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MEASUREMENT OF THE ADRENAL CORTEX RESERVE USING DEPOT β^{1-24}-CORTICOTROPHIN. II — IN THYROID DISEASES *

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SUMMARY

Mean plasma cortisol 4 to 6 hours after 1 mg Synacthen Depot in normal subjects, simple goiter and hypothyroidism were not significantly different. On the contrary after stimulation cortisol levels in untreated hyperthyroidism were significantly below than those of normals and significantly higher than those of primary and secondary hypoadrenalism. After several injections of Synacthen Depot 6 cases of hyperthyroidism showed reduced adrenal reserve. The study of adrenal reserve in hyperthyroidism after 1 to 14 months of methimazole shows a tendency of the adrenal reserve to improve with time. These observations led the author to the belief that the reduced adrenal reserve in this situation must be due mainly to a direct effect of thyroid hormones upon the adrenal cortex.

There has been much discussion about the action of thyroid hormones upon the adrenal cortex and cortisol metabolism. Studies in laboratory animals have shown that high levels of thyroid hormones induce adrenal hyperthrophy, whereas low levels cause atrophy (Money 1954; Fregly et al 1962). The majority of authors believe that the thyroid hormones influence the adrenal cortex and increase the peripheral catabolism of corticosteroids (Brown et al 1958; Peterson 1958 and 1959). This increased corticosteroid catabolism appears to be due to greater reduction of the A-ring of steroids, to increased activity of glucose-6-phosphate dehydrogenase and to a rise in 5 α-reductase in the liver microsomes (Tomkins and McGuire 1960); according to other authors, there is also an increased oxidation of C-11 hydroxyl radical (Hellman et al 1961). In hyperthyroidism the binding level of plasma 17-OHCS (Brown et al 1958) and the level of cortisol secretion (Cope and Black 1958; Peterson 1958) are increased, with a rise in the urinary excretion of corticosteroids and their metabolites (Peterson 1958; Felber et al 1959; Hellman et al 1961; Martin and Mintz 1965; Kenny et al 1967). However, plasma 17-OHCS and cortisol levels were normal (Levin and Daughaday 1955; Peterson 1958; Pittman 1971). There was an increase in the speed of disappearance of an injected dose of cortisol (Levin and Daughaday 1955; Brown et al 1958; Peterson 1958; Beisel et al 1964). In one study the levels of ACTH in plasma were measured and found to be raised in hyperthyroidism (Hilton et al 1962).

The reverse changes were found in patients with hypothyroidism: there was reduced catabolism of corticosteroids, with a fall in urinary steroid excretion (Levin and Daughaday 1955; Peterson 1958; Felber et al 1959; Hellman et al 1961; Martin and Mintz 1965; Kenny et al 1967) but normal plasma levels of corticosteroids. There was reduction of cortisol secretion (Peterson 1958) and decrease of cortisol clearance (Peterson 1958; Beisel et al 1964).

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These changes reverted to normal when the hyper or hypothyroidism was treated (Peterson 1958; Lessof et al 1969).

It was found that levels and binding capacity of corticosteroid-binding globulin (CBG) were normal in both hypo and hyperthyroidism (Doe et al 1964; Beisel et al 1964).

According to Pittman (1971), the stimulation of the adrenals by ACTH increases the abnormalities of cortisol metabolism which are present under basal conditions, in patients with thyroid dysfunction. Thus, after the administration of ACTH there was increased excretion of 17-OHCS in the urine of patients with hyperthyroidism and a reduction in those with hypothyroidism (Martin and Mintz 1965). On the contrary, stimulation of plasma 17-OHCS was below normal in hyperthyroidism and greater than normal in hypothyroidism (Brown et al 1958; Pittman 1971). However, Felber et al (1959) found in hyperthyroidism a normal response of urinary 17-OHCS in the first day of ACTH administration, with no increase during the second day of treatment with ACTH. These workers classified patients with hypothyroidism into two groups: the first group had a subnormal response during the two days of infusion, whereas the second group had a normal response on the first day and a greater-than-normal response on the second day. In the investigation reported by Havard et al (1970), the adrenals exhibited a normal response to ACTH stimulation.

