with corticosteroids (Kendig and Toone, 1951; Kendall and Ledis, 1952; Eisenoff *et al.* 1954; Glynn Williams, 1953; Kurzrok *et al.*, 1954). It might therefore be argued that premature infants with sclerema can now be saved with corticosteroids. However, in our series premature infants have survived without the use of these hormones.

The use of antibiotics might influence the course of sclerema neonatorum. Bower *et al.* (1960) had 9 survivors among 14 full-term infants with sclerema and cold injury who received antibiotics without the addition of adrenal steroids. Fairchild (1955), in commenting on a report of Buess, who treated three full-term infants successfully with cortisone and antibiotics, stated that "the incidence of increased cures comes at a time when antibiotics are used more frequently in the newborn period." Wickes (1956) in reporting the case of an infant with sclerema who survived after the use of cortisone and tetracycline, admitted that antibiotics played their part, but felt that improvement coincided with the hormone therapy. This investigation was not designed to test the efficacy of antibiotic therapy and no definite conclusions regarding its value can be drawn from our series.

The percentage of body surface affected by the sclerematous process seemed to influence the prognosis. Whereas there was only one survivor (full-term) among the 20 cases with extensive sclerema, three of the five premature infants survived when not more than three different areas of the body were involved. Of these latter babies, two received no hormonal therapy.

It might be expected that the prognosis of sclerema neonatorum would be better in full-term than in premature infants, and it is of interest that the only survivor in our series with extensive sclerema was a full-term baby.

Thus on the basis of our study and a critical review of the literature we conclude that there is as yet no certain evidence that corticosteroids are of value in the treatment of sclerema neonatorum.

Summary

The efficacy of treatment of sclerema neonatorum with or without hydrocortisone or A.C.T.H. was assessed in a series of 25 infants.

Of 11 children treated with hydrocortisone or A.C.T.H. there was remission of the sclerema in two cases. In a control group of 14 infants not receiving these hormones, there were three survivors.

The prognosis is influenced by the extent of the sclerematous process.

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CUSHING'S SYNDROME IN CHILDHOOD DUE TO ADRENAL HYPERPLASIA

BY

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Cushing's syndrome is rare in childhood. All the cases reported in children under 10 years of age have been due to an adrenal tumour, except four which were associated with adrenocortical hyperplasia. Chute, Robinson, and Donohue (1949) first reported a case in which the syndrome was not due to a tumour, in an 8-year-old girl who died post-operatively after partial adrenalectomy. Hubble and Illingworth (1957) described two examples of adrenal hyperplasia in children. One of these was an 8-year-old boy with Cushing's syndrome who presented with arrested growth. He was treated by adrenalectomy; seven-eighths of the left and the whole of the right adrenal were removed. He afterwards required maintenance therapy by cortisone and grew rapidly. Goldblatt and Snaith (1958) described a case in an infant, and Silver and Ginsburgh (1960) described another in an 8-year-old girl. Both these cases were treated by bilateral adrenalectomy in two stages.

We now report a case of Cushing's syndrome due to adrenocortical hyperplasia, with onset at age 9, in a boy who was treated with total bilateral adrenalectomy when he was 11 years old.

Case History

The patient was referred to hospital at the age of 10 years 2 months with a history of excessive gain in weight for one year. Previously he had been rather thin, with a poor appetite. His mother had noticed that he had stopped growing. He also had a history of periodic pain and pyrexia. On examination he was found to be obese, weight 121 lb. (54.9 kg.), height 55 in. (140 cm.), B.P. 145/112. He had a slight buffalo hump but no striae. He was put on a 1,000-calorie diet, to which he strictly adhered. During the next four months he lost 14 lb. (6.4 kg.) in weight and his blood-pressure fell to 125/95. In this period he developed frontal and temporal headaches and also complained of pains in the back, of increasing severity. There was a marked increase in growth of body hair.

On October 6, 1958, when he was aged 10 years 8 months, he was admitted to hospital for investigation.

