study throwing light on the question, in particular histology. But, as already noted, histological evidence is often associated with an interruption of the natural history of cystic disease by a mastectomy or partial mastectomy. Only clinical evidence can be conclusive for the natural history of cystic disease of the breast as it affects the human, and it is precisely clinical evidence that has been lacking. The present paper again illustrates the time required and the difficulty experienced in obtaining conclusive clinical evidence, and it may be that a current experience of 20 years is too short a time for final conclusions. But one certainly seems justified on such current experience in tentatively concluding that, with certain simple precautions, the regarding and treating of cystic disease of the breast as an innocent condition has not up to the present been shown to be fallacious by the frequency of development of carcinoma.

The criticism might possibly be made that, from the point of view of the liability of cystic disease to carcinoma, the eight cases with associated intracystic growth ought not to be treated as a separate group, but ought to be grouped with the one case of cystic disease treated by aspiration in which subsequent carcinoma did develop. But in reply it should be emphasized that in all these eight cases it was not a question of a tumour developing as a complication in a previously known cyst treated conservatively, but of eight patients who at their first attendance had tumours of the breast which happened to be associated with cysts, often not diagnosed clinically. There was no definite evidence in any of them that the cysts preceded the tumours, and in most it was at any rate equally probable that the reverse process occurred and that the tumours preceded the cysts. Certainly in the commonest group—the intracystic papillomata (five cases)—the cysts were probably due to distension of the associated duct with the blood shed by the papillomata, a process that in lesser degree is recognized as a common occurrence in the small intraduct papillomata in the ducts near the nipple.

We feel, therefore, that many of these cases belong to a separate group pathologically as well as being clearly recognizable as a separate entity clinically, and that part of the confusion in the past about the relation of cystic disease of the breast to carcinoma has arisen through wrongly grouping together two separate types of condition. Finally, since carcinoma and cystic disease are both common conditions, it must occasionally happen that the two will present clinically at the same time. The treatment of these cases is of course the treatment of the carcinoma, but it would be wrong to assume from simultaneous presentation a necessarily causal relation between the two conditions. This study therefore furnishes support for the view that cystic disease of the breast can with simple precautions be treated conservatively. It also furnishes support for the efficacy of the simplest form of conservative treatment—aspiration.

Summary

Of 76 cases of cyst of the breast treated conservatively, 65 of which have been followed for from 1 to 16 years, only one is known to have developed carcinoma, and that in the opposite breast.

Aspiration of a cyst is not necessarily followed by the development of further cysts, and, if it is, the tendency to cyst formation may disappear.

Of 810 cases of carcinoma of the breast only 10 had a previous clinical history of cyst.

In a further eight of these cases growth developed apparently simultaneously with and in relation to a cyst, but this group of cases readily lends itself to recognition clinically, and is probably a separate group pathologically.

With simple precautions, conservative treatment by aspiration is an efficient and safe treatment for cystic disease of the breast.

BIBLIOGRAPHY

Cheatle, G. L. (1934-5). *Brit. J. Surg.*, 22, 710.
—— and Cutler, M. (1931). *Tumours of the Breast.* London.
Geschickter, C. F. (1943). *Diseases of the Breast.* Philadelphia.
Patey, D. H. (1949) *British Medical Journal*, 1, 545.
—— (1951). *Arch. Mddx. Hosp.*, 1, 3.
Réclus, P. (1893) *Sem. méd., Paris*, 13, 353.
Willis, R. A. (1948) *Pathology of Tumours.* London.

A.C.T.H. IN DIAGNOSIS OF ADRENAL INSUFFICIENCY (THORN TEST)

BY

R. R. de MOWBRAY, B.M., M.R.C.P.
Registrar to the Endocrine Department, Guy's Hospital

AND

P. M. F. BISHOP, D.M., M.R.C.P.
Endocrinologist to Guy's Hospital and Chelsea Hospital for Women

In 1948 Forsham *et al.* investigated the metabolic and haematological response of human subjects to a single dose of 25 mg. A.C.T.H. They compared the response of 30 patients with Addison's disease with that of 10 normal subjects and 40 hospital patients with presumably intact adrenal cortical function. They found a mean fall of 74% in the number of circulating eosinophils in the individuals with normal adrenal cortical function, and a mean fall of only 4% in the patients with Addison's disease.