A normal response to metyrapone in patients with hyperthyroidism was described by Liddle et al (1962) and Kowal and Soffer (1963), although some patients had a subnormal response (Gold et al 1961; Brownie and Sprunt 1962). This test, however, is difficult to interpret in hyperthyroidism, as in this condition there is not always a total inhibition of 11 β-hydroxylase (Brownie and Sprunt 1962).

Jackson et al (1966) showed that the majority of patients with hyperthyroidism had a normal response to insulin-induced hypoglycaemia, although some individual patients had a reduced response.

The purpose of the present study was to measure the adrenal reserve, with the 4-6 hours Synacthen Depot test as described by us elsewhere (Galvão-Teles et al 1971; Galvão-Teles 1979) in patients with different thyroid diseases.

MATERIAL AND METHOD

SUBJECTS STUDIED

Patients with simple goiter — 16 euthyroid patients.

Patients with hypothyroidism — 13 patients: 10 with primary hypothyroidism, 3 with isolated TSH deficiency.

Patients with hyperthyroidism — 25 patients in 3 groups: group 1 — 17 patients studied before treatment; group 2 — 8 patients treated with methimazole (30--20 mg/day) for between 1 to 5 months: 5 were in the first group and 3 had not been studied before the initiation of treatment; group 3 — 12 patients treated with methimazole (20-15 mg/day) for between 6 to 14 months: 7 were also in group 1 and 5 out of this 7, also in group 2.

The results on these groups with thyroid diseases were compared with those found in normal subjects, in patients with primary adrenal insufficiency and secondary adrenal insufficiency, published by us in another paper (Galvão-Teles 1979):

Normals — 87 subjects, 21 males and 66 females, aged 18 to 64 years.

Primary adrenal insufficiency — 17 patients: 13 with Addison's disease and 4 with total bilateral adrenalectomy on corticosteroids.

Secondary adrenal insufficiency — 21 patients: 14 on steroids, 6 with panhypopituitarism and 1 with isolated ACTH deficiency.

The patients were not taking any drugs but those mentioned.

PROTOCOL AND METHOD

Details of the protocol and the method for the measurement of plasma cortisol (11-hydroxycorticosteroids — 11-OHCS) are given in our previous paper (Galvão-Teles 1979).

RESULTS

There was no significant difference in plasma cortisol levels of normal subjects (mean ± SD: basal — 20.9 ± 6.39 μg/100 ml; 4 to 6 hours — 62.9 ± 12.26 μg/100 ml) of patients with simple goiter (basal — 16.9 ± 5.92 μg/100 ml; 4-6 hours — 58.9 ± 9.60 μg/100 ml) and of patients with hypothyroidism (basal — 19.5 ± 5.21 μg/100 ml; 4-6 hours — 62.3 ± 15.44 μg/ml) (Table 1; Fig. 1).

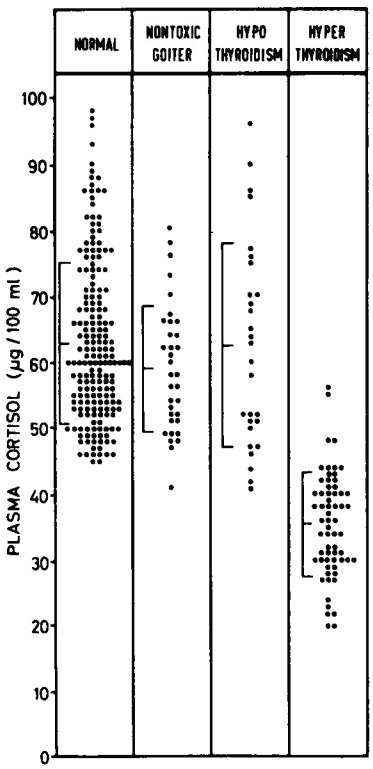

Fig. 1 — *Plasma cortisol 4-6 hours after Synacthen Depot in normal group, in group with simple goiter and in patients with hypo-and hyperthyroidism without treatment (means ± SD)*

Table 1

Plasma cortisol (basal and 4-6 hours after Synacthen Depot) in all groups. n-number of determinations

