-adrenal function in cases of pituitary adenoma we have used a metyrapone ("metopirone"; SU 4885) test. Our results in 15 patients with pituitary tumour and in five with suprasellar tumours are recorded here.

Material

Fifteen patients with intrasellar-space-occupying lesions were investigated (Table I). The youngest was aged 13 years and the oldest 69. All but three (Cases 13, 14, and

15) were previously untreated. In 10 the histological examination of the tumour confirmed the diagnosis of pituitary adenoma. In the remainder the presumptive diagnosis of pituitary adenoma was made on the physical signs and demonstration of typical changes in the x-ray picture of the skull and by air-contrast radiography. Admission to hospital of 14 patients was dictated by the onset of neurological signs and symptoms—generally visual failure; endocrine features were not a major cause of symptoms. Patient No. 15 was admitted to hospital for assessment of endocrine status prior to replacement therapy after treatment by partial pituitary adenectomy two years earlier.

Patients with pituitary tumour were classified on physical appearance as suggested by Mogenson (1957): those whose physical appearance is normal are called "normocrine"; those with characteristic skin pallor, absent pubic, axillary, and body hair, and in males scanty facial hair, are called "hypocrine." In the present series 11 patients were normocrine, two hypocrine, and two acromegalic.

Five patients with suprasellar-space-occupying lesions and chiasmal compression were investigated (Table II). Prior to diagnosis by exploration, or by air-contrast radiography, pituitary adenoma was in each case considered in the differential diagnosis.

Fourteen control subjects studied were hospital in-patients of comparable age, with varying degrees of debility, but without pituitary disease or other primary endocrine disorders (Table III).

Metyrapone Test

The test (Marks, 1962) was carried out in hospital, though subjects were not confined to bed unless this was otherwise indicated. Consecutive 24-hour urine samples were collected for seven days, using 2–5 ml. of chloroform as preservative. Urine samples were analysed for creatinine (King and Wootton, 1956), neutral 17-keto-steroids (17-KS) and 17-ketogenic steroids (17-KGS) (Norymberski *et al.*, 1953), and total 17-hydroxycorticosteroids (17-OHCS) (Appleby *et al.*, 1955). Mean daily creatinine excretion during the period of observation was designated a creatinine day. Daily urinary steroid excretions were expressed as milligrams of steroid per creatinine day. Despite certain theoretical objections, this method of

*Present address: Area Laboratory, at West Park Hospital, Epsom, Surrey.

†Pituitary adenomas are traditionally classified on histological grounds as chromophobe, eosinophil, or basophil. The chromophobe adenomata are now recognized as being a heterogeneous group; many appearing not to be "chromophobe" with new staining techniques.

expressing results has been found to provide the most satisfactory index of metyrapone responsiveness, partly because errors in the timing and collection are minimized, but possibly also because it reflects physiological variations from day to day.

Urine collected on Days 1 and 2 permitted basal excretions to be measured. Metyrapone base (enteric-coated capsules: 0.25 g. each) was given in divided doses every six hours for eight doses on Days 3 and 4. The usual dose of metyrapone was 3 g./day; this was arbitrarily decreased to 2 g./day in grossly underweight subjects, and increased to 4.5 g./day in grossly obese subjects. No drugs were given on Day 5 of the test. On Days 6 and 7 commercial crystalline bovine A.C.T.H. (40 units) was given by intramuscular injection 12-hourly for four doses. In some cases A.C.T.H. administration was omitted.

The maximum rise in urinary steroids above basal during administration of metyrapone—that is, Day 3, 4, or 5—was designated the metyrapone response.

Side-effects from metyrapone was slight. The commonest was dizziness occurring half to one hour after taking the capsules, becoming increasingly severe with succeeding doses. This complication was neither severer nor commoner in patients with pituitary dysfunction than in control subjects, and was never encountered when subjects remained recumbent for two hours after each dose of metyrapone. Severe complications necessitating abandoning the test were not experienced. Nevertheless, as a precaution against the possibility of Addisonian crisis occurring, intravenous hydrocortisone (100 mg.) was kept readily available for rapid termination of the test should this be necessary.

There is considerable confusion in the literature concerning the interpretation of the metyrapone test. This is due partly to the large variety of metyrapone tests which have been advocated and partly to the choice of control subjects. Metyrapone has been given at fixed dosage or

according to body weight; by intravenous infusion or orally; for one day or for two. The adrenal response has been measured in blood or urine; as a rise in Porter-Silber chromogen, as ketogenic steroids, or as total 17-OHCS. Some authors express the response to metyrapone as a percentage increase in urinary steroids over basal levels, others as the absolute rise in steroid values. The manufacturers of metopirone themselves have advised that with "the present stage of knowledge only gross variations in steroid excretions can be regarded as significant in interpreting the results of the metopirone test."