The fall in the eosinophil count was accompanied by a mean increase in the urinary uric-acid/creatinine ratio of 87% in the control series and of only 16% in the cases of Addison's disease. Both changes were maximal four hours after the injection of A.C.T.H. A normal eosinophil response, and at the same time an increase of 48% in the uric-acid/creatinine ratio, could, however, be elicited in patients with Addison's disease after they were given 20 mg. of 17-hydroxycorticosterone (compound F), suggesting that the response to A.C.T.H. was mediated by an increase in secretion of 11-oxysteroid compounds by the adrenal cortex. On the basis of these observations Forsham *et al.* devised a "four-hour test" of adrenal cortical function.

In a later article Thorn *et al.* (1951) reported a larger series of similar observations. In 50 cases of Addison's disease there was an average fall of only 7% in the eosinophil count, and in about one-third of the cases there was actually an increase. Patients with hypopituitarism showed an average fall of 31%, the magnitude of the change depending upon the degree and duration of adrenal cortical involution.

Thorn and his colleagues also introduced a 48-hour test, in which changes in the eosinophil count and in the urinary 17-ketosteroid excretion were measured, in response to the intramuscular administration of A.C.T.H. in divided doses over a period of 48 hours (Thorn and Forsham, 1949; Roche, Forsham, Forsham, and Thorn, 1950; Thorn *et al.*, 1951). This test was carried out in 100 subjects. In 35 patients with normal adrenal cortical function the eosinophil count fell by 77% after 48 hours; the urinary 17-ketosteroid excretion increased by an average of 10.1 mg. per 24 hours in 15 normal male subjects and of 7.2 mg. per 24 hours in 20 normal female subjects, whereas there was no significant change in patients with Addison's disease. In most cases of hypo-

pituitarism the eosinophil counts and the urinary 17-ketosteroid levels responded normally in the 48-hour test, but they did not do so in the four-hour test. Thorn and his colleagues therefore claimed that a 48-hour test was of value in distinguishing adrenal failure secondary to hypopituitarism from primary adrenal failure.

More recently Renold *et al.* (1951) reported that the intravenous infusion of 20 mg. of A.C.T.H. in saline over a period of 8 to 24 hours produced a marked adrenal cortical response, which was comparable to that obtained by the intramuscular injection of five to ten times this amount in six-hourly doses over a period of 24 hours. Administration of the same dose intravenously in the course of one minute did not produce any measurable response, and larger doses did not appear to increase the response in four patients who had become resistant to the hormone after intramuscular administration. There was still no response in cases of Addison's disease. No anaphylactic reactions were seen in over 100 patients.

Recant *et al.* (1950) introduced a four-hour adrenaline test. A subcutaneous injection of 0.3 mg. of adrenaline failed to induce a fall in the eosinophil count of 50% or more in 30 out of 34 cases of Addison's disease. By increasing the dose of adrenaline to 1.5 mg. and giving it in saline intravenously over a period of one hour they obtained a fall in the eosinophil count of up to 50% or more in patients with Addison's disease. The adrenaline test showed a greater impairment of response than did the A.C.T.H. test in cases of hypopituitarism. It was suggested that this was due to interruption of the hypothalamic-pituitary pathway; it is thought that adrenaline normally exerts its effect upon the adrenal cortex through this pathway, although it also acts directly upon the adrenal cortex itself, as shown in mice and rats (Long and Fry, 1945; Recant *et al.*, 1948; Speirs and Meyer, 1949). The normal response obtained in some cases of Addison's disease, in spite of the failure of response to A.C.T.H., suggested that endogenous secretion of A.C.T.H. had been stimulated and that remnants of adrenal cortical tissue had consequently become activated.

Material and Methods

The following is an account of the application of the Thorn test with A.C.T.H. to eight classical cases of Addison's disease, in six of which at least one crisis had occurred, to four cases of post-partum panhypopituitarism (Simmonds's disease), and to seven cases in which a diagnosis of adrenal insufficiency had been considered but not established. The four-hour test was used in all cases, except in two cases of Simmonds's disease; in one of these the 48-hour intramuscular test was performed, while in the other the intravenous test was employed.

Seven of the eight cases of Addison's disease were already under treatment with implantations of 300 mg. of D.C.A. (deoxycortone acetate) every six months. In each case the Thorn test was carried out six months after the last implant, by which time it was assumed that the effects of the D.C.A. had to a large extent worn off.

