from it. Nine patients (28%) were markedly improved. These results are roughly comparable to those of Yahr *et al.* (1968) and Cotzias *et al.* (1969a).

It is probable that some of the 12 patients in this series who derived slight benefit, or none, from L-dopa, or whose treatment was curtailed because of ill effects, might be helped by the drug if a more gradual build-up of the dose was used, as suggested by Cotzias *et al.* (1969a). It is probable, too, that treatment on the maximal tolerated dose should be prolonged for at least six months before presuming that L-dopa is ineffective in a particular patient.

Improvements in hypokinesis and rigidity were much more striking in this group than was amelioration of tremor. Cotzias *et al.* (1969a) indicated that tremor is the last feature to show improvement, and it may be that continuing treatment of our patients will result in more striking relief of tremor.

It is not possible to predict with certainty which Parkinsonian patients will derive most benefit from L-dopa treatment. There is no consistent correlation with age, with duration, or with severity of disease. The few patients in this series who had postencephalitic Parkinsonism were prone to develop unpleasant side-effects on low doses—which is consistent with the observations of Calne *et al.* (1969). It seems probable that a very gradual and prolonged build-up of the drug should be adopted in postencephalitic patients.

Most patients have some untoward side-effects at some stage while taking L-dopa. A substantial number of people suffer unpleasant or distressing reactions, but all the side-effects observed in this series were dose-dependent and readily reversible. Postural hypotension seems to be the only potentially dangerous complication of treatment. Further observations of large numbers of patients for periods of years are needed before the safety of L-dopa can be fully established.

There is now strong evidence that L-dopa offers a most effective treatment of Parkinsonism. It improves function for long periods, but it has yet to be shown whether the improvement produced is sustained indefinitely, or whether the drug alters the natural history of this disease.

I am grateful to my colleagues Dr. J. B. Stanton and Dr. E. H. Jellinek for permission to study patients under their care and to Dr. D. R. Wood for his help in running the trial. To Dr. Geoffrey Walsh I am indebted for his physiological studies on these patients, for the illustrations of tremor, and for much helpful discussion. I would like to acknowledge the help received from Miss Mary Harper, Miss Christine Allan, and Miss Irene Nash, who carried out many of the assessments in these patients. To Dr. H. Holgate and Roche Products Limited I am particularly grateful for generously supplying the L-dopa used in this study.