Few authors have distinguished between a diminished metyrapone response due to age and general ill-health from that due specifically to impaired pituitary function. The control subjects in the present study were chosen from among a hospital population as providing a group more

TABLE III.—*Urinary 17-OHCS mg./day. Fourteen Patients Without Endocrine Disease (Control Subjects)*

Case No.	Sex and Age	Diagnosis	Urinary 17-OHCS (mg./day)		
			Basal Excretion	Rise Above Basal	
				Metyrapone Response	A.C.T.H. Response
21	M 40	Chronic schizophrenia	10.6	49.0	10.0
22	F 63	Osteoporosis	5.8	43.0	56.0
23	M 52	Chronic schizophrenia	9.4	44.0	14.0
24	M 47	"	8.3	30.0	15.0
25	F 35	Obesity	15.6	28.0	
26	M 78	Neurofibromatosis	11.0	27.0	
27	F 32	Anorexia nervosa	5.6	26.0	
28	M 38	Chronic schizophrenia	7.5	20.0	10.0
29	F 30	Anorexia nervosa	7.8	17.5	70.0
30	F 44	Neurofibromatosis	8.3	17.7	29.0
31	F 36	Depression	4.9	14.6	58.0
32	F 44	Pulmonary T.B.	5.3	10.7	39.0
33	F 23	Undetermined	7.0	10.2	61.0
34	M 45	Obesity	9.5	10.5	

TABLE I.—*Fifteen Patients with Pituitary Adenoma*

Case No.	Sex and Age	Clinical Classification	Basis for Diagnosis	Water Diuresis (% of 1,500 ml. Water Load Excreted in 5 hr.)	Urinary 17-OHCS (mg./day)			Comments
					Basal Excretion	Rise above Basal		
						Metyrapone Response	A.C.T.H. Response	
1	F 46	Normocrine	Histological	92	8.2	15.3	82.0	Menopause at age 45 Lobectomy for carcinoma of lung 2 years ago Diabetes for 6 years
2	M 61	"	Radiological	111	11.2	18.0	79.0	
3	M 54	"	"	106	6.0	10.0		
4	F 45	"	Histological	17	8.6	9.4		Taller than average for age. No sexual development
5	M 13	"	"	45	5.5	10.0		
6	M 64	"	"	80	10.7	3.0	34.0	
7	M 60	Hypocrine	"		2.7	2.1	36.0	Appearance suggestive of myxoedema; but B.M.R. = 100%, ¹³¹ I-uptake = 35%
8	M 52	Normocrine	"	40	5.7	1.5	48.0	
9	M 62	"	"	17	4.2	1.0		
10	M 37	"	"		5.6	0.0	16.0	Looked and felt generally unwell Prostatectomy 7 years ago for benign prostatic hypertrophy Acromegaly 10 years + syringomyelia 10 years DXR to pituitary tumour 16 years ago
11	M 69	"	"	23	9.5	0.0		
12	M 50	Acromegalic	Radiological	68	10.7	20.0	47.0	
13	F 55	"	"	92	3.2	4.5	65.0	" "
14	M 47	Normocrine	"		11.4	9.6	28.0	
15	M 40	Hypocrine	Histological	48	1.8	4.5	14.0	

TABLE II.—*Five Patients with Suprasellar Tumours*

Case No.	Sex and Age	Basis for Diagnosis	Water Diuresis (% of 1,500 ml. Water Load Excreted in 5 Hours)	Urinary 17-OHCS (mg./day)			Comments
				Basal Excretion	Rise above Basal		
					Metyrapone Response	A.C.T.H. Response	
16	M 34	Surgical (no biopsy)		7.8	27.0		Muscular dystrophy for many years
17	M 63	Histological	120	6.0	21.0		Craniopharyngioma
18	F 39	Radiological	70	15.6	19.0		24 weeks pregnant: probably craniopharyngioma
19	F 60	"		10.1	19.0	35.0	Probably craniopharyngioma
20	F 33	Histological		9.2	19.0		Granuloma of base of brain involving chiasma

readily comparable with those in whom the metyrapone test has clinical application. Brownie and Sprunt (1962), using a similar metyrapone test, found in a group of healthy young subjects much larger metyrapone responses than we observed in our control patients without endocrine disease.