Procedures

1. *The Four-hour Test.*—The patient was allowed no food after 8 p.m. on the day before the test. On the following day the bladder was emptied and the urine discarded at 6 a.m. The patient then drank 200 ml. of water. The bladder was emptied again at 10 a.m. and the urine was kept for estimation of the uric acid and creatinine concentrations (the "pre-treatment" specimen). A chamber eosinophil count was also performed at 10 a.m., and immediately afterwards 25 mg. of A.C.T.H. was injected intramuscularly. A further 200 ml. of water was drunk, and at 11 a.m. the bladder was emptied again and the urine discarded. At 12 noon the patient drank a final 200 ml. of water. The bladder was emptied once again at 2 p.m., and this specimen was kept for estimation of uric acid and creatinine concentrations (the "post-treatment" specimen). A second chamber eosinophil count was also performed at 2 p.m.

Interpretation: a fall in the eosinophil count with a rise in the uric-acid creatinine ratio, each exceeding 50%, is regarded by Forsham *et al.* (1948) as indicating normal adrenal cortical reserve, whereas in the presence of Addison's disease the fall in eosinophil count is usually less than 20%.

2. *The 48-hour Intramuscular Test.*—Urine was collected throughout the 24 hours immediately preceding the test, and the whole amount was saved for estimation of the 17-ketosteroid level. On the morning of the test an eosinophil count was made. A.C.T.H., 25 mg., was then given immediately by intramuscular injection, followed by 10 mg. intramuscularly every six hours until 48 hours after the first injection. A further eosinophil count was made four hours after the last injection, and during the next 24 hours urine was collected again for another estimation of the 17-ketosteroid level. The patient was not in a fasting state during the test.

3. *The Intravenous Test.*—Urine was collected throughout the 24 hours immediately preceding the test and the whole amount was saved for estimation of the 17-ketosteroid level. After an initial eosinophil count an intravenous infusion of normal saline was set up containing the equivalent of 40 mg. of LA-1-a A.C.T.H. This amount was administered over a period of 18 hours. Two hours after the infusion was completed a further eosinophil count was performed, and during the next 24 hours the urine was again collected for estimation of the 17-ketosteroid level. The patient was not in a fasting state during the test.

The chamber eosinophil counts were performed by the eosin–acetone method of Forsham *et al.* (1948) in most cases. More recently, the method of MacFarlane and Cecil (1951) has been used.

The urinary uric acid and creatinine concentrations were estimated by the method of Folin (1914), and the 17-ketosteroid excretion by the method of Greenburgh *et al.* (1950), a modification of the method of Tompsett and Oastler (1946).

Results

Six of the eight proved cases of Addison's disease showed a fall in the eosinophil count of less than 50%; in five cases the fall was less than 20%. In the other two cases, however, the number of circulating eosinophils fell by 57% and 75% respectively (see Table). One of these (Case 7) was one of the most severe cases of Addison's disease in the whole series; this patient has been admitted to hospital in crisis or impending crisis on six occasions. The other patient (Case 8) was thought, on clinical grounds, to be recovering at the time at which the Thorn test was performed, but she died a fortnight later from a severe respiratory infection; at necropsy no trace of adrenal cortical tissue could be found even on histological examination, and there was generalized hypertrophy of lymphoid tissue and of the thymus.

Each of the four cases of panhypopituitarism showed a fall in the number of eosinophils of less than 50%. In one of these cases the 48-hour test was carried out; in another the intravenous test was used.

The initial eosinophil count varied between 50 and 800 (average 220) per c.mm. in the proved cases of Addison's disease, between 100 and 1,100 (average 482) per c.mm. in the cases of panhypopituitarism, and between 10 and 270 (average 121) per c.mm. in the cases in which a diagnosis of Addison's disease was not substantiated.

The percentage fall in the eosinophil count ranged from 0 to 75% (average 22%) in the proved cases of Addison's disease, from 9 to 39% in the cases of panhypopituitarism, and from 0 to 92% (average 49%) in the cases in which the diagnosis of Addison's disease was thought to be unlikely.

The changes in urinary uric-acid/creatinine ratio seemed to bear no relation to the changes in eosinophil count. In fact, only two patients in the whole series showed a rise of uric-acid/creatinine ratio of more than 50%. Both were known to be suffering from Addison's disease; one of them also showed a normal eosinophil response.

In Case 12 the urinary 17-ketosteroid figure rose from 2.1 to 5.4 mg. per 24 hours after the administration of A.C.T.H. by intravenous infusion over a period of 18 hours.