REFERENCES

Barbeau, A. (1962). *Canadian Medical Association Journal*, **87**, 802.
Birkmayer, W., and Hornykiewicz, O. (1961). *Wiener klinische Wochenschrift*, **73**, 787.
Bloom, F. E., Costa, E., and Salmoiraghi, G. C. (1965). *Journal of Pharmacology and Experimental Therapeutics*, **150**, 244.
Calne, D. B., Stern, G. M., Laurence, D. R., Sharkey, J., and Armitage, P. (1969). *Lancet*, **1**, 744.
Carlsson, A. (1959). *Pharmacological Reviews*, **11**, 490.
Carpenter, M. B., and McMasters, R. E. (1964). *American Journal of Anatomy*, **144**, 293.
Cotzias, G. C., Papavasiliou, P. S., and Gellene, R. (1969a). *New England Journal of Medicine*, **280**, 337.
Cotzias, G. C., Papavasiliou, P. S., Gellene, R. Aronson, R. B., and Mena, I. (1969b). In *Third Symposium on Parkinson's Disease*, edited by F. J. Gillingham and I. M. L. Donaldson, p. 178. Edinburgh, Livingstone.
Cotzias, G. C., van Woert, M. H., and Schiffer, L. M. (1967). *New England Journal of Medicine*, **276**, 374.
Denny-Brown, D. (1949). *Archives of Neurology and Psychiatry*, **61**, 99.
Denny-Brown, D. (1968). In *Handbook of Clinical Neurology*, vol 6, *Diseases of the Basal Ganglia*, edited by P. J. Vinken and G. W. Bruyn, p. 133. Amsterdam, North Holland Publishing Company.
Duvoisin, R., Barrett, R., Schear, M., Hoehn, M., and Yahr, M. (1969). In *Third Symposium on Parkinson's Disease*, edited by F. J. Gillingham and I. M. L. Donaldson, p. 185. Edinburgh, Livingstone.
Ehringer, H., and Hornykiewicz, O. (1960). *Klinische Wochenschrift*, **38**, 1236.
Fehling, C. (1966). *Acta Neurologica Scandinavica*, **42**, 367.
Godwin-Austen, R. B., Tomlinson, E. B., Frears, C. C., and Kok, H. W. L. (1969). *Lancet*, **2**, 165.
Greer, M., and Williams, C. M. (1963). *Neurology (Minneapolis)*, **13**, 73.
Hassler, R. (1938). *Journal für Psychologie und Neurologie*, **48**, 387.
Hoehn, M. M., and Yahr, M. D. (1967). *Neurology (Minneapolis)*, **17**, 427.
Hoehn, M. M., and Yahr, M. D. (1969). In *Third Symposium on Parkinson's Disease*, edited by F. J. Gillingham and I. M. L. Donaldson, p. 274. Edinburgh, Livingstone.
Rinne, U. K., and Sonninen, V. (1968). *European Neurology*, **1**, 180.
Rundles, R. W., and Papez, J. W. (1937). *Archives of Neurology and Psychiatry*, **38**, 550.
Trétiakoff, C. (1919). *Contribution à l'étude de l'anatomie pathologique du Locus niger de Soemmering*. Thesis, Paris.
Vogt, M. (1954). *Journal of Physiology*, **123**, 451.
Walsh, E. G. (1968). *Journal of Physiology*, **198**, 69P.
Walsh, E. G. (1969). *Journal of Physiology*, **202**, 109P.
Wilson, S. A. K. (1925). *Lancet*, **2**, 53.
Yahr, M. D., Duvoisin, R. C., Hoehn, M. M., Schear, M. J., and Barrett, R. E. (1968). *Transactions of the American Neurological Association*, **93**, 56.

Adrenal Function in Hypothyroidism

C. W. H. HAVARD,* D.M., M.R.C.P. ; V. F. SALDANHA,† M.D., M.R.C.P. ; R. BIRD,‡ PH.D., F.R.I.C.
R. GARDNER,§ F.I.M.L.T.

British Medical Journal, 1970, 1, 337-339

Summary: In ten patients with hypothyroidism the adrenal response to stimulation with tetracosactrin was found to be normal, and to be unchanged after they had been treated with thyroxine. Though the response to insulin hypoglycaemia was less in the hypothyroid phase, it was never outside the normal limits. Hence it seems unlikely that the adrenal response to stress is appreciably lowered in hypothyroidism.

*Physician, Royal Northern Hospital, London N.7.
†Pfizer Research Fellow.
‡Biochemist, Royal Northern Hospital, London N.7.
§Supported by research grant from North-West Metropolitan Regional Hospital Board.

Introduction

It is generally accepted that adrenal function is reduced in primary hypothyroidism. This has been attributed both to an inadequate response of the adrenal cortex to corticotrophin (Macgregor, 1964) and to an impairment of pituitary function (Lessof *et al.*, 1969). In myxoedema coma hydrocortisone is recommended because of the likelihood of associated adrenocortical insufficiency (Ingbar and Woeber, 1968). There is, however, considerable disagreement among those who have studied this problem. The cortisol secretion rate is known to be reduced in myxoedema (Cope, 1964); this is associated with a normal plasma corticosteroid level and a reduced excretion of urinary hydroxycorticosteroids (Levin and Daughaday, 1955).

These observations could well indicate a physiological response to a lesser need. The problem that concerns the physician is whether the adrenal response to stress is reduced in hypothyroidism.

We have therefore studied adrenal function in 10 patients with hypothyroidism before and after treatment with thyroxine.

