and a half years have been observed. The patient in the early stages of the disease is likely to respond better to treatment, but of three patients (Cases 8, 12, and 15) who had become refractory to radiotherapy, two, including one in the acute terminal stage (Case 8), were benefited by mercaptopurine.

No unpleasant side-effects have been observed, and evidence of serious bone-marrow depression has not followed prolonged dosage with mercaptopurine. The need for regular blood examination is, however, stressed.

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ADDENDUM.—The patient in Case 6 has since died following admission to hospital with widespread haemorrhage. There was leucopenia and thrombocytopenia, and marrow depression secondary to mercaptopurine therapy seemed the likely explanation.

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ADRENAL VIRILISM TREATED WITH STEROIDS

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Congenital adrenocortical hyperplasia is manifested as pseudohermaphroditism in females and macrogenitosomia praecox in males, both conditions being due to excess of adrenal androgens and being associated with increased urinary excretion of 17-ketosteroids. If the adrenal disturbance arises after the fourth month of foetal life, by which time the external genitalia have developed, the result in the female is virilism, characterized by hirsutism and hypertrophy of the clitoris. Wilkins and his colleagues (1950, 1951, 1952a, 1952b), the first to treat the condition with cortisone, observed a prompt fall in the 17-ketosteroid excretion and a striking improvement in the clinical features. These changes are due to the inhibitory effect of cortisone on the secretion of corticotrophin, which is responsible for the hyperplasia and the excessive production of adrenal androgens (Bartter *et al.*, 1951). The effects of long-term cortisone treatment of congenital adrenocortical hyperplasia have been described (Wilkins *et al.*, 1952a, 1952b; Goldberg, 1954), but there are few reports of such treat-

ment in patients in whom virilism developed later in life. Bishop *et al.* (1952), Hubble (1952), and Bastenie *et al.* (1953) have described cases treated for a short time with cortisone.

Segaloff *et al.* (1955), taking advantage of the very slow absorption of hydrocortisone acetate when injected intramuscularly, described the beneficial effects of this preparation in adrenal virilism when injected as infrequently as once a week or even once a fortnight.

More recently Δ^1 unsaturated forms of both cortisone and hydrocortisone, known as prednisone and prednisolone respectively, have been produced. They are much more active than the parent steroids but have little or no effect on the blood electrolytes. Kupperman *et al.* (1955) compared the effect of oral cortisone and prednisone in the treatment of adrenal virilism and concluded that prednisone is the steroid of choice, since they found that it was three to four times more active than cortisone and did not induce sodium retention.

The following four cases of virilism due to adrenocortical hyperplasia are reported with particular reference to the effects of treatment with cortisone, hydrocortisone acetate, prednisone, and prednisolone.

Case 1

The patient was a boy aged 3½ years. Excessive growth of the penis and the appearance of pubic hair were observed when he was aged 2. On examination his height was 3 ft. 6 in. (106.6 cm.) and weight 3 st. 3 lb. (19 kg.). The penis was enlarged and there was scanty pubic hair (Fig. 1); both testes were in the scrotum and were of normal size. Radiological examination of the skeleton showed a bone age of 11 years. Radiological examination of the pituitary fossa and tomograms of the adrenal regions were normal. Serum sodium and potassium were normal. The daily 17-ketosteroid excretion over a period of ten days ranged from 11.9 to 25.6 mg. per 24 hours (mean: 17.5 mg.). The intramuscular injection of 100 mg. of cortisone acetate on three alternate days caused the 17-ketosteroid excretion to fall to 1.5 mg. per 24 hours, thereby suggesting the presence of adrenocortical hyperplasia rather than a tumour.

FIG. 1.—Showing hypertrophy of penis and slight pubic hair in Case 1.

Treatment.—In September, 1954, treatment with cortisone was started in doses of 25 mg. by mouth three times daily. With this dosage the 17-ketosteroid excretion was maintained at 1 to 3 mg. per 24 hours, but it rose to 7.2 mg. when the dose was reduced to 25 mg. twice daily. In January, 1956, the 17-ketosteroid excretion was 2.9 mg. per 24 hours, the patient having received cortisone, 25 mg. three times daily, continuously for the previous eighteen months without any toxic effects.