Significance of Eosinophil Counts

There are several possible limitations of the use of eosinophil counts as an index of adrenal cortical function.

1. The test assumes that spontaneous fluctuations of the eosinophil count of more than 50% do not occur under normal conditions. The evidence on this point is conflicting. Hills *et al.* (1948) state that significant fluctuations were not observed in normal subjects, under basal conditions, and without the administration of A.C.T.H. Recant *et al.* (1950) found that the diurnal variation in the eosinophil count of six young adult males, under constant conditions in hospital, did not exceed 40% of the initial levels; the number of eosinophils usually rose gradually during the course of the afternoon. Kellgren and Janus (1951) found that in four healthy male subjects, under normal conditions, the eosinophil counts varied by up to 300% on different days in any one subject, but that the mean fluctuation in counts performed at two-hourly intervals on the same day was no more than 10% of the morning count in any one subject; there was, however, an occasional increase or decrease of about 40%. Abelson and Moyes (1950) found eosinophil counts ranging from +13% to −30% of the initial level in 13 patients with pulmonary tuberculosis under basal conditions.

Most other workers, however, have found considerable diurnal fluctuations in the eosinophil count under normal conditions. Rud (1947) found a marked fluctuation, even from minute to minute, and a typical rhythmical variation during the course of 24 hours. There was a decrease in the early morning hours, with a minimum count between about 9 and 11 a.m., followed by a rise, reaching a peak between noon and 1 p.m., and a maximum level at 5 p.m. He suggested that four counts should be made at intervals of 15 minutes on the afternoons of five or six successive days, and that an average should be taken of all these counts. Herbert and de Vries (1949) found diurnal variations of from 30% to 66% in four subjects under normal conditions. Broch and Haugen (1950) found marked variations under standard conditions and regarded a deviation of 50% as being within the normal range.

Fisher and Fisher (1951) performed 463 counts upon 170 normal persons. Of these, 238 were made on subjects who had been fasting for periods of 12 to 16 hours and 225 were made in a non-fasting state. Of the counts on fasting subjects 23% dropped by 40% or more between 8 a.m. and 12 noon and 11.6% fell by 50% or more; the variations ranged from a fall of 76% to a rise of 165.4%. About one-third of the counts remained the same and 7.3% rose by 50% or more. Only 13% of the non-fasting group showed a decrease of 40% or more between 8 and 11 a.m., but 9.3% dropped by 50% or more. The percentage fall between 11 a.m. and 3 p.m. was less: only 5.3% showed a fall of 50% or more. Over the whole period from 8 a.m. to 3 p.m., 18.6% of the counts fell by 40% or more, 13.3% fell by 50% or more, and 8% rose by 50% or more.

Swanson *et al.* (1952) studied the diurnal variation of eosinophil counts in five healthy subjects during their daily work, and in five patients with rheumatoid arthritis and three with ankylosing spondylitis under normal in-patient conditions. They found a diurnal variation similar to that observed by Rud (1947)—namely, a high early morning count, falling until about midday, followed by a slight rise, another fall in the early afternoon and a further rise towards evening. In the morning a spontaneous fall of more than 50% in the number of eosinophils occurred eight times (in 4 of the 13 subjects), usually within three to four hours. In the afternoon the fall was greater than 40% in only one case; the drop was complete within two hours, and was offset by a greater rise later on. The overall change during the course of the day varied from a fall of 55% to a rise of 128.6%, as compared with a range of −70% to +262% found by Rud in 53 series of counts in 41 subjects.

Swanson *et al.* therefore conclude that one should be cautious in attributing a fall in the eosinophil count to the administration of A.C.T.H. if a Thorn test is carried out during the morning, while a drop of more than 40% during the afternoon is more likely to be significant, especially if it lasts for more than two hours. They criticized the findings of Recant *et al.* (1950) and of Abelson and Moyes (1950) on the grounds that their counts were made at two-hourly intervals only, and that fluctuations might have escaped detection, since the maximum morning fall often took place at the third hour in their own series.

Forsham *et al.* (1948) originally stipulated that the A.C.T.H. test should be performed in the morning, with the patient in a fasting state. Roche, Thorn, and Hills (1950), however, allowed breakfast to be taken before the test, and Swanson *et al.* (1952) found that the midday rise and fall in eosinophil count bore no relation to meals, and that instead of a larger fall occurring after lunch than after breakfast the opposite was true. In one case they found that the midday change in the number of eosinophils still occurred during a one-day fast, though Rud observed that the count usually fell during the afternoon as a result of fasting, instead of rising, as in normal conditions. Swanson *et al.* showed that waking had a more important effect than food upon the eosinophil count, and that the morning fall occurred earlier in hospital patients, who woke earlier; but Rud found no evidence that either food or sleep *per se* markedly influenced the variations in the count, which he regarded as "relatively autonomous."

