routine tests of haemostatic function are invariably normal. No deficiency of platelet factor as evidenced by the normal thromboplastin generation tests was detected in either of the above patients.

In both patients the platelet count returned to normal and bleeding ceased after treatment with radioactive phosphorus.

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CUSHING'S SYNDROME IN CHILDHOOD

REPORT OF CASE OF ADRENOCORTICAL CARCINOMA WITH EXCESSIVE ALDOSTERONE PRODUCTION

BY

W. P. U. JACKSON, M.D., M.R.C.P., D.C.H.

B. ZILBERG, M.B., M.R.C.P.Ed., D.C.H.

B. LEWIS, Ph.D., M.B., A.R.I.C.

AND

D. MCKENZIE, M.Med.(Path.)

From the Endocrine Clinic and Laboratories of the Department of Medicine; and the Departments of Paediatrics and Pathology, Groote Schuur Hospital and the University of Capetown, South Africa.

Adrenocortical overactivity in childhood may produce two distinct syndromes. The adrenogenital syndrome is caused by excessive production of androgens, and may manifest itself in three ways. If it starts in intrauterine life in a female, pseudohermaphroditism results; post-natally in a girl it produces virilism; in a boy the "pocket Hercules" variety of isosexual precocity results. An excess of glucocorticoids, on the other hand, gives rise to Cushing's syndrome, without masculinization.

Almost all cases of Cushing's syndrome in childhood are caused by adrenocortical carcinoma. Wilkins (1948) collected 70 cases of cortical carcinoma from the literature, and in his book (Wilkins, 1950) he reviewed 26 cases of Cushing's syndrome, all under the age of 10 years. Twenty-two of these were in girls; as in the adult, Cushing's syndrome in childhood is more common in females. A few other cases have been reported since then, and Guin and Gilbert (1956) produced a further review. The two cases of Cushing's syndrome not associated with carcinoma were reported by Chute *et al.* (1949) (bilateral nodular hyperplasia) and Powell *et al.* (1955) (bilateral cortical adenomas).

Functioning adenomas of the adrenal cortex at any age produce either pure Cushing's syndrome or a pure adrenogenital syndrome. Overproduction of the other two groups of adrenocortical hormones, the oestrogens and mineralocorticoids, appears to be of little importance in childhood. Oestrogen excess, leading to precocious pubertal development of female type, is ex-

remely rare, while primary aldosteronism has not, to our knowledge, been described in childhood.

Unlike adrenal adenomas, carcinomas are biochemically pluripotent and produce excessive quantities of androgens, glucocorticoids, and also oestrogens (where these have been measured). In the case described below aldosterone was also found in great quantities in the urine. Consequently it is logical that the clinical picture may also be a mixed one in cases of carcinoma, being composed of features of Cushing's and the adrenogenital syndrome:

Since virtually all cases of Cushing's syndrome in childhood are caused by carcinoma one may expect to find evidence of the adrenogenital syndrome in all of them. On the other hand, only some adrenogenital cases (those with carcinoma) will show features of Cushing's syndrome. Now, in some ways the androgens and the glucocorticoids are mutually antagonistic, so that the resultant syndrome of excess of both may be variable. Thus androgens promote rapid skeletal growth and maturation, whereas cortisol (the chief glucocorticoid) abruptly terminates these. Androgens increase muscle bulk and power; cortisol diminishes these, producing fat from muscle and so increasing weakness. Cortisol actually opposes anabolism, leading to porosis of bone and gluconeogenesis with raising of blood sugar. Androgens tend to counteract these by promoting protein anabolism. In the case presented below the two opposing forces seemed so well titrated against each other that bone and tooth age and density, muscular configuration and power, and blood-sugar level did not appear to depart from the normal.

Case Report

A coloured girl was admitted to Groote Schuur Hospital at the age of 2½ years. Since the age of 1 year there had been an abnormally rapid gain in weight. At this age pubic and axillary hair first appeared. Three weeks before admission a facial eruption was noticed. There was no history of menstruation.

Physical examination revealed an obese child, with a Cushing-like facies and signs of virilism (Fig. 1). The obesity included limbs as well as trunk. Her height was 31½ in. (80 cm.) and weight 39 lb. (17.7 kg.). She had a plethoric appearance and a well-marked "buffalo-neck." There was an eruption on the face, which resembled adenoma sebaceum. Axillary and pubic hair were present and the clitoris was enlarged. Strong body odour was obvious. There was no true breast development. Her B.P. was 130/90; Hb, 15 g./100 ml.; P.C.V., 45%. The specific gravity of the urine was 1015. E.C.G. was normal. Blood chemistry: serum Na,

133 mEq/l.; serum K, 5.5 mEq/l.; serum Cl, 102 mEq/l.; CO_2 -combining power, 57 vols.%; blood urea, 32 mg./100 ml.; serum alkaline phosphatase, 5.3 units (Bodansky-Shinowara); serum albumin, 4.19 g./100 ml.; serum globulin, 2.89 g./100 ml.; thymol turbidity, 6.3 units; fasting blood sugar, 88 mg./100 ml.; urine concentration test, S.G. rose to 1025.