GROUP		PLASMA CORTISOL (μg/100 ml)	
		BASAL	4 — 6 H
NORMAL	mean ± SD	20.9 ± 6.39	62.9 ± 12.26
	(range)	(4 — 32)	(45 — 98)
	(n)	(94)	(188)
ADDISON'S DISEASE	mean ± SD	8.8 ± 4.51	9.8 ± 3.67
	(range)	(3 — 20)	(4 — 20)
	(n)	(26)	(45)
SECONDARY ADRENAL INSUFFICIENCY	mean ± SD	9.0 ± 6.44	21.3 ± 12.65
	(range)	(1 — 26)	(3 — 52)
	(n)	(30)	(47)
SIMPLE GOITER	mean ± SD	16.9 ± 5.92	58.9 ± 9.60
	(range)	(4 — 28)	(41 — 80)
	(n)	(16)	(34)
HYPOTHYROIDISM	mean ± SD	19.5 ± 5.21	62.3 ± 15.44
	(range)	(13 — 31)	(41 — 90)
	(n)	(12)	(28)
HYPERTHYROIDISM	mean ± SD	13.6 ± 10.43	35.3 ± 7.77
	(range)	(2 — 29)	(20 — 56)
	(n)	(32)	(63)
HYPERTHYROIDISM 1-5 Month's Treatment	mean ± SD	13.9 ± 6.29	38.9 ± 13.82
	(range)	(3 — 24)	(22 — 62)
	(n)	(9)	(18)
HYPERTHYROIDISM 6-14 Month's Treatment	mean ± SD	13.7 ± 4.16	44.1 ± 13.66
	(range)	(5 — 21)	(13 — 82)
	(n)	(15)	(29)

Thirty two Synacthen Depot tests were carried out in 17 patients with untreated hyperthyroidism (group 1). The basal values of plasma cortisol in this group of patients (mean±SD: 13.6±10.43 μg/100 ml) were significantly below those of normals (p less than 0.001) and significantly higher than those of the group with Addison's disease (8.8±4.51 μg/100 ml) (p less than 0.05). There was no difference between the basal values of the group with hyperthyroidism and those of the group with secondary adrenal insufficiency (9.0 ± 6.44 μg/100 ml) (Table 1). The mean (± SD) of plasma cortisol levels 4 to 6 hours after the injection in the hyperthyroid group was 35.3±7.77 μg/100 ml (range 20 to 56) (Table 1; Fig. 1). These values are significantly lower than those of the normal group, of patients with simple euthyroid goiter and of hypothyroid patients (p less than 0.001). On only 4 occasions in three patients were levels of plasma cortisol at the lower limit of normal range (45 μg/100 ml): in all other cases the

plasma cortisol was below normal. The levels of plasma cortisol reached after the injection of Synacthen Depot in the group with hyperthyroidism were significantly higher than those in the groups with Addison's disease (mean ± SD: 9.8 ± 3.67 μg/100 ml) (p less than 0.001) and with secondary adrenal insufficiency (mean ± SD: 21.3 ± 12.65 μg/100 ml) (p less than 0.001). There was no overlap of individual plasma cortisol values in patients with hyperthyroidism and in those with Addison's disease. On the other hand, there was much overlap of individual values in the groups with hyperthyroidism and with secondary adrenal insufficiency respectively.

In order to explore the possibility of recovery by the adrenal cortex after repeated stimulation with ACTH, injections of 1 mg Synacthen Depot were given at 48-hour intervals to 6 of the 17 patients with hyperthyroidism (Fig. 2). Each dot on the curve represents the highest level of plasma cortisol 4 or 6 hours after the injections of Synacthen Depot.

In patient A. C. normal levels of plasma cortisol were found 4 hours after the first injection (although at 6 hours the level was 40 μg/100 ml, which is below normal), further injections revealed a defective response to Synacthen Depot. In none of the remaining five patients was the response normal, i.e. in no case after the Synacthen injections was there a total recovery of the adrenal cortex. After three injections in patient A.C., 4 injections in patient E.A.C. and 5 injections in patient I.S.S. the levels of plasma cortisol at 4 to 6 hours were lower than the levels after the first injection.