2. The technique of eosinophil counting may be subject to considerable errors, as may any chamber cell count. Some workers have used modifications of Dunger's (1910) method. Rud (1947) used a magdala-red stain in acetone, and Forsham *et al.* (1948) an eosin-acetone preparation as diluent. Randolph (1944) found that the cells rapidly became lysed by this diluent and introduced phloxine and propylene glycol instead, which, he claimed, overcame these disadvantages and made identification of cells easier. Henneman *et al.* (1949) confirmed his findings, and Swanson *et al.* (1952) obtained consistent results, using Randolph's method, either on venous or on capillary blood. The eosin–acetone method of Forsham *et al.* (1948) was originally used in our cases, but later MacFarlane and Cecil's (1951) modification of Pilot's method, using a phloxine and propylene glycol diluent, was adopted. Both methods have given comparable results, but the method of Forsham *et al.* has the disadvantage that the cells are lysed unless the count is carried out immediately.

3. The initial eosinophil count in the Thorn test may be so low that the significance of a fall in the number of cells after the administration of A.C.T.H. may be difficult to assess, even if it is expressed as a percentage of the initial figure. Thus the initial counts in two of our cases of Addison's disease were 50 and 70 per c.mm., and in three of the cases in which adrenal insufficiency was not confirmed they were as low as 10, 40, and 80 per c.mm. In one of the two severe cases of Addison's disease which showed a fall in eosinophil count of more than 50%, the count was 70 per c.mm. before A.C.T.H. was given and 30 per c.mm. afterwards; though this represents a drop of 57%, the change appears unconvincing when expressed in absolute figures.

4. The fact that the eosinophil count can fluctuate by more than 50% in cases of Addison's disease severely limits its value in the diagnosis of adrenal insufficiency. It is quite possible that the fall in the number of cells in two of our cases of Addison's disease was independent of the administration of A.C.T.H. Although Thorn and his colleagues did not find a significant eosinophil response to the administration of A.C.T.H. in any of their cases of Addison's disease, they do mention a few cases in which a fall of more than 50% in the number of eosinophils was obtained in response to the administration of adrenaline, suggesting that sufficient remnants of adrenal cortical tissue may survive to give this response. Recant *et al.* (1950) also point out that in rare

instances of dissociation of adrenal cortical function there may be adequate secretion of 11-oxysteroid compounds, in spite of deficiency of other steroids; in such cases the eosinophil response will not reflect the whole adrenal cortical reserve.

5. Forsham *et al.* (1948) and Thorn *et al.* (1951) point out another limitation to the test—namely, that in rare cases A.C.T.H. given at the height of an acute allergic eosinophilia may fail to reduce the number of eosinophils. In such a case, they state that if 50 mg. of cortisone given by mouth (or 50 ml. of aqueous adrenal cortical extract given by injection) produces a fall in the eosinophil count of 50% or more, adrenal insufficiency is indicated rather than a refractory eosinophilia.

It might be expected that the eosinophil count should be higher in the presence of adrenal insufficiency than in normal subjects. Our series of cases is too small to allow any definite statement on this point, but only one case of Addison's disease and one case of hypopituitarism showed high counts (800 and 1,100 per c.mm. respectively). Forsham *et al.* found no difference between the initial counts in patients with Addison's disease and those of control subjects, though the counts varied widely as between different individuals.

Significance of Changes in the Urinary Uric-acid/creatinine Ratio

Forsham *et al.* stated that the urinary uric-acid/creatinine ratio remained remarkably constant from day to day, and that the increase in the ratio was mainly due to a rise of uric acid excretion, the urinary creatinine concentration usually remaining unchanged or diminished. They found, however, that the difference between the response to A.C.T.H. of normal individuals and that of patients with Addison's disease was not as clear-cut as the difference in eosinophil response. In the series reported here the changes in uric-acid/creatinine ratio seem to bear no relation to the changes in eosinophil counts. In fact, only 2 patients out of the 16 tested showed a rise of uric-acid/creatinine ratio of more than 50%. Both were known to be suffering from Addison's disease; one of them also showed a normal eosinophil response (see Table).