Results.—During the period of treatment the height increased by 4 in. (10 cm.); the penis remained the same size and the pubic hair partly disappeared.

Case 2

A girl aged 16 had been obese since early childhood. Menstruation began at the age of 11 and remained normal. During the past year there had been an increasing growth of hair on the face and back.

On examination she had generalized obesity, her weight being 12 st. 3 lb. (77.6 kg.). Facial hirsuties and male distribution of pubic hair were present. There was acne of the face and back. The external genitalia were normal, the clitoris was not enlarged, and pelvic examination revealed no abnormality of the ovaries. The daily excretion of 17-ketosteroids ranged from 34.9 to 43.7 mg. per 24 hours (mean 39.4 mg.).

Treatment.—To determine the effect of oral cortisone on the 17-ketosteroid excretion 100 mg. was given eight-hourly for five days; this caused the 17-ketosteroid level to fall from 40.5 to 17 mg. per 24 hours. When the treatment was stopped the level promptly rose to 34.5 mg. The administration of 100 mg. of cortisone intramuscularly eight-hourly for five days caused the 17-ketosteroid excretion to fall to 8.8 mg. per 24 hours by the fourth day. This observation confirms the finding that through its rapid absorption oral cortisone is not so effective in suppressing the secretion of corticotrophin as is intramuscular cortisone, which, being more slowly absorbed, has a more constant action. Intramuscular cortisone was continued for a further four days in doses of 50 mg. twelve-hourly and then stopped. An interesting feature was that after stopping intramuscular cortisone the daily 17-ketosteroid level continued to fall to a minimum of 4.9 mg. one week later, rising to only 10 mg. after two weeks, and to 20 mg. after seven weeks without treatment.

Maintenance therapy consisted of the administration of cortisone by mouth at first in doses of 50 mg. six-hourly and subsequently in doses of 25 mg. twice daily. This treatment was continued for three months, and during this period the 17-ketosteroid excretion was maintained at the satisfactory level of 6 to 7 mg. per 24 hours.

In November, 1955, oral prednisolone, 5 mg. twice daily, was substituted for cortisone, and the 17-ketosteroid level fell further to 4 mg. per 24 hours. Treatment was then changed to prednisone, 5 mg. twice daily. From the Table it can be

Effect of Various Steroids on the Urinary 17-Ketosteroid Excretion in Adrenocortical Hyperplasia

Case No.	Steroid	Route	Dose (mg.)	Frequency	17-K.S. mg./24 Hours (Mean)
1	Cortisone	I.M.	100	Alternate days	17.5
	"	Oral	25	Twice daily	1.5
	"	"	25	3 times daily	7.2
2	Cortisone	I.M.	100	8-hourly	39.4
	"	Oral	25	3 times daily	4.9
	"	"	25	Twice daily	3.3
	Prednisolone	"	5	"	6.7
	Prednisone	"	5	"	4.0
	"	"	5	3 times daily	6.8
3	Cortisone	I.M.	100	12-hourly	25.2
	"	Oral	50	6-hourly	8.7
	Hydrocortisone acetate	I.M.	250	Weekly	22.4
	"	"	250	Fortnightly	2.0
4	Cortisone	I.M.	100	12-hourly	26.6
	"	Oral	50	6-hourly	6.2
	Hydrocortisone acetate	I.M.	250	Weekly	18.6
	Prednisolone	Oral	10	6-hourly	7.0
	"	"	10	12-hourly	2.7
	"	"	5	3 times daily	3.5
	Prednisone	"	5	3 " "	4.8
	"	"	5	4 " "	6.3
	"	"	5	" " "	4.5

seen that this steroid was not quite so effective as prednisolone in equivalent doses and that 5 mg. of prednisone three times daily had approximately the same effect as 5 mg. of prednisolone twice daily.

Results.—Treatment has continued so far from August 12, 1955, to April 12, 1956. During this period the acne on

the face and back had disappeared and menstruation has remained normal. There was no loss of facial hair after four months of treatment, when it was removed by depilatory wax. Since then regrowth seems to have been retarded to some extent.

Case 3

A woman aged 20 gave a history of rapidly increasing hirsuties and obesity since the birth of her first child twelve months previously. Menstruation had been normal prior to the pregnancy; she had had one period two months after delivery, and since then there had been amenorrhoea.