Liddle *et al.* (1959) gave metyrapone orally for one day, or by intravenous infusion. These authors did not rigidly define their terms "limited pituitary reserve," but from their published data this appears to have been equated with a smaller than 5 mg. rise in urinary Porter-Silber chromogens (Porter and Silber, 1950). In a later account Liddle *et al.* (1962) state that "a minimum response is considered to be one in which 17-OHCS (Porter-Silber chromogens) rise above control values either by a twofold factor or by 10 mg./day." Gold *et al.* (1960) showed that urinary 17-KGS increased twice as much as Porter-Silber chromogens with metyrapone. Using an intravenous infusion technique, they found a mean rise in 17-KGS of 18.1 mg./24 hours in four normal men and of 10.6 mg. in six healthy women. Gold *et al.* (1961) considered a metyrapone response of less than 6 mg. of 17-KGS/24 hours as indicating impaired pituitary adrenal function. Arguelles *et al.* (1962) have shown that false-negative responses to metyrapone can be obtained when urinary steroids are measured as ketogenic steroids instead of as total 17-OHCS. The smallest metyrapone response (measured as 17-OHCS) observed in normal subjects by these workers was 10.4 mg./day.

Solem and Brinck-Johnsen (1961) stated that the response to metyrapone was "evaluated as much by when the increase in 17-OHCS begins to occur as by the extent of the absolute maximum increase." In the present study the maximum rise in urinary steroids, in all groups, most often occurred on the second metyrapone day (Day 4), but in three of the control and in four of the pituitary adenoma patients the maximum response was delayed until Day 5. A delayed response to metyrapone was also observed in patients without pituitary disease by Brownie and Sprunt (1962), from which it appears that the delayed responsiveness is in itself not indicative of impaired pituitary function.

For the purpose of discussion we have considered a metyrapone response of less than 10 mg./day (total 17-OHCS) in any subject to indicate specific impairment of pituitary-adrenal function. We, in common with others, have not attempted to allow for differences in body weight, age, or sex—factors which undoubtedly influence the extent of the metyrapone response.

Results

Mean basal steroid excretion values and the metyrapone responses for each of the classes of steroids measured in the pituitary adenoma, suprasellar tumour, and control groups are shown in Table IV.

The metyrapone response was greatest when expressed as rise above basal of total 17-OHCS excretion. Urinary 17-KGS showed changes similar to but smaller than 17-OHCS, confirming the observation of Arguelles *et al.* (1962).

Several subjects, controls as well as patients, showed little or no rise in 17-KS with metyrapone. Gennes *et al.* (1961) have also found that the excretion of 17-KS was hardly changed by metyrapone though consistently increased by A.C.T.H.

Changes in urinary 17-KS and 17-KGS therefore give no more clinically useful information in the metyrapone test than can be derived from analysis of total 17-OHCS and may, as shown by Arguelles *et al.* (1962), be misleading.

The minimum metyrapone response observed in control subjects during the present study was 10.2 mg./creatinine day (Table III). One obese subject who received only 3 g. of metyrapone instead of a more appropriate dose of 4.5 g. showed an only slightly greater rise than the minimum. In none of the five patients with suprasellar-space-occupying lesions was the metyrapone response less than 10 mg./creatinine day.

In 10 of the 15 patients with pituitary adenoma the metyrapone response was under 10 mg./day; in two, metyrapone produced no discernible rise in any of the urinary steroids.

Basal excretion of all classes of steroids was slightly but not significantly lower in the patients with pituitary tumour than in either control patients or those with suprasellar lesions. There was no correlation between basal steroid excretion and metyrapone response (Table I) in any group.

A water-diuresis test (Marks and Hornabrook, 1960) was carried out routinely in patients with pituitary tumour, the results of which agreed well with those given by metyrapone. In two of three patients responding to metyrapone the water-diuresis test was normal; in the third, an acromegalic, it was equivocal. Of seven patients not responding to metyrapone only two, one of whom was acromegalic, gave a normal water diuresis.

There was in every case a prompt rise in urinary steroids after A.C.T.H. This occurred even when the metyrapone response was grossly impaired or absent.

Discussion

The present investigation confirms the clinical usefulness of the metyrapone test, which offers, for the first time, a means of recognizing "limited pituitary adrenal reserve" (Liddle *et al.*, 1959; Solem and Brinck-Johnsen, 1961; Gold *et al.*, 1961; Brownie and Sprunt, 1962). It also confirms the observations (Gold *et al.*, 1961) that basal urinary steroid excretion is an inadequate and misleading index of pituitary-adrenal function in patients with pituitary neoplasms.