Radiographs of the long bones showed normal bone age and no osteoporosis. An intravenous pyelogram revealed normally functioning kidneys. The left kidney was depressed and a mass was visible above this kidney. Chest x-ray examination revealed no abnormality.

1a

1b

1c

1d

FIG. 1.—Appearance before (1a and 1c) and 12 weeks after (1b and 1d) adrenalectomy.

The 24-hour urinary output of 17-ketosteroids was 39 mg., that of 17-ketogenic steroids (Norymberski) 11.6 mg., and of aldosterone 75 μg . (expected normals for these three steroids are, respectively, under 2 mg., under 3 mg., and under 10 μg . per 24 hours).

Urinary sodium and potassium studies were made over six consecutive days. During this time basal readings were obtained and the effects of a potassium load and of prednisone administration were observed. (See section on steroids below.)

The combination of features of Cushing's syndrome and virilism at this age strongly suggested adrenocortical carcinoma, which was supported by high urinary steroid output. Pyelography indicated that the tumour was on the left side.

Course and Treatment

On March 24, 1957, 50 mg. of cortisone was given by intramuscular injection. On the morning of the 25th this was repeated, and that afternoon left-sided adrenalectomy was performed (Professor J. H. Louw), while the patient received an intravenous infusion of N/2 saline with 50 mg. of soluble cortisol (hydrocortisone). Twelve hours post-operatively the blood pressure dropped from 140/90 to 100/70. Fifty units of soluble cortisol was given intravenously and 50 mg. intramuscularly. 50 mg. of cortisone was then given intramuscularly twice daily for three days. This was replaced by oral cortisone in decreasing dosage until it was withdrawn after five days, when corticotrophin Z, 25 units, was injected intramuscularly on two occasions. Intravenous infusions were maintained for two days after operation. The subsequent post-operative course was uneventful.

Five weeks after the operation the patient had lost 3 lb. (1.4 kg.). She was no longer as plethoric as before; the facial eruption had diminished, and the body odour was less obvious. Blood pressure had dropped to 105/70. Twelve weeks after the operation her appearance had changed dramatically (Fig. 1). She had lost 4 lb. (1.8 kg.) more, her facial skin was quite clear, the buffalo-hump had disappeared, the body odour had disappeared, and the clitoris was smaller. Hirsuties was still considerable. The 24-hour urinary output of 17-ketosteroids had fallen to 1 mg.

Seven months after the operation the clitoris was of normal size and the pubic hair had almost disappeared.

Endocrine Studies

In addition to estimation of hormone output levels in basal state, the effect upon these of potassium loading and of prednisone was investigated. In primary hyperaldosteronism (due to adrenal adenoma) the aldosterone output may become demonstrably abnormal only during periods of high potassium intake (Eales and Linder, 1956). The tumour in such instances resembles the normal adrenal glomerulosa in its secretory response to hyperpotassaemia. In the present case we therefore observed the effect of an extra 100 mEq of potassium in the diet.

Secondly, the dependence of the adrenal tumour on the pituitary was studied by following the plasma cortisol and urinary steroid hormone excretion during the administration of Δ^1 -cortisone (prednisone) in doses of 5 mg. twice a day. Prednisone is one of the most potent suppressors of the secretion of corticotrophin by the pituitary.

Estimations of intake and urinary output of sodium and potassium were undertaken at the same time, to ascertain whether the cortical steroids were producing excessive retention of sodium or loss of potassium.

The urinary 17-ketogenic steroids and 17-ketosteroids were determined by the method of Norymberski, Stubbs, and West (1953), plasma cortisol by that of Lewis (1957), and urinary aldosterone by the physico-chemical procedure of Neher and Wettstein (1956). The ketogenic steroids are a measure of the metabolites of cortisol predominantly, but the excretory product of 17-hydroxyprogesterone also contributes to these urinary steroids. 17-Hydroxyprogesterone is andro-

genic, but is probably not secreted by the normal adrenal; it is an intermediate product in the course of the biosynthesis of glucocorticoids. Further confirmation of the nature of the substance measured by the Neher and Wettstein procedure was provided by chromatography of the acetylated urinary extract in benzene/formamide, whereby the appropriate quantity of a substance with the Rf value of aldosterone diacetate was demonstrated. The material also migrated with aldosterone in the system iso-octane/*tert*-butanol-water (Eberlein and Bongiovanni, 1955).