Forsham *et al.* pointed out certain limitations of the uric acid excretion as an indicator of reactivity to A.C.T.H. (1) Uric acid clearance may be nearly maximal in cases of dehydration, gout, leukaemia, or renal insufficiency, and a further increase may be impossible. (2) In patients with severe liver damage the formation of uric acid from its precursors may be impaired, thus limiting the rise in uric acid concentration in the blood and urine in response to A.C.T.H. (3) Reduction in the rate of breakdown of uric acid, as in hypothyroidism, might limit the response to A.C.T.H.

In Case 15 of this series there was tuberculous disease of the kidney, and in Case 19 the patient was suffering from chronic nephritis, so that renal disease probably vitiated this part of the test. In Case 16 the fluid and electrolyte balance was so deranged and the patient so uncooperative that an estimation of the uric-acid/creatinine ratio was impracticable.

Broch and Haugen (1950) found a great variation in the urinary uric-acid/creatinine ratio under standard conditions, and regarded a deviation of 50% as within the normal range.

Taussky *et al.* (1951) also pointed out the limitations of changes in the uric-acid/creatinine ratio as an index of adrenal cortical function. They found that fasting, by itself, led to a considerable rise in the ratio in normal subjects. This rise was not generally as pronounced as that which followed the administration of A.C.T.H., but it could account for an appreciable part of it. In contrast, the eosinophil count did not vary significantly with starvation alone. The degree of increase in the uric-acid/creatinine ratio, after fasting or after administration of A.C.T.H., seemed to vary inversely with the level of uric acid excretion during the control period, the latter being influenced by the purine content of the diet.

Thorn *et al.* (1951) have therefore abandoned the estimation of the uric-acid/creatinine ratio in testing for adrenal responsiveness.

Discussion

Although the series recorded here is a small one, it contains enough evidence to suggest that the Thorn test does not give an entirely reliable indication of adrenal cortical function. A normal eosinophil response to a single injection of 25 mg. of A.C.T.H. was obtained in two patients (Cases 7 and 8) with severe Addison's disease, one of whom died shortly afterwards and showed no trace of adrenal cortical tissue at necropsy. A normal eosinophil response does not therefore rule out the diagnosis of Addison's disease, though it would be dangerous to ignore a response of less than 50% in a doubtful case. In Case 14, for instance, the diagnosis of Addison's disease was in considerable doubt, and the eosinophils fell by 69%; in view of the findings in Cases 7 and 8 Addison's disease could not be excluded by the Thorn test alone. In Case 13 the diagnosis of Addison's disease had more to support it on

Table of Results of Thorn Test

Case No.	Diagnosis	Eosinophils/c.mm.		Urine (Initial)			Urine (4 Hours after A.C.T.H.)			% Change of Eosinophils	% Change of U-a/C. Ratio
		Initial	4 hrs. after A.C.T.H.	Uric Acid mg./100 ml.	Creatinine mg./100 ml.	Uric-acid/ Creatinine Ratio	Uric Acid mg./100 ml.	Creatinine mg./100 ml.	Uric-acid/ Creatinine Ratio		
1	Addison's disease	280	260	60	80	0·75:1	91	92	0·99:1	−7%	+32%
2	,, ,,	200	160	55·8	115	0·49:1	80	124	0·64:1	−20%	+31%
3	,, ,,	250	230	40	147	0·27:1	33·7	134	0·25:1	−8%	−7%
4	,, ,,	200	200	12	108	0·11:1	16	132	0·12:1	No fall	+9%
5	,, ,,	50	55	10·3	35	0·29:1	42·5	81	0·52:1	,,	+79%
6	,, ,,	800	750	10·3	89	0·11:1	8	70	0·12:1	−6%	+9%
7	,, ,,	70	30	32	124	0·25:1	42	109	0·39:1	−57%	+56%
8	,, ,,	120	30	72·8	128	0·57:1	62·5	144	0·44:1	−75%	−23%
9	Panhypopituitarism	450	320	33·6	101	0·33:1	24·6	83	0·3:1	−23%	No increase
10	,,	1,100	1,000	38·1	112	0·33:1	115	45·5	0·4:1	−9%	+21%
11	,,	160 to 100 (over 24 hours)	80 (no further change after 48 hours)	—	—	—	—	—	—	−20%	—
12	,,	280	170 (after i.v. infusion for 18 hours)	—	—	—	—	—	—	−39%	—
13	?Addison's disease	270	160	38	80	0·47:1	56	93	0·6:1	−41%	+28%
14	,, ,,	80	25	122	124	0·98:1	92·5	116	0·8:1	−69%	−18%
15	Renal tuberculosis	140	10	41	88	0·465:1	46	95	0·48:1	−92%	+3%
16	Anorexia nervosa	10	25	—	—	—	—	—	—	No fall	—
17	,, ,,	200	150	64	294	0·22:1	36	150	0·24:1	−25%	+9%
18	Anxiety state	40	20	38	120	0·32:1	42	97	0·435:1	−50%	+36%
19	Chronic nephritis	110	40	13·9	55	0·25:1	12·7	51	0·25:1	−64%	No change

