Review Article

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The Adrenal Cortex in Childhood

Part 2: Pathological Aspects*

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III—Adrenocortical Hyperfunction

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IV—Adrenocortical Hypofunction

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III: Adrenocortical Hyperfunction

(1) Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is the most important cause of the adrenogenital syndrome in infancy and childhood. It is a classic example of an 'inborn error of metabolism' and represents the clinical expression of a hereditary defect in the biosynthesis of cortisol. Studies on patients with this disorder have enriched our knowledge on the biosynthesis and metabolism of adrenocortical steroids, the psychosexual orientation and maturation in man, and the effects of androgens on growth and skeletal maturation. A most comprehensive review of the adrenogenital syndrome has been given recently (Bongiovanni and Root, 1963), while two other extensive papers on CAH have appeared in this journal during recent years (Wilkins, 1962b; Raiti and Newns, 1964).

At least 3, and possibly 4, hereditary defects in the biosynthesis of cortisol have been described. An impaired biosynthesis of cortisol, whether due to a relative defect of 21-hydroxylation (Jailer, 1953), of 11-hydroxylation (Eberlein and Bongiovanni, 1956), or of 3β-dehydrogenation (Bongiovanni, 1961), will ultimately lead to compensatory hypertrophy of the adrenal cortex by excessive ACTH secretion via the negative feedback action between the anterior pituitary gland (ACTH) and the adrenal cortex (cortisol) (Fig. 1). The diagnosis of a specific defect is greatly facilitated by studying the increased production and excretion of steroid precursors (and their metabolites) which accumulate before the enzyme block. This has been schematically presented in Fig. 5 of Part 1 of this article (Visser, 1966).

The typical clinical symptoms in affected male and female patients are caused by the excessive secretion of adrenal androgens associated with the most common variants of CAH: the 21- and 11-hydroxylation defects. Generally abnormalities of the external genitalia are present at birth in the female patient. Adrenocortical activity in the foetus begins as early as the third month of gestation, before the completion of the development of the genital ducts and the external genitalia. By the eighth week of embryonal life (23 mm. stage), both the Wolffian and Müllerian ducts are developed (Fig. 2). During the third month (63 mm. stage) the Müllerian ducts develop in the female into the uterus and fallopian tubes, in the male the Wolffian ducts develop into the epididymis, vas deferens, and seminal vesicles.

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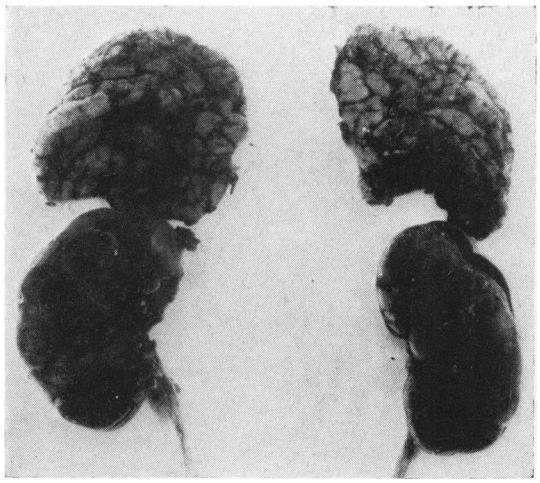

FIG. 1.—*Hyperplasia of the adrenal glands in an infant with CAH (21-hydroxylation defect; salt-losing variant).*

After the third month a communication between the vagina and the urogenital sinus is established, and at about the 162 mm. stage the urethral and vaginal orifices become separated. In the male the genital tubercle develops into a penile organ, in the female it fails to grow. In the male the labioscrotal folds fuse in the midline beginning posteriorly: this results in the formation of a scrotum and a penile urethra. The labioscrotal folds do not fuse in the female, so that in the fifth month a vulva has been formed containing the orifices of urethra and vagina. In his classic animal experiments Jost (1953) showed that a 'male organizer substance' produced by the foetal testes is necessary for normal masculine genital organogenesis. Castration of the male rabbit foetus in an early undifferentiated stage resulted in complete feminine external genitalia. The increased elaboration of androgenic substances during embryonic life in patients with CAH results in hypertrophy of the clitoris and variable fusion of the labioscrotal folds (*female pseudohermaphroditism*) (Fig. 3, 4). In most cases a persistent urogenital sinus is found; the internal duct system has developed normally and normal infantile ovaries are present. These female babies resemble males with hypospadias and bilateral cryptorchism; in a few cases a complete penile urethra has been described, and in these female babies sexual differentiation becomes extremely difficult as they have the appearance of true male babies with cryptorchism. In all cases of ambiguous external genitalia, and in all 'normal' male babies with bilateral cryptorchism at birth, it is wise to carry out the simple test for sex chromatin.

The clinical findings and differential diagnosis of abnormalities in sex differentiation at birth have been well discussed by Wilkins (1957), van Wyk (1962), Gordon and Dewhurst (1962), and others. Wilkins (1960) pointed out that androgenic drugs given to the mother in early pregnancy can produce exactly the same abnormalities of external genitalia in the foetus as are seen in newborn patients with CAH.