Clinical Findings

He was a plethoric moon-faced boy with acne on the forehead. The sides of his face and neck and his back were covered with fine hair. His pubic and axillary hair had developed, his penis and testes were still small. He now had a marked buffalo hump and showed the characteristic appearances of Cushing's syndrome (Fig. 1). His B.P. was 130/105, Hb 14.9 g./100 ml., W.B.C. 9,100, eosinophils nil. Fasting blood sugar was 89 mg./100 ml. Glucose tolerance: after 40 g. glucose the blood sugar rose to 177 mg./100 ml. in two hours. The blood sugar showed a normal response to the insulin-sensitivity test, using 4 units of soluble insulin intravenously. Serum sodium, potassium, chloride, calcium, and blood urea were normal. Urine: albumin nil, deposit normal, culture sterile. The 24-hour urinary output of 17-ketosteroids was 53.1 mg., of 17-hydroxycorticosteroids 60 mg., of creatinine 0.325 g., and of creatine 0.258 g. Patterson's (1947) test for dehydroisoandrosterone was negative. The adrenal suppressing effect of 9 α -fluoro-16 α -hydroxyprednisolone was then determined (Table I).

Triamcinolone (4 mg. four times daily) reduced the urinary 17-ketosteroids from 53.1 to 28.2 mg./24 hours after eight days' treatment, and to 24.7 mg./24 hours after 16 days' treatment. The 17-hydroxycorticosteroids were reduced from 60 to 49.5 mg./24 hours after eight days' treatment. After three weeks of triamcinolone there was no further fall in these urinary steroids. There was no improvement in the boy's symptoms on this treatment.

Dr. E. E. Hill (Department of Clinical Endocrinology, Birmingham), using the Morris method for fractionation of the total 17-ketogenic steroids into 11-desoxy and 11-oxygenated 17-ketogenic steroids (Morris, 1959), reported that the 17-ketogenic steroids were high for a child of this age (Table II), but, unlike congenital adrenal hyperplasia and virilism, the ratio of the 11-desoxy/11-oxygenated ketogenic steroids was normal (Hill, 1960).

X-ray films of the spine showed generalized osteoporosis. His skeletal age was approximately 10 years. An intravenous pyelogram was normal. Both kidneys were in the

normal position and there was no evidence of suprarenal calcification. Perirenal insufflation of air (Dr. W. E. C. Astle): no suprarenal tumour was demonstrated; the left suprarenal was visualized and the appearances were consistent with slight hyperplasia; the right suprarenal was not visible.

The case was then shown to Professor D. V. Hubble, who confirmed that this was Cushing's syndrome, caused by adrenal hyperplasia, and suggested total adrenalectomy. Before carrying out such a drastic operation it was decided to watch the boy's progress for a time. During the next

FIG. 1.—Appearance before adrenalectomy.

three months, however, he deteriorated. The pains in his back were more acute and he became weaker and more miserable. X-ray examination of the spine showed collapse of the twelfth thoracic and first lumbar vertebrae due to osteoporosis.

On March 13, 1959, he was readmitted for adrenalectomy. His blood-pressure was then 190/120–160/130. The effect of A.C.T.H. was tested two weeks before operation (see Table I). Treatment with A.C.T.H. gel (40 I.U. b.d.) for two days increased the output of 17-ketosteroids from 30.5 mg. to 91 mg./24 hours, and the 17-hydroxycorticosteroids from 79.7 mg. to 220 mg./24 hours.

Operation

A diagnosis of Cushing's syndrome due to adrenal hyperplasia having been established, an operation was carried out by one of us (G.G.C.) on April 2, 100 mg. of cortisone having been given intramuscularly two hours before operation. The incision used was the anterior transverse upper abdominal approach. The right adrenal was mobilized first, and this was carried out satisfactorily, 50 mg. of hydrocortisone again being given intravenously while the gland was being completely removed. The left adrenal was then removed completely, 50 mg. of hydrocortisone again being given intravenously; but this dissection was complicated by some haemorrhage from rupture of the left adrenal vein at its junction with the left renal vein. When this happened his blood-pressure fell to 30 mm., but when the haemorrhage was controlled it rose immediately to 130 mm. The abdomen was closed in layers.

Post-operatively a further 100 mg. of cortisone was given the same day, making a total of 300 mg. This dose was continued for the next two days and then gradually reduced

TABLE I.—Excretion of Urinary Steroids

Date	Treatment	17-Keto-steroids (mg./24 Hours)	17-Hydroxy-corticosteroids (mg./24 Hours)
9/10/58	Nil	53.1	60.0
29/10/58	After 8 days triamcinolone 16 mg./day	28.2	49.5
5/11/58	After 16 days triamcinolone 16 mg./day	24.7	—
12/11/58	On triamcinolone 12 mg./day	26.3	48.7
15/3/59	Nil	48.1	108
16/3/59	Nil	30.5	79.7
17/3/59	A.C.T.H. gel 40 I.U. x 2	51.8	195
18/3/59	Nil	91	220
19/3/59	Nil	27.3	170
20/3/59	Nil	35.8	116
2/4/59	Bilateral adrenalectomy		
	Maintenance therapy		
22/4/59	Cortisone 62.5 mg./day	1.7	26.7
8/1/60	Cortisone 12.5 mg./day. Fludrocortisone 0.1 mg./day	1.6	7.8