Results

The steroid determination (Table I) showed a striking excess of aldosterone, 17-ketosteroids, and 17-ketogenic steroids in the urine and of cortisol in the plasma, represent-

TABLE I

	Urinary 17- ketosteroids mg./24 Hours	Urinary 17- ketogenic Steroids mg./24 Hours	Plasma Cortisol μg./100 ml.	Urinary Aldosterone μg./24 Hours
March 3: Normal diet	39	11.6	—	—
" 5: " "	—	—	32	75
" 6: Potassium load ..	48	5.8	—	—
" 7: " "	—	—	37	75
" 8: Prednisone ..	43	6.9	—	—
" 9: " "	37	4.0	26	—
" 25: " "	Adrenalectomy	—	—	—
April 7	—	—	—	10
" 15	2.8	—	—	—
May 10	—	—	4	2
" 11	1.0	—	—	—

ing hypersecretion of mineralocorticoid, androgen, and glucocorticoid. Fractionation of the 17-ketosteroids showed an abnormal amount of dehydroepiandrosterone. This is the main constituent of the "β-fraction" as segregated by digitonin precipitation, and is believed to be strongly suggestive of adrenocortical carcinoma.

Potassium loading (100 mEq in addition to normal diet) failed to augment the massive aldosterone output. Prednisone (given for only 48 hours) showed a possible suppressing effect on cortisol and 17-ketosteroid secretion on the second day, but the results were not conclusive and this suppression, if present, was not great.

Sodium and potassium "balance" data are presented in Table II. Urine collections were difficult, and were analysed only on those days when collections were virtually complete.

TABLE II.—Electrolyte Balance

	Sodium (mEq/24 Hours)		Potassium (mEq/24 Hours)	
	Intake	Urine	Intake	Urine
March 5: Normal diet ..	45.4	22.3	63.9	32.3
" 6: High K intake ..	43.8	41.0	149.9	74.9
" 8: High K intake and prednisone	47.0	36.4	157.2	78.8
" 9: " "	45.1	33.0	152.9	81.4

We observed no evidence of any considerable retention of sodium, and certainly no excessive loss of potassium. The high potassium intake appeared to augment the urinary sodium. The prednisone had no effect on the electrolyte balance.

The gratifying clinical response to adrenalectomy was mirrored in the hormone studies, which declined to normal levels (and have remained so during a six-months follow-up).

The Adrenocortical Tumour

The specimen (Fig. 2) consisted of a triangular mass of tissue weighing 36 g. and measuring 5 cm. along each border and 3 cm. in thickness. The outer surface was smooth and encapsulated. A small breach at one point was apparently due to operative trauma. At one pole there was a projecting tag of orange-yellow tissue measuring 1.5 by 2 by 1 cm.

On cut section the greater portion was lobulated and bright orange-yellow, a smaller portion appearing more fleshy and brown.

Sections stained with haematoxylin and eosin showed a highly anaplastic carcinoma (Fig. 3). The majority of the cells of the tumour were extremely bizarre in shape and varied considerably in size. The cytoplasm of many cells was finely granular and vacuolated. The nuclei showed many irregularities and mitotic figures were numerous. The tumour cells were divided haphazardly into groups by a fairly extensive network of thin-walled vessels. There was no haemorrhage into the tumour, and no obvious vascular infiltration was noted.

Closely applied to the tumour on its external surface was a well-marked fibrous tissue capsule. On the outer surface of this, and separated by it from the tumour, was a tag of compressed normal-looking adrenal gland tissue.

FIG. 2.—Left adrenal gland after removal.

FIG. 3.—Photomicrograph of the tumour and its "capsule." (×500.) Note extreme pleomorphism of cells, and large hyperchromatic nuclei with several mitotic figures.

A frozen section showed varying amounts of fat in different areas. In some areas cells were loaded with fat; in others it was evident as fine droplets in the cytoplasm.

Ponceau-fuchsin staining of a section fixed in formal-saline showed the cytoplasm of the tumour cells to be loaded with vivid red fuchsinophil granules which were not evident in the attached portion of normal adrenal.

Discussion

Diagnosis.—In this child the clinical features of Cushing's syndrome and virilism suggested the diagnosis of adrenocortical carcinoma. The very high urinary output of 17-ketosteroids provided confirmatory evidence. An interesting

feature here was the apparent metabolic "balance" produced by the concomitant hypersecretion of glucocorticoids, mineralocorticoids and androgens. Thus there was no disturbance in muscular strength, bone growth, or electrolyte balance. The marked body odour probably was due to excessive apocrine activity. The tumour was lateralized by intravenous pyelography combined with tomography. Presacral air insufflation was rendered unnecessary by this manoeuvre. It is noteworthy that the length of this history (18 months) was not incompatible with a localized carcinoma in this case.