On rare occasions the genitalia of the female infant may be normal, and the symptoms of virilization may only become evident in later infancy, childhood, or adolescence, or even in adulthood (Decourt, Jayle, and Baulieu, 1957; Jayle, Weinmann, Baulieu, and Vallin, 1958; Brooks, Mattingly, Mills, and Prunty, 1960; Lipsett and Riter, 1961). A female infant with normal external genitalia, but with pubic hair and progressive virilization during early life, was reported by Marie, Kostich-Joksitch, Bricare, Salet, Sée, and Levèque (1957) who suggested that excessive secretion of androgens had not occurred until after the fifth month of foetal life, when development of the external genitalia was complete. It is difficult to say if such patients have a 'mild' form of congenital adrenal hyperplasia, or acquired adrenocortical hyperplasia, or tumour.

In the untreated female patient with CAH, somatic growth and osseous development become far advanced for the age of the patient. By the fifth year of life, height-age may be 8 years, and bone-age 10 years. Epiphysial fusion occurs early and will lead to a dwarfed adult, despite having been excessively tall in childhood. It is remarkable that most infants with CAH do not show signs of advanced osseous development at birth, though changes of the external genitalia indicate the excessive secretion of androgens during foetal life.

Usually pubic hair appears by the age of 2 to 4, followed shortly by axillary hair. Other symptoms of progressing virilization are acne, deepening of the voice, further enlargement of the clitoris with frequent erections, and later on coarse masculine facial hair and even baldness. There is increased muscular development and, though the untreated female patients in early childhood may look feminine, in later years they look more masculine, particularly when at the age of puberty development of the breasts fails to occur.

In males, CAH cannot usually be recognized in early infancy, except when symptoms of the salt-losing syndrome occur (Fig. 5). However, the penis of young male infants with the disorder may be enlarged, and hyperpigmentation of the scrotum

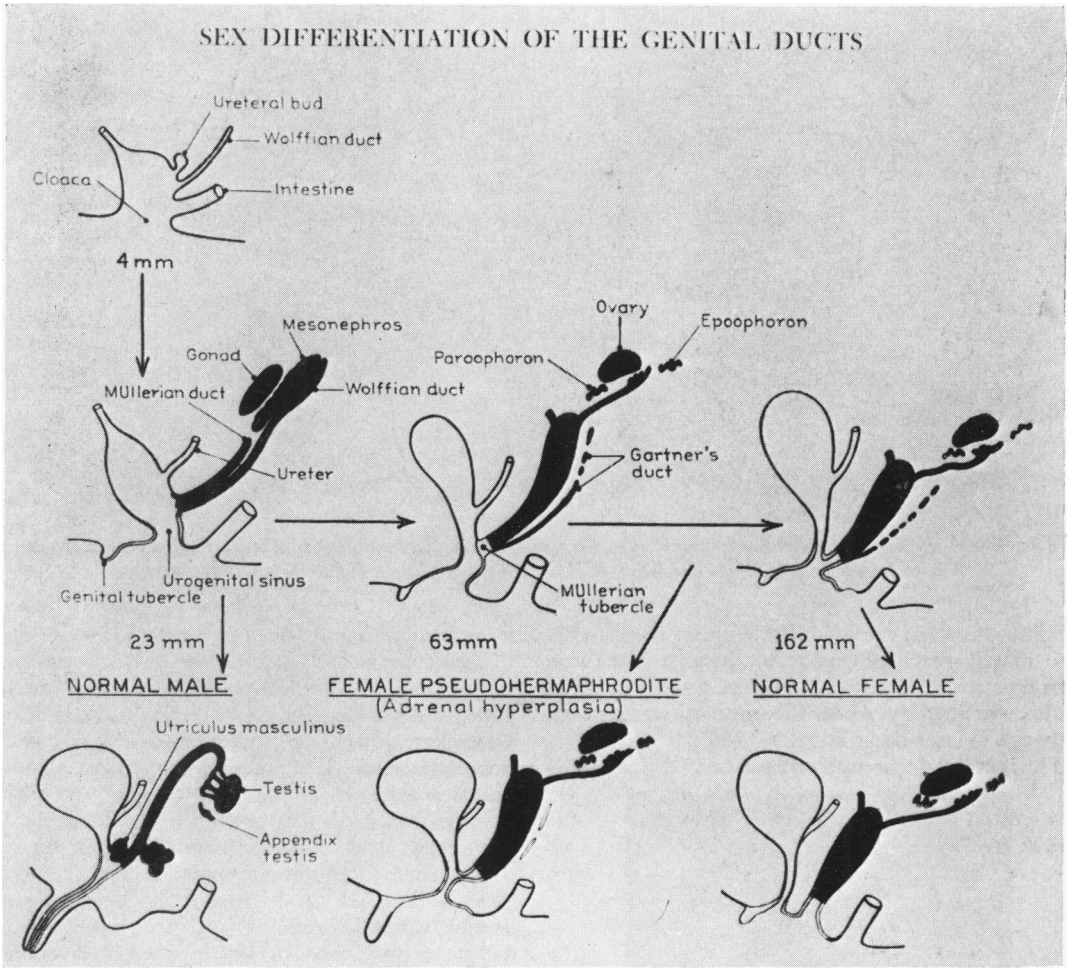

FIG. 2.—*Sex differentiation of the genital ducts. Normally the differentiation of the genital ducts corresponds to the sex of the gonad. When there is failure of function of the foetal testis during the early period of duct differentiation, there is an entirely female development of the genital tract. Deficiency of foetal testicular secretion at a somewhat later period of differentiation accounts for ambisexual development seen in male pseudohermaphrodites (as in lipoid adrenal hyperplasia and the 3β-dehydrogenation defect). Excessive secretion of androgen in patients with CAH does not prevent normal female development of the Müllerian ducts, but causes masculine development of the phallus and more or less fusion of the labioscrotal folds.* (*From Wilkins, L.* (*1957*). The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. *Charles C. Thomas, Springfield, Ill., U.S.A., reproduced by permission of the publisher.*)