Fifteen patients, with hyperthyroidism treated for 1 to 14 months were studied (table 1, Fig. 3). At the time of testing, all the patients were clinically euthyroid. The basal plasma cortisol values in 9 tests in 8 patients treated for 1 to 5 months (group 2) (mean ± SD — 13,9 ± 6,29 μg/100 ml) and in 15 tests in 12 patients treated for

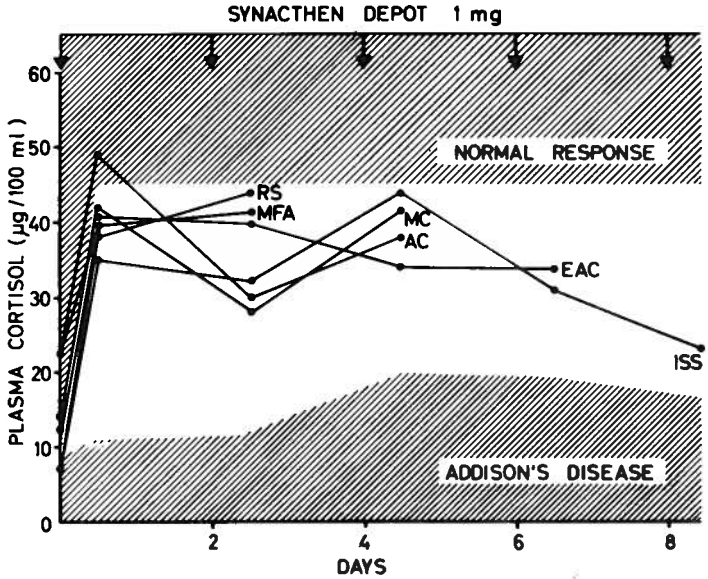

Fig. 2 — *Response of plasma cortisol to multiple injections of Synacthen Depot administered at intervals of 48 hours to patients with hyperthyroidism. The shaded areas represent the normal group's response (above) and the response of the group with Addison's disease*

6 to 14 months (group 3) (13.7 ± 4.16 μg/100 ml) were identical with one another and with those in the group of patients with hyperthyroidism before treatment.

The mean (± SD) plasma cortisol after Synacthen Depot in the group of patients treated for 1 to 5 months was 38.9 ± 13.82 μg/100 ml, which is not significantly different from the results in the group of untreated hyperthyroid patients, but significantly different from the normal group (p less than 0.001). In two cases the values were normal at 4 and at 6 hours, whereas in another patient the values were normal at 6 hours but less than normal (39 μg/100 ml) at 4 hours. In all remaining cases the values were below normal (Fig. 3).

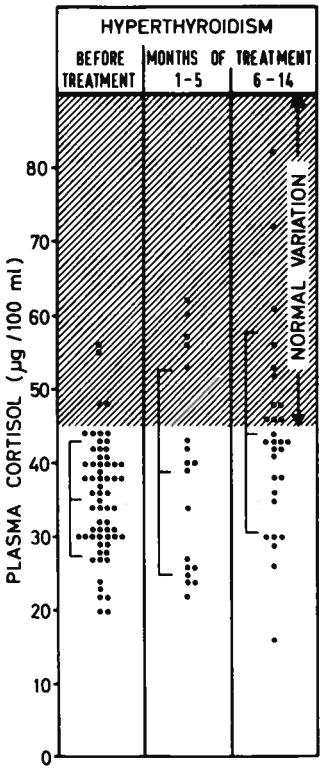

Fig. 3 — *Plasma cortisol 4-6 hours after Synacthen Depot in groups of patients with hyperthyroidism before treatment and after treatment for 1 to 5 months and for 6 to 14 months (Means ± SD). The shaded area represents the normal response*

In the group treated for 6 to 14 months the mean (± SD) of 15 tests was 44.1 ± 13.66 μg/100 ml, significantly higher than the group of patients with untreated hyperthyroidism (p less than 0.001). There was, however, no significant difference between the two treated groups (p less than 0.2). In the group treated for 6 to 14 months, of the 15 tests carried out 5 were totally normal, whereas in one the plasma cortisol at 6 hours was normal, but slightly below the lower limit of normal at 4 hours (43 μg/100 ml). There was great overlap in individual findings in the three groups of patients with hyperthyroidism (Fig. 3).

There is a tendency for the adrenal reserves to improve as the duration of treatment increases (Table 2).