Materials and Methods

The 10 patients selected for investigation were unequivocal cases of clinical hypothyroidism, and none of them had been treated previously. Their ages ranged from 13 to 74 years (Table I). Seven had primary hypothyroidism, as shown by low initial serum protein-bound iodine (PBI) and radioactive ^{131}I uptake with failure of these values to rise after injection of thyroid-stimulating hormone (Thytropar) 10 i.u. intramuscularly daily for three days. In four of these cases tests for autoantibodies were carried out and significantly high titres to thyroglobulin were found (1 : 25 to 1 : 5,120). In only one patient (Case 4) were the laboratory data equivocal, but the clinical evidence and response to treatment left little doubt that she was hypothyroid

TABLE I

Case No.	Age	Sex	P.B.I. (μg./100 ml.)	^{132}I 24 hours ^{131}I 4 hours	After Thyroid-stimulating Hormone	Comment
1	50	F	3·0	24 hr. 25%		Primary hypothyroidism
2	55	F	2·5	24 hr. 27%		,,
3	45	F	2·5	4 hr. 21%	4 hr. 13%	,,
4	24	F	4·0	24 hr. 32%	24 hr. 28%	,,
5	74	M	0·9	24 hr. 16%	24 hr. 18%	,,
6	13	M	2·0	24 hr. 7%	24 hr. 8%	,,
7	16	F	1·0	24 hr. 3%	24 hr. 3%	,,
8	44	F	2·8	24 hr. 15%	24 hr. 64%	Pituitary hypothyroidism
9	33	F	2·5	4 hr. 9%	4 hr. 41%	,,
10	31	F	3·5	24 hr. 26%	24 hr. 55%	,,

The remaining three patients were considered to have hypothyroidism secondary to pituitary hypofunction; an increase in protein-bound iodine and ^{131}I uptake after injection of thyroid-stimulating hormone was found and none of them had positive tests for autoantibodies in significant titre.

All the patients were treated with L-thyroxine replacement in a dose of 0·3 mg daily, and the tests of adrenal function were repeated when the patients were judged to be euthyroid clinically—that is, after a period varying from three to six months.

Corticosteroids in plasma were measured by the method of Mattingly (1962) with the Beckman ratio fluorometer, and the serum protein-bound iodine was estimated by the method of Bird and Jackson (1962)—the normal range is 3·5 to 7·5 μg./100 ml. Radioactive iodine uptake studies were undertaken in all patients, with ^{131}I in eight and ^{132}I in two. The normal 24-hour uptake for ^{131}I is 25-50% and the four-hour uptake for ^{132}I is 19-40%. The normal response to thyroid-stimulating hormone is a 15% or greater increase above the baseline. Blood sugar was measured by the AutoAnalyzer microglucose method (Technicon method N-9).

Adrenal Stimulation.—Tetracosactrin (Synacthen) 0·25 mg was injected intramuscularly. Blood samples were taken into plastic heparinized tubes before injection and at 30 and 60 minutes after injection, the response being recorded as the increment in μg./100 ml. above the baseline.

Insulin Sensitivity Test.—Blood was taken before injection for the determination of the baseline blood sugar and plasma corticosteroid values. The patient was then given soluble insulin 0·15 unit/kg. of body weight intravenously, and further blood samples were taken every 30 minutes for three hours for the estimation of blood sugar and plasma corticosteroids. An insulin-induced hypoglycaemia producing a fall in blood sugar to less than 40 mg./100 ml. was accepted as a satisfactory stress. The corticosteroid response is reported as the increment above the baseline value.