On examination she had generalized obesity, her weight being 14 st. 6 lb. (91.6 kg.), and considerable hirsuties on the face, arms, and legs; pubic hair was of male type (Figs. 2 and 3). Blood pressure was 140/65. There was no hypertrophy of the clitoris. Radiological examination of the pituitary fossa and intravenous pyelograms were normal. The glucose-tolerance curve and serum sodium and potassium were normal. The daily 17-ketosteroid excretion ranged from 23.5 to 27.6 mg. per 24 hours (mean, 25.2 mg.). Curettage of the uterus produced only very scanty curettings of the endometrium, which was in the resting phase. Intramuscular injection of cortisone in doses of 100 mg. twelve-hourly caused the 17-ketosteroid excretion to fall to 8.7 mg. by the sixth day.

Treatment.—Treatment with 100 mg. of cortisone injected intramuscularly twelve-hourly was continued for a total of twelve days and the 17-ketosteroid level was thereby maintained at about 10 mg. per 24 hours. Oral cortisone, 50 mg. six-hourly, failed to maintain this level, and the excretion rose to 25 mg. per 24 hours. Increasing the dose to 75 mg. six-hourly was also ineffective, the 17-ketosteroid output ranging from 15.8 to 22.5 mg. per 24 hours. Resumption of intramuscular cortisone, 100 mg. twelve-hourly, again caused a prompt fall to 5.1 mg. After 16 days, hydrocortisone acetate was substituted in the dosage of 250 mg., injected intramuscularly at weekly intervals. After three weeks' treatment the 17-ketosteroid level fell to the very low value of 2 mg. per 24 hours. Injections of 250 mg.

FIG. 2.—Case 3. Showing facial hirsuties.

FIG. 3.—Showing generalized obesity in Case 3.

were therefore given at intervals of two weeks, and the resulting level was between 6 and 7 mg.

Results.—Effective treatment in the form of intramuscular cortisone or hydrocortisone acetate has been given for six months. Within one month of resuming intramuscular cortisone menstruation returned and has continued to occur regularly. A second uterine curettage carried out eight weeks after the first produced abundant endometrium in an oestrogenic phase. There was no loss of the excessive hair after three months, and the patient thereupon removed the facial hair by shaving. One month later there was slight regrowth, and subsequently the patient considered that growth had been much retarded.

Case 4

This patient, aged 19, complained of increasing growth of hair on the face and severe acne for the previous year. Menstruation remained normal. On examination she was tall and thin, her height being 6 ft. 0½ in. (185 cm.). The breasts were small; there was excessive hair on the face

FIG. 4.—Facial hirsuties in Case 4.

and chest, and the pubic hair was of male distribution; acne was present on the face and back (Figs. 4 and 5). The external genitalia were normal and pelvic examination revealed no abnormality. The daily 17-ketosteroid excretion ranged from 24.8 to 31.6 mg. per 24 hours (mean, 26.6 mg.). The intramuscular injection of 100 mg. of cortisone twelve-hourly for six days caused the 17-ketosteroid excretion to fall to 6.2 mg. per 24 hours.

Treatment.—Treatment with oral cortisone, 50 mg. six-hourly, failed to maintain the low 17-ketosteroid level, which rose to 18.6 mg. per 24 hours. Increasing the dose after nine days to 75 mg. six-hourly led to wide fluctuations, ranging from 6.8 to 23.4 mg., while 100 mg. six-hourly maintained the excretion at about 16 mg. per 24 hours. A percentage of this figure represents 17-ketosteroids derived from the large amount of cortisone administered.

Resumption of intramuscular cortisone, 100 mg. twelve-hourly, caused the 17-ketosteroids to fall promptly to 5 mg. per 24 hours. After four days intramuscular hydrocortisone acetate was substituted in a dosage of 250 mg. at weekly intervals. This produced a 17-ketosteroid level of 7 to 10 mg. per 24 hours. After four weeks, oral prednisolone was substituted in a dosage of 10 mg. six-hourly with an even more marked response, the level falling to 2.7 mg. Even when the dose was reduced to 5 mg. three times

FIG. 5.—Case 4. Showing height of patient.

daily the 17-ketosteroid level was only 4.8 mg. Substitution of prednisolone by prednisone in the same dosage of 5 mg. three times a day produced a slight rise in excretion to 6.3 mg., while with 5 mg. of prednisone four times a day the level fell to 4.5 mg. per 24 hours (see Table).