Steroid Findings.—Despite the probable zonation of function within the normal adrenal cortex (Chute *et al.*, 1949; Landing, 1955), the tumour, a strikingly undifferentiated carcinoma, possessed the ability to synthesize all the three major groups of adrenal hormones. While the simultaneous hypersecretion of glucocorticoid and androgen by adrenal tumours is commonplace, and that of glucocorticoid and aldosterone has been described, the present case offers a remarkable example of pluripotency of an adrenal tumour. The increase in aldosterone excretion was notable not only for its magnitude but also for the absence of its expected effect on electrolyte excretion or serum potassium level. The opposing effect of androgens in promoting potassium retention may be relevant in this connexion. In common with some cases of Conn's syndrome of primary aldosteronism, sodium metabolism was not grossly disturbed; arterial hypertension was, however, present. Possible explanations for lack of electrolyte disturbances include the simultaneous hypersecretion of an unknown sodium-diuretic hormone; alternatively, some combination of known hormones may possess sodium-diuretic activity, or conceivably the renal tubular epithelium may lose its responsiveness to aldosterone.

Treatment.—When there is no evidence of secondary deposits, adrenalectomy is indicated in cases of adrenocortical carcinoma. When there is doubt about which adrenal is involved, the transperitoneal approach is favoured. Adrenalectomy may be followed by a period of hypoadrenalism, because the opposite adrenal is usually atrophic. To prevent this, cortisone is usually given pre-operatively and continued during the operation and in the immediate post-operative period. When cortisone is withdrawn, corticotrophin may be given in an effort to stimulate the remaining adrenal gland. In our patient there was a precipitous drop in the blood pressure 12 hours post-operatively. This was believed to be an indication for intravenous cortisol. It suggested that the remaining adrenal was atrophic and not also carcinomatous. The change in the appearance of the patient 12 weeks after the operation was very gratifying. A striking feature was the disappearance of the strong body odour. Though androgen overactivity as judged by the 17-ketosteroid excretion was now controlled, the hirsuties and clitoral enlargement did not disappear until a further four months had passed. These signs of virilism usually take a long time to regress and may in some instances be permanent, in which case clitoridectomy may be necessary.

Prognosis.—If the offending adrenal is removed before metastases have developed, the chances of complete cure appear to be good. Unfortunately, in many cases of Cushing's syndrome in childhood the progress is rapid and adrenalectomy useless. Our patient seems to be fortunate, and the probability of cure must be considered high, since steroid excretion has returned to a normal level.

Summary

The relationship between Cushing's syndrome in childhood and adrenocortical carcinoma is briefly considered. A "mixed picture" of Cushing's and adrenogenital syndromes is characteristic, and is illustrated by a reported case. In this patient an excessive production of glucocorticoids, androgen, and mineralocorticoids (aldosterone) was demonstrated. In some ways the

usual clinical effects of each of these steroids were annulled by the opposing effects of the others.

The offending adrenocortical carcinoma was removed. Its histological appearance is described. The operation was followed by a remarkable improvement, with return to normal in the child's appearance and her hormone output.

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MULTIPLE EPIPHYSIAL DYSPLASIA

BY

HERBERT BARRIE, M.D.

CEDRIC CARTER, B.M., M.R.C.P.*

AND

JOHN SUTCLIFFE, M.B., M.R.C.P., F.F.R.

Hospital for Sick Children, Great Ormond Street, London

Multiple epiphyseal dysplasia is an uncommon condition, but is likely to be of interest to general practitioners on account of its marked familial features. Although Fairbank (1947) did not stress the genetic aspect in his original description, a number of affected families have since been recorded. Often a correct diagnosis in one member of a family will uncover several previously undiagnosed or misdiagnosed cases. Recognition of this condition is of more than academic interest, since many patients derive benefit from appropriate physiotherapy, while harm may result from treatment based on the wrong diagnosis. To make this condition more widely known, we report three further affected families, with descriptions of the clinical, radiological, and genetic features of these and previously published case reports. The family trees are shown in Figs. 1, 2, and 3. The clinical features are summarized in the Table.

Historical Note.—In 1935 Fairbank suggested the term "epiphyseal dysplasia" for a patient with multiple irregular epiphyseal ossification. To this title "generalisata" was added, but it was changed later to "multiplex" when the epiphyseal changes were found to be multiple rather than generalized. Twelve years later he published a masterly account of the clinical and radiological features of the disease based on a study of 20 patients, many of whom had previously been reported as atypical examples of a variety of conditions, including achondroplasia, stippling of the epiphyses (dys-

*Medical Research Council, Clinical Genetics Research Unit.