Table 2

Plasma cortisol basal and 4-6 hours after Synacthen Depot in groups of patients with hyperthyroidism before and after treatment

PATIENT	PLASMA CORTISOL (μg/100 ml)										
	GROUP I BEFORE TREATMENT			GROUP II 1 — 5 MONTHS OF TREATMENT				GROUP III 6 — 14 MONTHS OF TREATMENT			
	BASAL	4 H	6 H	BASAL	4 H	6 H	MONTHS	BASAL	4 H	6 H	MONTHS
A. R. N.	10	22	27	15	40	40	(2)	14	36	35	(6)
C. P.	20	30	30	8	25	26	(5)	—	38	43	(10)
M. C. P.	6	38	44					16	43	53	(8)
								12	52	56	(10)
F. C.	13	40	38					20	48	46	(6)
								9	43	42	(12)
I. S. S.	12	31	35								
	19	32	30								
	29	44	40								
	2	31	28	3	27	26	(1)				
	6	30	23	24	24	24	(2)	13	30	30	(9)
M. L. A. R.	13	20	29	12	43	22	(2)	13	30	29	(9)
								17	42	40	(11)
R. A. A. S.	5	38	31								
	3	41	44	15	42	34	(4)	12	26	16	(8)

DISCUSSION

Values of basal plasma cortisol and of plasma cortisol after Synacthen Depot were normal in patients with simple goiter and with hypothyroidism. These results confirm those of Havard et al (1970) and, in part, those of Felber et al (1959) but they disagree with those of Brown et al (1958) and Pittman (1971).

In patients with hyperthyroidism the basal plasma cortisol levels are significantly lower than those of normal individuals and significantly higher than those of patients with primary adrenal insufficiency. However, there is considerable overlap.

The majority of authors believe that, in hyperthyroidism, the changes in cortisol metabolism are more important than changes in adrenal reserve. On the other hand, studies of reserve with ACTH have proved inconclusive: the reserves have been described as normal (Liddle et al 1962; Kowal and Soffer 1963) or reduced (Gold et al 1961; Brownie and Sprunt 1962).

Various authors (Sakiz and Guillemin 1965) have suggested that inhibition of TSH release is accompanied by a rise in ACTH secretion. Steinetz and Beach (1963) concluded that the thyroid hormones indirectly influence the adrenals, by increasing the release of ACTH by the pituitary. High levels of ACTH measured directly, have been reported by Hilton et al (1962) in a group of patients with hyperthyroidism.

In the authors group of patients with hyperthyroidism the adrenal reserve was reduced but not absent, the plasma cortisol levels 4-6 hours after 1 mg Synacthen Depot being significantly below those in normal individuals and significantly higher than those in patients with primary adrenal insufficiency. This shows that the adrenal cortex can respond to exogenous ACTH (and probably to stress), but in a subnormal manner without maximal stimulation; this correlates with the low basal levels. On the other hand, the lack of recovery of adrenal reserve after several injections of Synacthen Depot at 48-hour intervals in 6 of 17 cases shows that the reduced adrenal function in hyperthyroidism is not due essentially to ACTH deficiency. For these reasons, the authors believe that the reduced adrenal reserve in this situation must be due principally to a direct action of thyroid hormones upon the adrenal cortex. Also in favour of this interpretation is the fact that, in many patients treated for several months and kept in a state of euthyroidism, the cortical reserve continues diminished. However, in the present series, there was a tendency for recovery to occur as treatment was continued.

These results are in agreement with those reported by Moore and Callas (1972). These authors found that changes in the zona fasciculata of albino rats with hyperthyroidism were different from the ultrastructural changes reported by other workers (Lever 1956; Sabatini and De Robertis 1961) in the adrenal cortex, after ACTH stimulation. These facts (Moore and Callas 1972) suggest indirectly that the thyroid hormones affect the adrenal cortex.

Moreover, studies of thyroxine turnover (Ingbar and Freinkel 1958; Nicoloff and Dowling 1968) and of triiodothyronine (Woeber et al 1970) in patients with hyperthyroidism showed that turnover of these hormones can remain high years after the correction by treatment of the hyperthyroidism. This may account for delay in cortical recovery during treatment.