TABLE II

11-Desoxy Fraction II	11-Oxygenated Fraction III	Ratio II/III
6 mg./24 hours	14.8 mg./24 hours	0.4
5.6 "	18.2 "	0.3

over the next four weeks to 12.5 mg. daily. He continued to have hypertension (B.P. 130/100–160/100) for four weeks after operation. His blood-pressure then slowly fell to 115/75.

Progress

From the second week post-operatively there was a steady improvement in his appearance and general condition. He gradually lost his hirsuties and obesity. Three months after adrenalectomy he seemed years younger and looked like a normal boy of 11. He started to grow four months after operation and gained 4½ in. (11.4 cm.) in six months, and 9½ in. (24 cm.) in 18 months (Fig. 2).

FIG. 2.—Arrested growth for two years followed by rapid increase in height, starting four months after adrenalectomy. The fall of 1 in. (2.5 cm.) was due to vertebral compression.

X-ray films showed normal development of his epiphyses throughout the follow-up period. His skeletal age was now slightly in advance of 13 years and there was no longer any osteoporosis. His weakness and lassitude greatly improved but five months after operation it was noted that he still did not have as much energy as a normal boy, and that he tired easily in hot weather in spite of extra salt in his diet. He was then given fludrocortisone (9 α -fluorohydrocortisone) 0.1 mg. daily, in addition to cortisone. This produced a great improvement. After trying various dose levels it was found

FIG. 3.—Appearance 11 months after adrenalectomy.

that doses of cortisone 15 mg. daily and fludrocortisone 0.1 mg. daily were satisfactory in maintaining normal health and blood-pressure.

A year after operation he was leading a normal vigorous life and could cycle 10 miles (16 km.) without fatigue (Fig. 3). At the time of writing he had been followed up for two years and remained fit and well.

Histology

Professor T. Symington kindly examined the H. and E. sections and reported that the appearances show a prominent zona glomerulosa on the surface of the gland, while the rest of the cortex forms a fairly uniform picture. Most of the cells are compact in type—that is, eosinophilic cytoplasm—some of them are vacuolated and obviously contain lipid material. These appearances of eosinophilic compact cells, extending almost the whole length of the zona fasciculata, are more like that found in the adrenogenital syndrome than that usually found in the hyperplastic gland from a case of Cushing's syndrome, but a similar picture can be obtained from Cushing's syndrome if the gland is removed after A.C.T.H. treatment or after death.

The glands, which were obviously much enlarged, were not weighed, as it was hoped to carry out enzyme studies, which eventually was not practicable.

Discussion

This boy stopped growing at the age of 9 and developed the characteristic picture of Cushing's syndrome—obesity with moonface and buffalo hump, hirsuties, acne, osteoporosis, and marked hypertension.

The urinary 17-ketosteroids and 17-hydroxycorticosteroids, which were both very high, showed a marked fall when triamcinolone was given. The suppression of exaggerated adrenocortical activity by exogenous steroids is characteristic of adrenal hyperplasia and not of a tumour (Wilkins, 1957). When hyperplasia is associated with the adrenogenital syndrome, in which there is excess of corticotrophin due to defective synthesis of cortisol, the suppression by exogenous steroids is complete and the urinary 17-ketosteroids return to normal (Jailer, Gold, and Wallace, 1954). Similarly, in Cushing's syndrome suppression also occurs when adrenal hyperplasia is present (Cope, 1956). This probably indicates that the adrenal hyperactivity is under the control of corticotrophin stimulation (Cope and Harrison, 1955). However, in our case the adrenal suppression was incomplete after three weeks of steroid therapy, and the urinary 17-ketosteroids were 26.3 mg. and the 17-hydroxycorticosteroids 48.7 mg./24 hours. The dose of triamcinolone was adequate to have produced corticotrophin suppression, but despite this excessive adrenocortical activity continued. This presumably indicates that the overactivity of the adrenal cortex was in some degree independent of corticotrophin control.