Discussion

Each of the patients described was regarded as suffering from virilism due to adrenocortical hyperplasia, since the high 17-ketosteroid excretion was rapidly reduced to normal by cortisone injected intramuscularly (Jailer *et al.*, 1954). This response has been used as a measure of the inhibition of excessive secretion of corticotrophin, and it is apparent from the Table that there are considerable differences in the efficiency of oral cortisone in the four cases. In Case 1, a small boy with macrogenitosomia praecox, the dosage of oral cortisone required was 25 mg. three times daily. This is in accordance with the experience of Wilkins *et al.* (1952b). Similarly in Case 2, a girl aged 16 whose symptoms of virilism developed at about the age of puberty, only 25 mg. of oral cortisone twice daily was required to maintain the 17-ketosteroid level at a figure below 8 mg. per 24 hours, the level recommended by Wilkins for older patients. On the other hand, in Case 3, in which the signs of virilism appeared after pregnancy, and in Case 4, in which signs also developed at a later age, oral cortisone was incapable of depressing the 17-ketosteroid excretion to the required level of 8 mg. per 24 hours.

If very high doses of cortisone are given, as in Case 4, falsely high 17-ketosteroid figures are obtained, because these substances are partly derived from the cortisone administered.

In Cases 3 and 4 hydrocortisone acetate injected intramuscularly in doses of 250 mg. weekly or fortnightly was fully effective in depressing the output of 17-ketosteroids. Segaloff *et al.* (1955) observed that hydrocortisone acetate, when injected intramuscularly, is usually regarded as being relatively inactive on account of its very slow absorption, but this property is turned to advantage in the treatment of adrenal virilism, in which a sustained inhibition of corticotrophin is required.

In Case 2 oral prednisone proved to be about five times more active than oral cortisone in depressing the 17-ketosteroid excretion, while in Case 4 comparison is superfluous, since the response to oral cortisone was highly unsatisfactory. Judged by the depression of 17-ketosteroids in Cases 2 and 4, prednisone appears to have approximately two-thirds to three-quarters of the activity of prednisolone. The potency, however, of these two substances is so high that this slight difference has no significance.

No toxic effects have been observed with any of the steroids employed in the treatment of these four patients. This is in contrast with 9- α -fluorohydrocortisone, which although an even more active inhibitor of corticotrophin, induces fluid retention and oedema so readily that its use in the treatment of adrenal virilism is impracticable (Kupperman *et al.*, 1955).

Although potent methods are now available for inhibiting the excessive secretion of corticotrophin in virilism due to adrenocortical hyperplasia, the clinical results in the older age group are not all that may be desired. Wilkins and others have indeed reported striking clinical improvement in children; and in older patients menstruation may be established, the acne may disappear, and breast development may be promoted, but the hirsuties, which is the greatest concern of these patients, usually fails to show any great improvement. In these older patients the justification for prolonged treatment depends upon the severity of the symptoms. When the treatment is considered advisable, oral prednisolone or prednisone is the most effective and convenient means of reducing the excessive 17-ketosteroid excretion to normal; alternatively, hydrocortisone acetate, injected intramuscularly weekly or fortnightly, may be employed.

Summary

Four patients suffering from virilism due to adrenocortical hyperplasia were treated with cortisone, hydrocortisone acetate, prednisone, or prednisolone for periods ranging from six to eighteen months. Oral cortisone was effective in reducing to normal the 17-ketosteroid excretion in the two younger patients, aged 3½ and 16 years, but was ineffective in the two older patients, aged 19 and 20 years.

Prednisone and prednisolone were the most active in depressing the 17-ketosteroid levels, prednisone being about five times more potent in this respect than oral cortisone and having from two-thirds to three-quarters of the activity of prednisolone.

Hydrocortisone acetate injected intramuscularly weekly or fortnightly was also effective.

Growth of excess hair was retarded to some extent; acne disappeared in three patients in whom it was present; and menstruation was established in one patient with secondary amenorrhoea.