However, the reduced basal levels of plasma cortisol found by the authors in hyperthyroidism cannot be explained by the above considerations: an abnormality of ACTH metabolism has to be postulated. This problem will be resolved only by measuring ACTH in such a situation.

RESUMO

Tem sido muito discutida a acção das hormonas tiroideias sobre o córtex suprarrenal e o metabolismo do cortisol. Neste trabalho, a reserva cortical foi determinada pelo doseamento do cortisol plasmático 4 e 6 horas após uma injecção intramuscular de 1 mg de Synacthen Depósito. Foram estudados 16 doentes com bócio simples em eutiroidismo, 13 com hipotiroidismo e 25 com hipertiroidismo. Os resultados encontrados nestes grupos foram comparados com os obtidos em 87 indivíduos normais, 17 com insuficiência suprarrenal primária e 21 com insuficiência suprarrenal secundária. O cortisol plasmático, após Synacthen Depósito, não era estatisticamente diferente nos indivíduos normais, com bócio simples e com hipotiroidismo. Pelo contrário, após estimulação, os níveis de cortisol plasmático no grupo com hipertiroidismo eram significativamente inferiores ($p < 0{,}001$) aos níveis encontrados nos grupos de normais, e significativamente superiores ($p < 0{,}001$) aos níveis nos grupos com insuficiência suprarrenal primária e secundária. Seis casos com hipertiroidismo revelaram uma reserva cortical diminuída, após múltiplas injecções de Synacthen Depósito. O estudo da reserva cortical, no grupo de doentes com hipertiroidismo após 1 a 14 meses de tratamento com metimazole, mostrou uma tendência da reserva suprarrenal a normalizar-se com o tempo. Estas observações levaram o autor a pensar que a diminuição da reserva cortical no hipertiroidismo é devida principalmente a um efeito directo das hormonas tiroideias no córtex suprarrenal.

REFERENCES

BEISEL WR, DIRAIMONDO VC, CHAO PY, ROSNER JM, FORSHAM PH: The influence of plasma protein binding on the extra-adrenal metabolism of cortisol in normal, hyperthyroid and hypothyroid subjects. *Metabolism* 13: 942, 1964.

BROWN H, ENGLERT E Jr, WALLACH S: Metabolism of free and conjugated 17-hydroxycorticosteroids in subjects with thyroid disease. *J Clin Endocr* 18: 167, 1958.

BROWNIE AC, SPRUNT JG: Metopirone in the assessment of pituitary-adrenal function. *Lancet* 1: 773, 1962.

COPE CL, BLACK EG: The behaviour of 14C-cortisol and estimation of cortisol production rate in man. *Clin Sci* 17: 147, 1958.

DOE RP, FERNANDEZ R, SEAL US: Measurement of corticosteroid-binding globulin in man. *J Clin Endocr* 24: 1029, 1964.

FELBER JP, REDDY WJ, SELENKOW HA, THORN GW: Adrenocortical response to the 48-hour ACTH test in myxedema and hyperthyroidism. *J Clin Endocr* 19: 895, 1959.

FREGLY MJ, BRIMHALL RL, GALLINDO OJ: Effect of the antithyroid drug propylthiouracil on the sodium balance of rats. *Endocrinology* 71: 693, 1962.

GALVÃO-TELES A: Measurement of the adrenal cortex reserve using depot β^{1-24}-corticotrophin. I. In adrenal insufficiency. *Acta Med Port* 1: 185, 1979.

GALVÃO-TELES A, BURKE CW, FRASER TR: Adrenal function tested with tetracosactrin depot. *Lancet* 1: 557, 1971.

GALVÃO-TELES A, REBELO M, GOMES MAM, GOMES MJM, FARO L, BOTELHO L: Adrenal reserve in thyroid diseases assessed by 4-6 h β^{1-24}-ACTH test. *J Steroid Bioch* 5: 370, 1974 (abst).

GOLD EM, KENT JR, FORSHAM PH: Clinical use of a new diagnostic agent, methopyrapone (SU-4885), in pituitary and adrenocortical disorders. *Ann Int Med* 54: 175, 1961.

HAVARD CWH, SALDANHA VF, BIRD R, GARDNER R: Adrenal function in hypothyroidism. *Br Med J* 1: 337, 1970.