may occur (Fig. 5). After birth there is rapid somatic growth and osseous development. The penis becomes large and pubic hair appears. Patients often reach the age of 2 or 3 years before the symptoms of virilization attract attention. The testes remain infantile in size in CAH, whereas in true sexual precocity they are enlarged. Acne, deepening of the voice, and masculine muscular development appear. Epiphysial fusion occurs early, so that most become 'short adults'. However, we recently observed two brothers, 9 and 13 years of age, with untreated CAH (21-hydroxylation type) with heights of 154 and 168 cm. and bone-ages 13 and 15 years, respectively. In both boys symptoms of increased growth rate and of virilization did not attract attention until after the age of 5.

It seems that in children with increased production of androgens, ultimate height depends upon the 'quality' and the 'quantity' of the androgenic substances. Children with CAH take intermediate

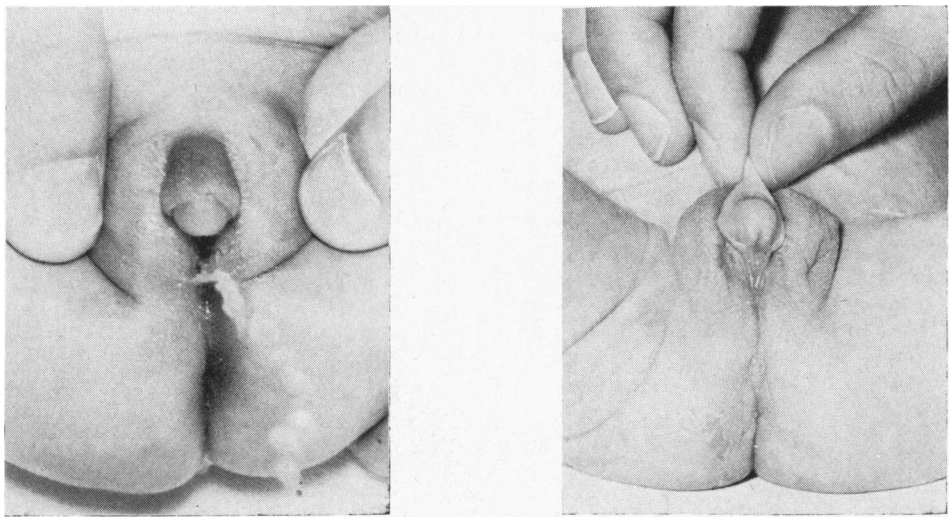

FIG. 3 and 4.—*Hypertrophy of the clitoris and variable fusion of the labioscrotal folds in two girls (sex chromatin positive) with female pseudohermaphroditism (CAH, 21-hydroxylation defect, salt-losing variant).*

positions between those with premature adrenarche, who mostly reach normal adult height, and those with true sexual precocity, who are mostly dwarfed adults, particularly when the process starts at an early age (Visser and Croughs, 1965).

The increased urinary excretion of 17-ketosteroids

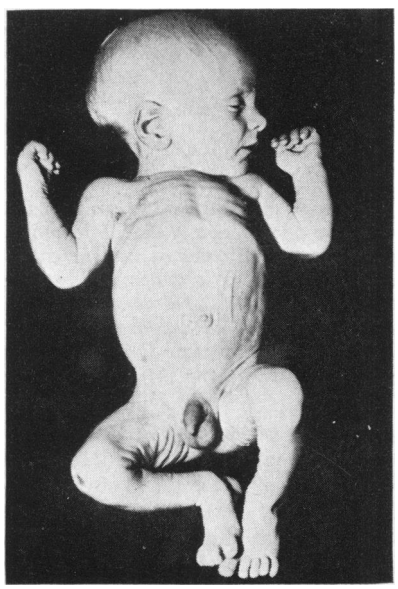

FIG. 5.—*Male infant with congenital adrenal hyperplasia (21-hydroxylation defect, salt-losing variant). Note the enlarged penis and pigmentation of the external genitalia, and severe dehydration.*

is probably mainly due to increased secretion of C_{19}-precursors such as DHA and androstenedione, rather than to metabolism of C_{21}-steroids (Brooks, 1960; Fukushima, Bradlow, Hellman, Zumoff, and Gallagher, 1961). However, these adrenal androgens have relatively weak biological potency, and the question arises as to whether, in CAH, the adrenal secretes a more potent androgen than testosterone. We have studied production and excretion of testosterone in 11 infants and children (5 boys, 6 girls) with CAH (21-hydroxylation defects), using isotope dilution methods. In production studies. 0·5 μc. testosterone-H_3 was injected intravenously, Excretion was between 11-261 μg./24 hr., production 342-11,400 μg./24 hr. (excretion in normal children before puberty is < 5 μg./24 hr., production $< 0{\cdot}5$ mg./24 hr.) (Degenhart, Visser, Wilmink, and Frankena, 1965b). Although the adrenal androgens DHA and androstenedione can be peripherally metabolized to testosterone (Van de Wiele, McDonald, Gurpide, and Lieberman, 1963), and some testosterone derived in this way is conjugated to glucuronide without having entered the plasma as free biologically active testosterone, our results in infants and children with CAH indicate that at least part of the testosterone produced must be biologically active.