Troen and Rynearson (1956), using urinary steroid excretion as their major criterion, reported absence of

TABLE IV.—Mean Basal Steroid Excretion and Metyrapone Response in Patients Studied

	No. of Cases	Control			Metyrapone Response		
		Mean Steroid Excretion mg./day			Mean Rise Above Basal mg./day		
		17-OHCS	17-KGS	17-KS	17-OHCS	17-KGS	17-KS
Pituitary tumours .. {	15	7.0 (1.8-11.4)	4.9 ⁽¹¹⁾ (0.7-9.8)	4.9 (0.3-9.8)	7.2	5.6 ⁽¹¹⁾ (0-22.0)	3.6 (0-21.0)
Suprasellar tumours .. {	5	9.7 (6.0-15.6)	9.4 ⁽⁴⁾ (7.1-12.0)	6.5 (3.0-12.8)	21.0 (19-27)	13.0 ⁽⁴⁾ (11.2-15.9)	5.0 (0-8.8)
Controls .. {	14	7.8 (4.9-15.6)	5.1 ⁽⁵⁾ (3.5-6.7)	5.4 (1.3-13.1)	25.0 (10.2-49.0)	16.0 ⁽⁵⁾ (10.3-26)	7.2 (1.4-16.0)

Suffix indicates number of cases examined when less than the total. Figures in parentheses are limits observed.

significant anterior pituitary insufficiency in 97 of 163 cases of pituitary adenoma prior to operation. They reported varying degrees of pituitary dysfunction, ranging from mild (41 cases) to severe hypopituitarism (25 cases) in the remainder.

Liddle *et al.* (1959) found limited pituitary-adrenal reserve in six out of nine patients with pituitary chromophobe adenoma. In a series of nine patients with chromophobe adenomas studied prior to treatment by Gold *et al.* (1961) only one responded normally to metyrapone. Only 2 of the 11 previously untreated patients with chromophobe adenoma reported here gave a normal metyrapone response. Thus, of 29 patients examined pre-operatively, only 5 (17%) showed intact pituitary-adrenal function on the basis of their response to metyrapone.

The results of the metyrapone test in patients with acromegaly have shown limited pituitary-adrenal reserve in 28% of the 14 cases examined (Liddle *et al.*, 1959; Gold *et al.*, 1961; present series), a much lower incidence than with chromophobe adenoma.

Although all types of suprasellar-space-occupying lesions can occasionally cause panhypopituitarism, none in the present series of five patients showed impaired pituitary-adrenal function. It is perhaps relevant that all were adults, in whom the association of hypopituitarism with suprasellar tumour is far less common than in children.

Gold *et al.* (1961) studied the response to metyrapone in five patients with tumours in or around the base of the brain. The response was normal in three in whom the hypothalamus was uninvolved and subnormal in two in whom the hypothalamus was encroached upon. Oppenheimer *et al.* (1961) studied the response to metyrapone in five patients with suprasellar-space-occupying lesions. Four responded normally, one abnormally. Hökfelt and Luft (1959) interpreted the metyrapone response as normal in three of four patients with suprasellar-space-occupying lesions.

The aetiology of impaired pituitary-adrenal function in pituitary adenoma is uncertain. It is generally believed to result from destruction of normal hypophysial tissue by non-secretory adenoma cells, but this view has been challenged (Russfield *et al.*, 1956).

Recently an alternative hypothesis—namely, that pituitary adenomata develop in response to a pre-existing endocrine abnormality—has received support (Russfield *et al.*, 1956; Caughey, 1957; Jefferson, 1957a; Marks, 1959; Van Wyk and Grumbach, 1960).

The data presented here are consistent with this hypothesis. Adrenal function is not impaired until late in surgical or necrotic destructive lesions of the pituitary both in animals and in man (Hubble, 1952; Ganong and Hume, 1956; Van Buren and Bergenstal, 1960) long after gonadotrophic, thyrotrophic, and somatotrophic function has already been impaired. In patients with pituitary chromophobe adenomata, on the other hand, pituitary-adrenal dysfunction is among the earliest and most constant abnormalities. This makes it appear probable that in some cases defective A.C.T.H. secretion, either alone (Cleveland *et al.*, 1960; Odell *et al.*, 1960) or in combination with defective gonadotrophic secretion (Maddock *et al.*, 1953), precedes and predisposes to pituitary tumour formation. Unquestionably, many of the patients who subsequently develop pituitary chromophobe adenomata resemble in their physical appearance, during the often long prodromal period (Jefferson, 1957a), the patients with selective

pituitary, A.C.T.H., and gonadotrophic dysfunction described by Maddock *et al.* (1953).

Summary

A metyrapone test was used to assess pituitary-adrenal function in 15 patients with pituitary adenoma. Ten showed impaired pituitary function, sometimes as the only manifestation of pituitary insufficiency. Measurement of basal-steroid excretion is a poor index of pituitary-adrenal function; the water-diuresis test is sensitive though non-specific.

Five adults with suprasellar-space-occupying lesions were studied. None had impaired pituitary-adrenal function.

The possibility that impaired pituitary-adrenal function might precede pituitary adenoma formation is discussed.

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