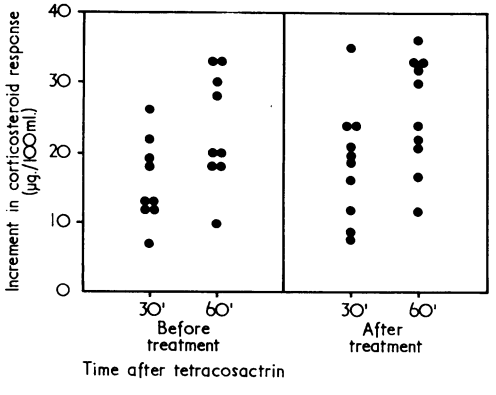
Results

Basal Plasma Corticosteroid Levels.—The plasma corticosteroid circadian rhythm did not change in the presence of hypothyroidism. There was no significant difference at 9 a.m. between the mean plasma corticosteroid level of the hypothyroid group and our normal range. At 9 a.m. the values were 14·0 μg./100 ml. for the hypothyroid group and 14·6 μg./100 ml. for the normals. The corresponding values at midnight were both less than 8 μg./100 ml.

Response of Plasma Coricosteroids to Tetracosactrin.—The mean plasma corticosteroid response measured at 30 and 60 minutes after tetracosactrin is given in Table II. Though the mean post-treatment corticosteroid values at both 30 and 60 minutes were higher, the difference did not reach statistical significance. The patients' individual increments are shown in the Chart.

TABLE II.—*Plasma Corticosteroid Response Following Tetracosactrin (Increment above Baseline)*

Time in Minutes	Mean Plasma Corticosteroids (μg./100 ml.) Before Treatment	After Treatment	Difference	S.E. of Difference	*t*	P
30	16·0	18·9	2·9	±1·8	1·6	>0·05
60	23·3	26·0	2·7	±2·0	1·3	>0·05



Scattergram to show the response to tetracosactrin stimulation in the group of hypothyroid patients before and after treatment with thyroxine. The maximum response to tetracosactrin was not impaired in hypothyroidism.

Response of Plasma Corticosteroids to Insulin-induced Hypoglycaemia.—The plasma corticosteroid response following insulin-induced hypoglycaemia is given in Table III. It will be seen that throughout the test the post-treatment values were higher than those before treatment though the differences reached the 5% level of significance only at 60 minutes.

TABLE III.—*Plasma Corticosteroid Response to Insulin-induced Hypoglycaemia (Increment Above Baseline)*

Time in Minutes	Mean Plasma Corticosteroids (μg./100 ml.) Before Treatment	After Treatment	Difference	S.E. of Difference	*t*	P
30	3·9	6·0	+2·1	±2·8	0·9	>0·05
60	11·8	18·4	+6·6	±2·8	2·4	<0·05
90	15·1	20·9	+5·8	±4·3	1·4	>0·05
120	14·3	15·5	+1·2	±4·4	0·2	>0·05
150	9·0	11·6	+2·6	±2·4	1·1	>0·05
180	5·3	8·0	+2·7	±2·3	1·2	>0·05

No correlation was found between the duration of the disorder or the degree of hypothyroidism as assessed clinically or by serum protein-bound iodine estimations and the plasma corticosteroid response, either in the time of peak response or in the maximum rise.

Discussion

The circadian variation in plasma corticosteroid levels in the hypothyroid patients did not differ significantly from our control values, nor did it alter after treatment with thyroxine. Our results differ from those of Martin and Mintz (1965), who found the diurnal variation of plasma corticosteroids reduced in hypothyroidism. The explanation for the difference is uncertain. Many of our patients had serious degrees of hypothyroidism. The removal of corticosteroids from the blood is slower in myxoedema than in normal individuals (Brown *et al.*, 1958). It is therefore possible to maintain a normal plasma corticosteroid concentration in the presence of a reduced cortisol secretion rate. Tests of adrenal reserve therefore become of paramount importance.

The ability of the adrenal glands to respond to direct stimulation with tetracosactrin was normal in all our patients, though they showed considerable variation in the duration and degree of hypothyroidism. Moreover, the adrenal response showed no significant change after treatment with thyroxine.