It has been demonstrated recently that androstenedione, DHA, and testosterone *in vitro* inhibit 11-hydroxylation in corticosteroid biosynthesis. C_{21}-hydroxylation of progesterone and 17-hydroxyprogesterone was not inhibited, but of pregneno-

lone and 17-hydroxypregnenolone it was markedly so (Sharma and Dorfman, 1964). This competitive inhibition of 11- and 21-hydroxylation in corticosteroid biosynthesis by adrenal androgens would superimpose *in vivo* a further deficit on a subnormal corticoid production, and may explain the observation that there is an increased urinary excretion of tetrahydro-S in patients with 21-hydroxylation defect, which decreases to normal after treatment with glucocorticoids (Birke, Diczfalusy, Plantin, Robbe, and Westman, 1958; Degenhart, Visser, Wilmink, and Croughs, 1965a).

In about 30% of the patients with a 21-hydroxylation defect the *salt-losing syndrome* is present—hyponatraemia, hyperkalaemia, and metabolic acidosis, changes typical of Addison's disease.

Patients with the 11-hydroxylation defect generally demonstrate hypertension, which may be the result of the production of large amounts of deoxycorticosterone (Wilkins, Lewis, Klein, Gardner, Crigler, Rosemberg, and Migeon, 1951; Eberlein and Bongiovanni, 1956; Green, Migeon, and Wilkins, 1960).

A few cases with 3β-dehydrogenation defect have been reported, and most of them were salt losers (Bongiovanni, 1961, 1962a). In this early defect in the biosynthesis of adrenocortical steroids, the biosynthesis of adrenal and testicular androgens is more or less impaired (Fig. 3, Part 1). This may result in a very peculiar clinical picture of incomplete masculine genital organogenesis in affected males (male pseudohermaphroditism) and normal external genitalia in affected females. Impairment of the testicular biosynthesis of the 'male organizing substance' during early embryonic development can explain these findings. Bongiovanni (1962b) describes a genotypic male patient with female external genitalia.

A clinically similar condition has been described by Prader *et al.* as *lipoid adrenal hyperplasia* (Prader and Gurtner, 1955; Prader and Siebenmann, 1957). O'Doherty (1964; N. J. O'Doherty, 1965, personal communication) has reported two female sibs with normal external genitalia, who both died in spite of intensive treatment. The 9 cases of lipoid adrenal hyperplasia reported up to the present were all salt-losers and all died. Several of the infants with 3β-dehydrogenation defect also died, and these two variants of CAH have been the most difficult to control. The lipoid adrenal hyperplasia may be due to a very early defect in the corticosteroid biosynthesis, between cholesterol and pregnenolone (20, 22-desmolase defect?).

In many patients with CAH the defects in the biosynthesis of adrenocortical steroids are compensated by the increased stimulation of endogenous ACTH and probably angiotensin, resulting in normal production of cortisol and aldosterone (Bongiovanni and Eberlein, 1958). However, this is achieved at the great cost of enlargement of the adrenal glands with excessive production of androgens.

Using isotope dilution techniques, we have studied the secretion rates (SR) of aldosterone and cortisol in 9 infants and children with CAH (21-hydroxylation defect), 3 with the salt-losing type (Degenhart *et al.*, 1965a). Aldosterone-SR was normal in the 'non salt-losers' (60-125 μg./24 hr.) and after salt-deprivation a two- to threefold increase was observed (100-380 μg./24 hr.). Extremely low values were found in the 'salt-losers' (< 10 μg./24 hr.) and there was no increase during salt-deprivation. Cortisol-SR before ACTH was in the normal range for all patients (4·2-34 mg./24 hr.; 12-33 mg./m.^{2} 24 hr.) except for one infant with the salt-losing type. ACTH raised cortisol-SR in all 'non salt-losers' (17-104 mg./24 hr.) but the increase was less than could be expected under normal conditions, and the relative defect in the biosynthesis of cortisol was demonstrated in this way. Cortisol-SR after ACTH in the 'salt-losers' was distinctly low as compared with the 'non salt-losers' (Table I).