HELLMAN L, BRADLOW HL, ZUMOFF B, GALLAGHER TF: The influence of thyroid hormone on hydrocortisone production and metabolism. *J Clin Endocr* 21: 1231, 1961.

HILTON JG, BLACK WC, ATHOS W, McHUGH B, WESTERMANN CD: Increased ACTH-like activity in plasma of patients with thyrotoxicosis. *J Clin Endocr* 22: 900, 1962.

INGBAR SH, FREINKEL N: Studies of thyroid function and the peripheral metabolism of I^{131}-labeled thyroxine in patients with treated Graves' disease. *J Clin Invest* 37: 1603, 1958.

JACKSON IMD, HASSAN THA, PRENTICE CRM, BROWNING MCK: Insulin-induced hypoglicemia as a test of pituitary-adrenal function in thyrotoxicosis. *J Clin Endocr* 26: 545, 1966.
KENNY FM, ITURZAETA N, PREEYASOMBAT C, TAYLOR FH, MIGEON CJ: Cortisol production rate. VII. Hypothyroidism and hyperthyroidism in infants and children. *J Clin Endocr* 27: 1616, 1967.
KOWAL J, SOFFER LJ: Pituitary reserve in myxedema and thyrotoxicosis. *Ann Int Med* 59: 79, 1963.
LESSOF MH, LYNE C, MAISEY MN, STURGE RA: Effect of thyroid failure on the pituitary-adrenal axis. *Lancet* 1: 642, 1969.
LEVER JD: Cytological studies on the hypophysectomized rat in adrenal cortex: the alterations of its fine structure following ACTH administration and on lowering the Na/K ratio. *Endocrinology* 58: 163, 1956.
LEVIN ME, DAUGHADAY WH: The influence of the thyroid on adrenocortical function. *J Clin Endocr* 15: 1499, 1955.
LIDDLE GW, ISLAND D, MEADOR CK: Normal and abnormal regulation of corticotropin secretion in man. *Recent Prog Horm Res* 18: 125, 1962.
MARTIN MM, MINTZ DH: Effect of altered thyroid function upon adrenocortical ACTH and methopyrapone (SU-4885) responsiveness in man. *J Clin Endocr* 25: 20, 1965.
MONEY WL: The interrelation of the thyroid and adrenals. In: The thyroid. Brookhaven Symposium in Biology. N.° 7. Upton, Brookhaven National Laboratory, 1954. p. 137.
MOORE NA, CALLAS G: The effects of hyperthyroidism on the fine structure of the zona fasciculata of the rat adrenal cortex. *Anat Rec* 174: 451, 1972.
NICOLOFF JT, DOWLING JT: Studies of peripheral thyroxine distribution in thyrotoxicosis and hypothyroidism. *J Clin Invest* 47: 2000, 1968.
PETERSON RE: The influence of the thyroid on adrenal cortical function. *J Clin Invest* 37: 736, 1958.
PETERSON RE: The miscible pool and turnover rate of adrenocortical steroids in man. *Recent Prog Horm Res* 15: 231, 1959.
PITTMAN JA: Adrenal cortex. In: The thyroid. Third Edition. Eds. S. C Werner and S H Ingbar. Harper & Row, Publishers. New York, Evanston, San Francisco, London. p. 644, 1971.
SABATINI DD, DeROBERTIS EDP: Ultrastructural zonation of adrenocortex in the rat. *J Biophys Biochem Cytol* 9: 105, 1961.
SAKIZ E, GUILLEMIN R: Inverse effects of purified hypothalamic TRF on the acute secretion of TSH and ACTH. *Endocrinology* 77: 797, 1965.
STEINETZ BG, BEACH VL: Some influences of thyroid on the pituitary-adrenal axis. *Endocrinology* 72: 45, 1963.
TOMKINS GM, McGUIRE JS Jr: The effect of thyroid hormones on adrenal steroid metabolism. *Ann N Y Acad Sci* 86: 600, 1960.
WOEBER KA, SOBEL RJ, INGBAR SH, STERLING K: The peripheral metabolism of triiodothyronine in normal subjects and in patients with hyperthyroidism. *J Clin Invest* 49: 643, 1970.

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