Lessof *et al.* (1969) studied the effect of thyroid failure on the pituitary-adrenal axis and concluded that impairment of pituitary function was not uncommon in myxoedema. They investigated the function of the pituitary-adrenal axis in primary myxoedema by assessing the plasma corticosteroid response to stimulation with tetracosactrin and lypressin (lysine vasopressin) before and after treatment. Other investigators have used the metyrapone test. Interpretation of the metyrapone test is complicated in myxoedema as many patients have an abnormally low excretion of urinary oxogenic steroids. Variation in the renal clearance of these oxogenic steroids in myxoedema may account for conflicting results obtained with this test. Liddle *et al.* (1962) found the response normal in patients with hypothyroidism, while Gold *et al.* (1961) found a subnormal response.

The plasma corticosteroid response to insulin-induced hypoglycaemia has been shown to be the most satisfactory measure of the stress response (Landon *et al.*, 1963), for this is a standard reproducible stress which assesses the integrity of the entire cerebro-hypothalmic-pituitary-adrenal axis. It is also likely to provide a more physiological challenge than the lypressin or metyrapone tests.

It is obvious that the plasma corticosteroid response to insulin hypoglycaemia is less in the hypothyroid phase, but, in no patient was it outside the normal range (Landon *et al.*, 1963). After treatment with thyroxine a brisker response was observed which was significant at 60 minutes. The lesser response could be interpreted as a marginal impairment of the stress response in hypothyroidism. The stress stimulus was adequate as a fall in blood sugar to less than 40 mg./100 ml. in the first 30 minutes was achieved in each case. In three hypothyroid patients the reduced thyroid function was due to a selective deficiency of thyroid-stimulating hormone. In all three the urinary levels of luteinizing hormone were normal, as were the serum growth hormone responses to hypoglycaemia. Skull *x*-ray pictures were also normal. It might be expected that these patients in particular would show a deficient adrenocortical response to stress. In none of them was the plasma corticosteroid response to hypoglycaemia significantly different from that of the other hypothyroid patients in this group.

We would agree with Greenberg (1969) that, though long-standing hypothyroidism can hardly be expected not to influence other endocrine functions, an adrenal crisis is a rare occurrence in primary hypothyroidism unless the patient is in myxoedema coma. Even in patients in coma it would seem probable that hypothermia, hypercapnia, and cardiac failure are more important causes of death than adrenal failure.

We thank Mr. Michael Curwen for statistical advice. We are also grateful to the North-West Metropolitan Regional Hospital Board and G. D. Searle & Co. Ltd. for grants towards the cost of equipment.

References

Bird, R., and Jackson, D. J. (1962). *Clinical Chemistry*, **8**, 389.
Brown, H., Englert, E., jun., and Wallach, S. (1958). *Journal of Clinical Endocrinology and Metabolism*, **18**, 167.
Cope, C. L. (1964). *Adrenal Steroids and Disease*, p. 163. London, Pitman Medical.
Gold, E. M., Kent, J. R., and Forsham, P. H. (1961). *Annals of Internal Medicine*, **54**, 175.
Greenberg, S. R. (1969). *Lancet*, **1**, 836.
Ingbar, S. H., and Woeber, K. A. (1968). In *Textbook of Endocrinology*, 4th ed., edited by R. H. Williams, p. 258. Philadelphia, Saunders.
Landon, J., Wynn, V., and James, V. H. T. (1963). *Journal of Endocrinology*, **27**, 183.
Lessof, M. H., Lyne, Cynthia, Maisey, M. N., and Sturge, R. A. (1969). *Lancet*, **1**, 642.
Levin, M. E., and Daughaday, W. H. (1955). *Journal of Clinical Endrocrinology and Metabolism*, **15**, 1499.
Liddle, G. W., Island, D., and Meador, C. K. (1962). *Recent Progress in Hormone Research*, **18**, 125.
Macgregor, A. G. (1964). In *The Thyroid Gland, vol. 2*, edited by R. Pitt-Rivers, and W. R. Trotter, p. 121. London, Butterworths.
Martin, M. M., and Mintz, D. H. (1965). *Journal of Clinical Endocrinology and Metabolism*, **25**, 20.
Mattingly, D. (1962). *Journal of Clinical Pathology*, **15**, 374.