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Medical Memorandum

Atrial Septal Defect with Mitral Stenosis (Lutembacher's Syndrome) in a Woman of 81

Longevity in any form of congenital heart disease is rare, but probably is most often met with in atrial septal defects associated with mitral stenosis (Lutembacher's syndrome). Askey and Kahler (1950) describe the case of a man with this syndrome who lived to the age of 72 in spite of auricular fibrillation for the last 15 years. They also quote the classical case of Firket (1880), a woman who had eleven pregnancies and three abortions and died at the age of 74; and those of Bonnabel (1906), two patients who lived to be "over 70." Sailer (1936) describes the condition in a man of 67, and Pyke and Symons (1951) in a man aged 72. Increasing interest in both geriatrics and congenital heart disease will probably result in the discovery of many more such cases, but meanwhile the following case of Lutembacher's syndrome in a woman of 81 seems to be worthy of record.

CASE REPORT

The patient was admitted to hospital on December 12, 1954, with a diagnosis of "bronchitis with heart failure." Signs of heart failure first began to show in 1948 when a blood pressure of 180/110 mm. Hg was noted. In 1950 she had oedema of both legs and an apical systolic murmur was heard over the praecordium. The pulse was regular at that time. Albuminuria was noticed in 1951 and the regular doses of mersalyl she had been having were discontinued. In 1953 the legs again became oedematous and it was neces-

sary to restart treatment with mersalyl. She had taken to her bed about a week before admission because of vague pain across the lower part of the chest and a distressing cough. Her previous history was otherwise unhelpful. She had no serious illnesses before 1948 and there was no history of rheumatic fever. She had had six normal pregnancies and no miscarriages. Three sons were alive and well, one son had died at the age of 18 months, and two daughters had died from "pneumonia" both at the age of 28.

On examination she was sensible but depressed. There was slight cog-wheel rigidity at the wrists and her facial expression resembled that of early Parkinsonism. She had no oedema, anaemia, or clubbing of the fingers, and her pulse was irregular at a rate of 96 per minute. The apex beat could be felt in the axilla and a loud systolic murmur heard over the apex. The blood pressure was 180/120 mm. Hg. A few scattered dry sounds were heard in the chest and fine moist sounds over the lower lobe of the right lung. There were no other abnormalities on systemic examination. The urine showed a trace of albumin and scanty hyaline and granular casts. Radiography of the chest was reported on as follows: "The transverse diameter ratio is 14/22 cm. The enlargement of the heart is mainly to the left, and the middle portion of the left border shows a smooth convexity. The aortic knuckle is enlarged and shows atheromatous calcification. The right hilar shadow is markedly increased, the left hilar shadow being concealed by the cardiac outline."

In spite of treatment the congestion of the lungs became progressively worse and she died on January 5, 1955.

Post-mortem examination was restricted to the thorax and abdomen. There was hypertrophy of the left ventricle; the right auricle was dilated and the left auricle normal. Of the valvular openings only the mitral showed macroscopic changes; severe stenosis was present admitting the tip of the little finger. The mitral ring was calcified in part. In the interatrial septum was a roughly circular defect measuring 2 cm. across. The aorta was of normal size and atheromatous. The pulmonary artery was dilated and showed a little atheroma, the right branch being partly occluded by an organized ante-mortem thrombus thought to be a few weeks old. The bronchi showed chronic inflammatory changes and both lungs were very oedematous, the right one with several superficial infarcts. The kidneys were of equal size, scarred and atrophic, with atherosclerosis of the vessels. The left renal artery was partly occluded by a large atheromatous plaque. There were no other changes of note.

LIFE EXPECTANCY

McGinn and White (1933), in reviewing 24 patients with atrial septal defect and mitral stenosis, found the average age at death to be 35 years. Roesler (1934), examining 62 patients with atrial septal defect 30 of whom had definite mitral stenosis in addition, found the expectancy of life to be 36 years. In spite of this there are examples on record to show that the septal defect may coexist with mitral stenosis and the patient live a tolerable life well beyond this expectancy. The patient described brought up a family of six children and lived a very active life for 75 years before signs of heart failure appeared and from which she died six years later. How such a combination of lesions, both of which may be of a severe degree, can allow of such a long and useful life is ill understood.

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