There was a great increase in adrenocortical activity as soon as A.C.T.H. was given, and the urinary 17-hydroxycorticosteroids rose 220 mg. on the second day. This response to exogenous A.C.T.H. stimulation suggests that the adrenal cortex was not under maximal stimulation by corticotrophin. When the adrenals were removed, two weeks after A.C.T.H. had been given, they showed microscopical changes resulting from this stimulation by A.C.T.H.—that is, eosinophilic compact cells extending from the zona reticularis along almost the whole length of the zona fasciculata. These changes in the hyperplastic adrenals in Cushing's syndrome, if the glands have been removed after A.C.T.H. therapy,

have previously been recorded (Symington *et al.*, 1958 ; Symington, 1959). The microscopical appearances in fact resembled those found in the adrenogenital syndrome, in which condition there is an excess of corticotrophin. It has been suggested that Cushing's syndrome may be due to hypersensitivity of the adrenals to corticotrophin, which is not present in excessive amounts (Christy, Wallace, and Jailer, 1955).

A raised urinary pregnanetriol is characteristic of adrenal hyperplasia due to the adrenogenital syndrome. In this case, however, the mean ratio of the 11-desoxy/11-oxygenated ketogenic steroids was 0.35 (Table II), which is normal. The ratio of these fractions in the adrenogenital syndrome is much higher and averages 2.3 (Hill, 1960).

The responses to 9 α -fluoro-16 α -hydroxyprednisolone and A.C.T.H., together with the negative Patterson test for dehydroisoandrosterone, indicated that this boy was suffering from adrenocortical hyperplasia and not from an adrenal adenoma or carcinoma.

The prognosis in Cushing's syndrome due to adrenocortical hyperplasia recorded in adults is bad and the average expectation of life without treatment is about five years (Bishop, 1954). Bilateral total adrenalectomy is the treatment of choice, and in our opinion the anterior transverse upper abdominal approach is a highly satisfactory one for this procedure (Aird and Helman, 1955). Partial adrenalectomy is unreliable, as the patients are apt either to relapse or to require maintenance cortisone, anyway, in order to prevent adrenal crises.

The results of total adrenalectomy on this boy have been most satisfactory and he has been very well for the past 20 months on small maintenance doses of cortisone and fludrocortisone. He now has the normal appearances and vigour of a boy of 12. His genitalia are developing with puberty, which seems to be taking place normally. He started to grow four months after adrenalectomy and he now shows a pubertal spurt of growth.

Summary

A case of Cushing's syndrome due to adrenocortical hyperplasia developing in a 9-year-old boy is described, in which the presenting symptoms were obesity and arrested growth.

He was treated successfully by total bilateral adrenalectomy through a transabdominal incision.

The diagnostic tests differentiating this condition from adrenal tumour are described, and the results compared with those found in the adrenogenital syndrome. A follow-up report is given over two years, with particular reference to growth and development.

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Preliminary Communications

An Isotope Test of Calcium Absorption *

At the present time the measurement of calcium absorption requires full calcium balance procedures. A valid calcium balance takes at least three or four weeks to perform and the determination of the state of calcium absorption in any individual subject is therefore time-consuming and costly. It is probably fair to say that many of the problems of calcium absorption remain unsolved largely because of the technical difficulties involved in their study.

The availability of radioisotopes of calcium and strontium, and in particular the availability of calcium-47, which is a γ -emitting isotope with a relatively short half-life, suggested the possibility that a simple isotopic procedure might be developed for the measurement of calcium absorption. The fate of ingested isotopes of calcium and strontium has been studied (Staub, 1954 ; Blau *et al.*, 1954 ; Bronner and Harris, 1956 ; Samachson, 1960), but no standardized test procedure has been established. The present paper describes a simple isotopic procedure for estimating calcium absorption based on plasma activity two hours after oral administration of the isotope.

METHODS

The isotope was usually given with 250 mg. of calcium as calcium chloride not less than one hour after the last meal ; no further food was allowed for at least one hour after the oral dose had been given. Some concentrated orange juice was also given to render the mixture more palatable. Samples of venous blood were taken at intervals after the administration of the dose, and the plasma activity was determined and expressed as a percentage of the dose per litre of plasma. In a few cases the isotope was given with calcium carbonate carrier. The isotope was equilibrated for 24 hours with the carrier before administration, and filtration of the material showed that only about 10% of the radioactivity was filterable.

The dose used was 7.5 μ c of calcium-47 (half-life 4.7 days) or 5 μ c of calcium-45 (half-life 152 days). The calcium-45 was given only to subjects over the age of 40.

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