Normal or subnormal cortisol-SR has been reported in other patients with the salt-losing type of CAH (Bertrand, Loras, Gilly, Roux, Saez, and Frederich, 1963; Kenny, Malvaux, and Migeon, 1963). Very low aldosterone-SR in 5 children with the salt-losing variant of CAH has recently been reported by Bryan, Kliman, and Bartter (1962), while a very low excretion of aldosterone metabolites

TABLE I

Cortisol Secretion Rate (F-SR), Aldosterone Secretion Rate (ALD-SR), and Testosterone Excretion and Production in 'Non Salt-losers' and 'Salt-losers' with Congenital Adrenal Hyperplasia

	F-SR		ALD-SR		Testosterone Excretion and Production
	Before ACTH	3rd Day of ACTH	Before Salt Deprivation	During Salt Deprivation	
'Non salt-losers' ..	Normal	Subnormal increase	Normal	Normal increase	Highly increased
'Salt-losers'	Low normal	Small increase	Very low	No increase	Highly increased

TABLE II

Pathogenesis of Salt-losing Syndrome in Infants and Children with Congenital Adrenal Hyperplasia (21-hydroxylation defect)

Clinical and Laboratory Data to Account for	Explanation
ALD—SR very low, also during salt-deprivation	← Impaired biosynthesis of aldosterone
Sodium-diuretic effect of ACTH during treatment with DOCA (also in 'non salt-losers')	← Mineralocorticoid-antagonizing activity of 17-OH-progesterone (and progesterone)
Condition improves during treatment with cortisol	← Superimposed inhibition of 11- and 21-hydroxylation by adrenal androgens

in 9 patients was found by New, Miller, and Peterson (1964). During sodium depletion, secretion and excretion of aldosterone did not increase significantly. 'Salt-losing' and 'non salt-losing' types of CAH (21-hydroxylation defect) are two different genotypes (Childs, Grumbach, and Van Wyk, 1956; Prader, Anders, and Habich, 1962). Our findings suggest that they also differ biochemically, possibly by virtue of two different genetically controlled changes in the 21-hydroxylation process, resulting in a different defect in the hydroxylation of progesterone and 17-hydroxyprogesterone.

The salt-loss can be adequately explained by a low production of aldosterone (Table II). Progesterone and 17-hydroxyprogesterone antagonize the renal tubular effect of mineralocorticoids (Landau and Lugibihl, 1958; Jacobs, Van der Poll, Gabrilove, and Soffer, 1961; Visser, Degenhart, Cost, and Croughs, 1964), and these steroid precursors may further limit renal conservation of sodium in patients with CAH (21-hydroxylation defect). This may also explain the sodium-diuretic effect of ACTH in these patients, when treated with mineralocorticoids. In the untreated newborn infant on a low-sodium intake this mineralocorticoid-antagonizing activity of 17-hydroxyprogesterone may even lead to a negative sodium balance with hyponatraemia. However, such a child may produce aldosterone normally and is not a typical 'salt-loser'. Sodium balance then becomes positive on treatment with glucocorticoids alone. There is at present no evidence for the existence of a specific salt-losing steroid (for discussion see Visser *et al.*, 1964).

Genetic studies in patients with CAH indicate that the defects in the biosynthesis of adrenocortical steroids are due to a recessive autosomal heredity with clinical expression in the homozygous state. There is no true difference in the sex ratio (Childs *et al.*, 1956; Prader *et al.*, 1962; Prader and Anders, 1962). Up to the present it has not been possible to detect the heterozygous carrier of the gene (Childs *et al.*, 1956; Cleveland and Migeon, 1960). Prader (1958) has estimated an incidence of the gene of 1 : 37·5 in the general population in Switzerland, which leads to one adrenogenital syndrome patient among every 5,000 births in Switzerland. The incidence of the gene is probably between 1 : 50 and 1 : 100 in different populations. Childs *et al.* (1956) studied 76 affected individuals among 181 sibs in 56 families. In only one family was there consanguinity, the parents being first cousins. In 3 out of 8 families with 12 affected children (all 21-hydroxylation defects) who came under our care during recent years, there was consanguinity between the parents.

A high incidence of consanguinity has been reported for the few cases of lipoid adrenal hyperplasia.

Treatment. Wilkins *et al.* reported in 1950 that the administration of cortisone in relatively small dosages to patients with CAH led to a decrease of the urinary 17-ketosteroids (Wilkins, Lewis, Klein, and Rosemberg, 1950; Wilkins *et al.*, 1951). Since then it has become possible to treat patients with CAH in such a way that a normal pattern of growth and development can be maintained. When treatment with glucocorticoids is begun in early life and is adjusted properly, the patient will reach normal adult height.

Therapy with glucocorticoids not only suppresses pituitary ACTH secretion and hence the production of adrenal androgens, but also provides a supply of the deficient hormone to cover conditions of stress. Therapy with mineralocorticoids corrects the salt-water loss of the salt-losing patient, and the hypertension of the patient with the 11-hydroxylation defect. Treatment of the salt-losing patient will be discussed further under adrenocortical hypofunction (IV (1)).

When treatment with glucocorticoids is started, larger doses of steroids are required to suppress the excessive endogenous ACTH secretion than are required later on, when adequate suppression can be maintained by doses of glucocorticoids which are not in excess of the physiological requirements. Excessive amounts of glucocorticoids inhibit protein anabolism and retard growth, overtreated patients showing ultimately all the aspects of Cushing's syndrome.

The drugs of choice are cortisol or cortisone acetate for oral or intramuscular use, respectively. Prednisone has been used with good results (1 mg. prednisone is equivalent to 4 mg. cortisol), but there is no need for other synthetic glucocorticoids, and several side-reactions of some of these drugs make their use undesirable (Green, Cleveland, and Wilkins, 1961).