clinical grounds, and there was only a 41% fall in the number of eosinophils; this is suggestive evidence of adrenal insufficiency, but enough time has not yet elapsed to enable the diagnosis in the case to be confirmed by a therapeutic test with D.C.A. In Case 17 there was no real evidence of adrenal insufficiency; yet the eosinophil count fell by only 25% after the administration of A.C.T.H.

While the diagnosis of Addison's disease may present no great problem in severe cases with classical pigmentation, hypotension, and crises, in a number of cases the blood pressure and blood chemistry are normal, pigmentation is atypical, and crises have not occurred. In the latter type of case the only clinical evidence for the diagnosis may be a combination of slight pigmentation, asthenia, and gastro-intestinal disturbance. Laboratory tests may be negative and there may be no calcification of the adrenal glands. The urinary 17-ketosteroid level may be reduced, but this is less helpful in the male in view of the testicular component. The Robinson–Power–Kepler test (1941) is perhaps the most helpful, but false positive results may be obtained in a number of conditions other than adrenal insufficiency (Levy *et al.*, 1946).

It is evident that there is still no single diagnostic test for Addison's disease which is completely reliable, and that, while a combination of the various tests may often be helpful, the diagnosis must in the last resort be made on clinical grounds.

Summary

The response of the eosinophil count and the uric-acid/creatinine ratio to the administration of A.C.T.H. was estimated in eight proved cases of Addison's disease, four cases of panhypopituitarism, and seven cases in which a diagnosis of adrenal insufficiency had been considered but not established.

Six of the eight patients with Addison's disease showed a fall of less than 50% in the eosinophil count. The other two showed falls of 57% and 75%, though in the former case the initial count was comparatively low and the change may not have been significant. Both these patients were suffering from a severe form of the disease, and the second of them died a fortnight after the test as a result of a severe respiratory infection; at necropsy no trace of adrenal cortical tissue could be found. In each of the four patients with hypopituitarism the eosinophil count fell by less than 50%. In the third group of cases four out of seven showed a normal eosinophil response; the other three showed subnormal responses, but one of them may prove to be a case of Addison's disease.

A number of workers have shown that the eosinophil count may fluctuate widely during the course of the day, and that the changes may exceed 50% of the initial level. Thus a fall in the eosinophil count exceeding 50% after the administration of A.C.T.H. does not exclude adrenal insufficiency, though a fall of less than 50% is strongly suggestive of such a diagnosis.

Changes in the uric-acid/creatinine ratio are of no value as an index of adrenal responsiveness.

The Thorn test is a useful addition to existing diagnostic methods, but it is subject to the limitations common to most laboratory tests, and the diagnosis must still, in the last resort, be made on clinical grounds.

We are grateful to Dr. R. L. Waterfield and his assistants in the department of haematology for carrying out the eosinophil counts, and to Dr. W. H. H. Merivale and his assistants in the department of clinical pathology for performing the uric acid and creatinine estimations.