Maintenance doses of cortisol vary and it is necessary to consider every individual separately. Useful criteria are the response of the urinary 17-KS; the long-term clinical response, particularly statural growth and skeletal maturation; and the possible appearance of side-effects of glucocorticoids. Recommended maintenance doses for cortisol are 10-30 mg./day for age 0-5 years, 25-50 mg./day for 5-10 years, and 50-100 mg./day for 10 years and above. Cortisol when prescribed orally should be given in 3 to 4 doses a day as alcoholic cortisol, not as cortisol acetate which is less well absorbed in the gastro-intestinal tract. It should be emphasized that major stress situations, such as infections, injuries, and operations, should be managed by a two- to tenfold increase in the dosage for the duration of the critical situation (see IV (3)).

Patients with CAH should be periodically examined, growth rate and skeletal maturation carefully controlled, and urinary excretion of 17-KS regularly determined.

One aspect of medical treatment is of considerable interest in regard to the correlation of the onset of puberty with bone-age rather than with chronological age. When treatment with glucocorticoids is started at a later age and bone-age is considerably advanced, symptoms of gonadal maturation may occur in a very short time. Thus adrenal suppression permits an appropriate function of the gonads at puberty, but puberty is highly correlated with bone-age. A girl of 6 years, with a bone-age of 13, may show development of the breasts and the beginning of menses within a few months of starting treatment.

The following growth charts may illustrate some of the problems in medical treatment in regard to statural growth and skeletal maturation (Visser, 1965). In these charts the 10, 50, and 90 percentiles for length are those for Dutch children of de Wijn and de Haas (1960). The standard curves for growth velocity (cm. per year) were constructed using data from the growth velocity curves of Bayer and Bayley (1959) for North-American children, and of Prader, Tanner, and von Harnack (1963) for West-European children. Predicted mature height (PMH) was calculated using the radiographic atlas of Greulich and Pyle (1959) for the estimation of the bone-age, and the tables of Bayley (1962) and Bayley and Pinneau (1952).

Fig. 6 shows the growth curves of a boy with CAH (21-hydroxylation type, no salt-loss) before and after treatment. The diagnosis of CAH was not made until the age of 7 years, when other symptoms of virilization were evident. At this time bone-age was 13½ years. His growth velocity decreased sharply after treatment was started. With prednisone 7·5 mg./day in two doses, growth velocity became normal for age. His predicted adult height was calculated as ~ 165 cm., and there is every indication that he will reach his adult height at an age of about 13 years.

Fig. 7 shows the course of growth in a girl who was treated with glucocorticoids from the age of 1½ years (21-hydroxylation type, no salt-loss). Between the ages of 2 and 4½ she received prednisone 7·5-10 mg. per day. Her bone-age during this time increased only from 2 to 3 years and her height from 85 to 95 cm., a growth velocity much too low for this age period. There were other symptoms of overtreatment with glucocorticoids at the age of 4½ years: obesity, moon facies, and hypertension. She complained of headache and the fundi of her eyes showed papillary oedema. Treatment was stopped for a time, and the symptoms of overtreatment disappeared rapidly. During the following period, on cortisol treatment 10-20 mg./day, a catch-up growth was observed with a growth velocity of more than 13 cm. per year. From the age of 6 years and 3 months (bone-age 6 years) she was treated with prednisone 5 mg./day and the growth velocity became normal. It is of interest that her predicted adult height did not change much during the whole period of treatment, and this indicates that bone maturation and statural growth were inhibited by glucocorticoids to the same extent. It is our opinion that treatment with glucocorticoids should never be discontinued, it being considered as substitution therapy, at least during stress situations. Increased production of adrenal androgens is undesirable during later life, certainly in females; and long-term stimulation of the adrenal glands by ACTH may lead to adrenocortical neoplasia (Hamwi, Serbin, and Kruger, 1957; Holman, Merveille, and Nichols, 1964).

The surgical aspects of therapy are primarily concerned with the correction of the external genitalia in the female patient. The time for the operation has been discussed, and most authors agree that this should be done in the first 4 years of life. However, it is often wise not to operate too early, because of technical difficulties and the risks of surgical stress. Details of correction of labio-

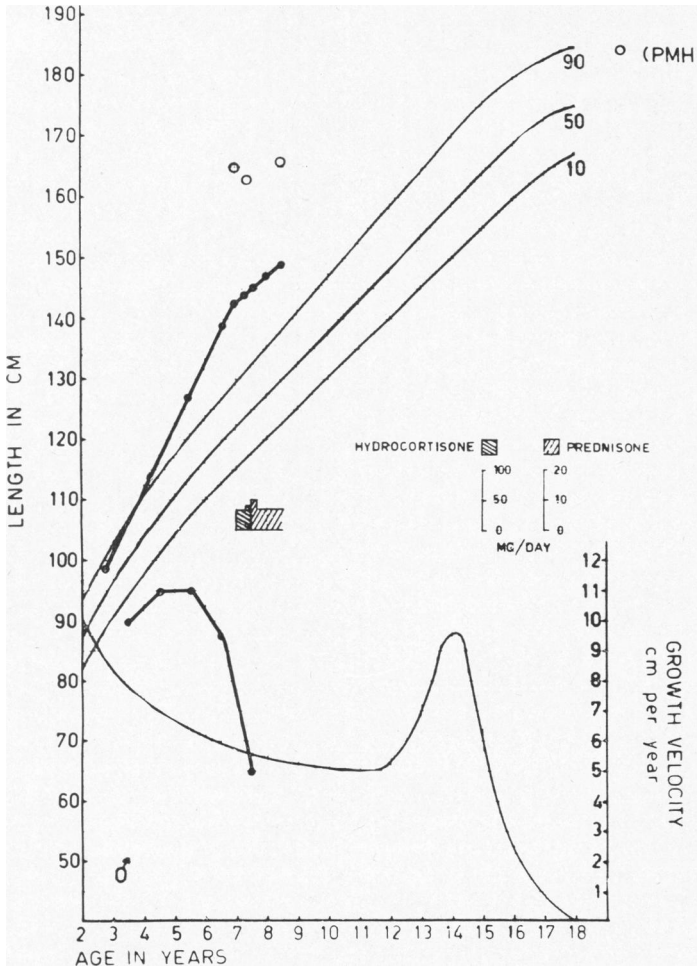

FIG. 6.—*Effect of glucocorticoid treatment on length and growth velocity in a boy with CAH (21-hydroxylation defect, no salt-loss). PMH = predicted mature height.*

scrotal fusion have been discussed by Jones and Jones (1954) and Jones and Wilkins (1961). Treatment of the enlarged clitoris has been described by Lattimer (1961): a large clitoris often diminishes in size after some years of medical treatment and operation should not be performed too early. Lattimer has described a procedure with preservation of the glans, which may be important for normal sexual experience in later life.

For an extensive discussion on medical and other treatment of CAH the reader is referred to Wilkins (1957), Blizzard and Wilkins (1957), and Bongiovanni and Root (1963). The psychological aspects of the treatment of CAH have been discussed by Money (1955), Hampson, Money, and Hampson (1956), and Bongiovanni and Root (1963). It has been generally accepted that reversal of sex in children after 2-3 years is inadvisable.

A series of reports of successful pregnancies in females with CAH has appeared (Gans and Ser, 1959; Laron, 1959; Mason, 1961; Swyer and Bonham, 1961). The fertility of the treated female seems to be good, and if the patient is treated properly pregnancy can be maintained without problems. Glucocorticoid treatment during pregnancy has to be adjusted, the best criterion probably being the urinary excretion of 17-KS which should not be raised too much. If the father is normal, all the children will be heterozygous for the disorder. If the father is a heterozygote, half the children will

have the disease. Little is known about the fertility of treated male patients with CAH.

(2) Premature Adrenarche

Pubic or axillary hair may develop at an early age without the appearance of the other symptoms of sexual maturation. The syndrome has been called *precocious sexual hair*, *isolated precocious sexual pilosity*, *premature pubarche*, and *premature adrenarche*. Four series of patients have been reported: Silverman, Migeon, Rosemberg, and Wilkins (1952), 28 girls and 1 boy; Thamdrup (1955), 12 girls and 5 boys; Ferrier, Shepard, and Smith (1961), 11 girls; Arnal, Dresch, and Prader (1961), 6 girls and 2 boys. In the first two series of patients a high incidence of brain damage among the patients was found. Bone maturation and height are reported as advanced for age in most patients, but there is no evidence that predicted adult height is decreased.

Urinary excretion of 17-KS has been found slightly or moderately raised (Ferrier *et al.*, 1961), but in only 1 out of 8 patients of Arnal *et al.* (1961) was 17-KS excretion slightly increased. Zurbrügg and Gardner (1963) studied two girls with precocious sexual hair, and fractionated urinary C_{19}-

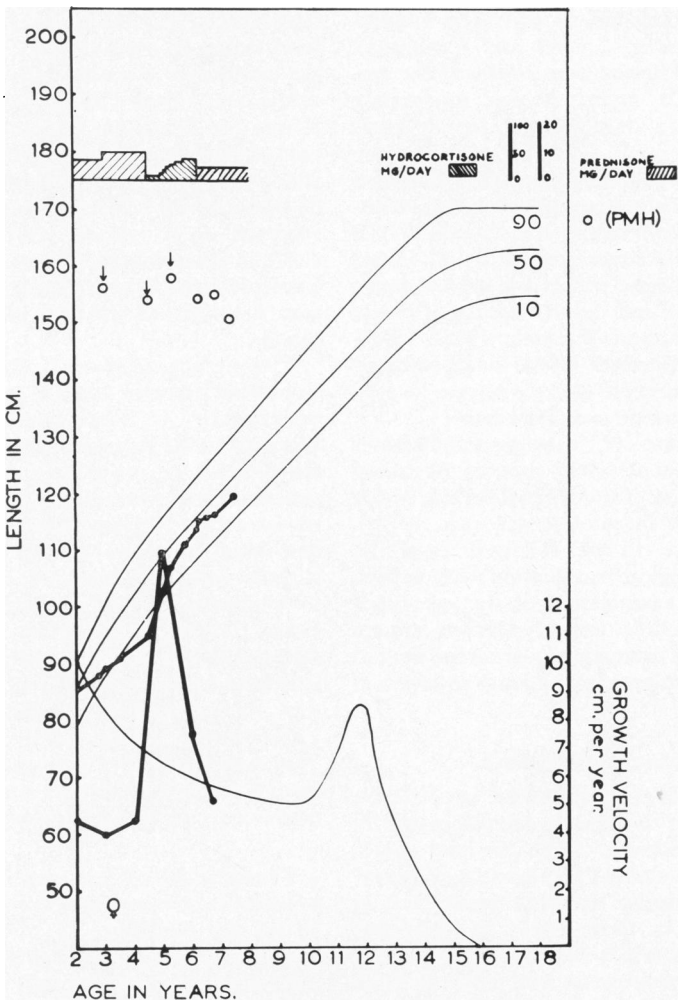

FIG. 7.—*Effect of glucocorticoid treatment on length and growth velocity in a girl with CAH (21-hydroxylation defect, no salt-loss). PMH = predicted mature height.*

steroids. They found raised excretion of aetiocholanolone and androsterone, while excretion of 11-oxy-17-KS was not appreciably different from values in controls.