REFERENCES

Abelson, D., and Moyes, E. N. (1950). *Lancet*, **2**, 50
Broch, O. J., and Haugen, H. N. (1950). *Acta endocr., Kbh.*, **5**, 143.
Dunger, R. (1910). *Münch. med. Wschr.*, **57**, 1942.
Fisher, B., and Fisher, E. R. (1951). *Amer. J. med. Sci.*, **221**, 121.
Folin, O. (1914). *J. biol. Chem.*, **17**, 469.
Forsham, P. H., Thorn, G. W., Prunty, F. T. G., and Hills, A. G. (1948). *J. clin. Endocr.*, **8**, 15.
Greenburgh, H., Merivale, W. H. H., Tickner, A., and Watson, D. (1950). *Guy's Hosp. Rep.*, **99**, 165.
Henneman, P. H., Wexler, H., and Westenhaver, M. M. (1949). *J. Lab. clin. Med.*, **34**, 1017.
Herbert, P. H., and de Vries, J. A. (1949). *Endocrinology*, **44**, 259.
Hills, A. G., Forsham, P. H., and Finch, C. A. (1948). *Blood*, **3**, 755.
Kellgren, J. H., and Janus, O. (1951). *British Medical Journal*, **2**, 1183.
Levy, M. S., Power, M. H., and Kepler, E. J. (1946). *J. clin. Endocr.*, **6**, 607.
Long, C. N. H., and Fry, E. G. (1945). *Proc. Soc. exp. Biol., N.Y.*, **59**, 67.
MacFarlane, J. C. W., and Cecil, G. W. (1951). *British Medical Journal*, **2**, 1187.
Randolph, T. G. (1944). *J. Allergy*, **15**, 89.
Recant, L., Forsham, P. H., and Thorn, G. W. (1948). *J. clin. Endocr.*, **8**, 589.
—— Hume, D. M., Forsham, P. H., and Thorn, G. W. (1950). Ibid., **10**, 187.
Renold, A. E., Forsham, P. H., Maisterrena, J., and Thorn, G. W. (1951). *New Engl. J. Med.*, **244**, 796.
Robinson, F. J., Power, M. H., and Kepler, E. J. (1941). *Proc. Mayo Clin.*, **16**, 577.
Roche, M., Forsham, P. H., Forsham, C. C., and Thorn, G. W. (1950). *J. clin. Endocr.*, **10**, 834.
—— Thorn, G. W., and Hills, A. G. (1950). *New Engl. J. Med.*, **242**, 307.
Rud, F. (1947). *Acta psychiat., Kbh.*, suppl. 40, p. 1.
Speirs, R. S., and Meyer R. K. (1949). *Endocrinology*, **45**, 403.
Swanson, J. N., Bauer, W., and Ropes, M. (1952). *Lancet*, **1**, 129.
Taussky, H. H., Swan, R. C., and Shorr, E. (1951). *Proc. Second clin. A.C.T.H. Conf.*, edited by John R. Mote, **1**, p. 273. Churchill, London.
Thorn, G. W., and Forsham, P. H. (1949). *Rec. Progr. Hormone Res.*, **4**, 229.
—— —— Frawley, T. F., Wilson, D. L., Renold, A. E., Fredrickson, D. S., and Jenkins, D. (1951). *Amer. J. Med.*, **10**, 595.
Tompsett, S. L., and Oastler, E. G. (1946). *Glasg. med. J.*, **27**, 281.

TOXIC REACTIONS DUE TO INTRAVENOUS IRON

BY

I. M. LIBRACH, M.B., D.P.H., D.C.H.

Medical Officer in Charge, Ilford Isolation Hospital

The work of Nissim (1947) and Wilkinson and Slack (1949) on intravenous iron needs no introduction. Although its therapeutic value is undisputed, iron is nevertheless a dangerous drug. The dangers of its oral use, especially in children, are well known. That it can cause reactions intravenously is also becoming increasingly obvious. These are usually mild, but severe ones have been reported (Govan and Scott, 1949; Mooney, 1950; Slowik, 1950; Ramsey, 1950; Birch and Till, 1951). Two further cases are here recorded and discussed.

Case 1

A housewife aged 24 was admitted on November 22, 1950, with chronic pulmonary tuberculosis. This started in 1945, and had recently been complicated by amyloid disease manifested by massive albuminuria. On December 6 the haemoglobin was 40%, plasma proteins 7.2 g. (albumin 1.1 g., globulin 6.1 g.). A course of oral iron (tab. ferr. sulph. co.) was given, with poor response. On December 18 intravenous therapy was begun. "Ferrivenin," 100 mg. (5 ml.), was injected on December 18, 22, and 27. Within one minute of the last injection an epileptiform fit occurred, lasting four minutes. On recovering, the patient said her eyes became blurred after the injection, but she remembered nothing else. She afterwards complained of lumbar pain lasting 30 minutes, then pain in the chest for 24 hours.

On January 10, 1951, her haemoglobin was 72%. On February 9 a different preparation, "neo-ferrum," was used intravenously, 100 mg. (5 ml.) being injected slowly. A few seconds later she complained of a burning sensation at the