Two theories have been advanced to explain this variation in the pattern of sexual development: (1) increased sensitivity of sexual hair follicles to normal levels of androgens present during the pre-adolescent period (Wilkins, 1957), and (2) premature increase in the secretion of adrenal androgens before the pituitary gonadotrophic mechanism becomes activated (Silverman *et al.*, 1952).

We have studied the urinary excretion of 6 individual 17-ketosteroids and of testosterone in 4 girls (ages 6 years and 10 months to 8 years and 2 months) with precocious sexual hair (first appearance at ages $3\frac{1}{2}$ years to 7 years and 8 months). Bone maturation and height were advanced for age. Urinary total 17-KS excretion was moderately raised. One girl had been treated for epileptic convulsions.

There was significant increased urinary excretion of 11-deoxy-17-KS (dehydroepiandrosterone, aetiocholanolone, and androsterone) and 11-oxy-17-KS as well. Values for testosterone excretion (mean value 7·5 μg./24 hr.) were within the normal range for adolescent girls and adult women (Visser, Degenhart, Frankena, and Wilmink, 1965). Zurbrügg, Jacobs, and Gardner (1964) have reported increased urinary excretion of testosterone in a 7-year-old girl with precocious axillary hair.

Our findings and those of Zurbrügg and Gardner (1963) and Zurbrügg *et al.* (1964) support the theory of premature activation of the adrenal cortex, which normally takes place in adolescence (see I (2)). These patients have to be followed carefully. Periodically a neurological examination with electroencephalogram and examination of the eye fundi are necessary to exclude central nervous system diseases. Idiopathic premature adrenarche should be considered as a benign constitutional variation of sexual development.

(3) Cushing's Syndrome

The syndrome was first described in 1932 by Cushing, who thought that the disease was primarily due to a basophil adenoma of the pituitary gland. The most important clinical and laboratory symptoms are those caused by excessive production of cortisol. In addition there may be increased production of other steroids by the adrenal glands, such as androgens, oestrogens, and mineralocorticoids. Intermediate clinical forms between 'pure' Cushing's syndrome, Conn's syndrome, and adrenogenital syndrome have been described. Prolonged administration of glucocorticoids may give a clinical syndrome which is similar to the spontaneous disease. Outstanding symptoms of the syndrome are obesity, the characteristic 'moon facies', hypertension, glucosuria, and decreased glucose tolerance test, weakness, purple striae, and menstrual disturbances in older female patients. Virilizing symptoms are common. An important sign in children is stunting of growth. Cushing's syndrome may result from adrenal tumours (adenoma or carcinoma) or from bilateral adrenal hyperplasia.

Cushing's syndrome is rare in children, but has been reported at all ages, even in infancy. Wilkins (1957) saw 26 children under 10 years of age. In a large series of 50 patients reviewed by Soffer, Iannaccone, and Gabrilove (1961) only 8 patients were under 20 years of age. In children under 10 the syndrome is usually the result of an adrenal carcinoma. Both Chute, Robinson, and Donohue (1949) and Silver and Ginsburg (1960) described a case of bilateral adrenal hyperplasia in an 8-year-old girl; Hubble and Illingworth (1957) reported an $8\frac{1}{2}$-year-old boy; Thursby-Pelham and Crowe (1961) reported a 10-year-old boy; probably 3 other children under 10 years of age with bilateral adrenal hyperplasia have been described. This author has seen a 9-year-old girl with bilateral adrenal hyperplasia.

The pathogenesis of Cushing's syndrome with associated bilateral adrenal hyperplasia is not fully understood. In some patients a small basophil adenoma in the anterior pituitary gland is found, but the situation is confused by the occurrence of such tumours after total adrenalectomy in patients with the syndrome (Salassa, Kearns, Kernohan, Sprague, and MacCarty, 1959). There is evidence for a slightly increased secretion of ACTH in patients with bilateral adrenal hyperplasia (Nugent, Eik-Nes, Kent, Samuels, and Tyler, 1960; Ney, Shimizu, Nicholson, Island, and Liddle, 1963), which is also indicated by the relative resistance of ACTH secretion to suppression by glucocorticoids (Liddle, 1960; Slater, Hartog, Fraser, and Rantzen, 1962). This suppression test is of great value in the diagnosis of Cushing's syndrome caused by adrenal hyperplasia or by autonomous adrenal tumours.

Treatment. When Cushing's syndrome is due to adrenal tumours the treatment should be surgical. When the syndrome is associated with adrenal hyperplasia treatment is more difficult. Subtotal adrenalectomy may give only temporary remission, and total adrenalectomy may lead to a pituitary tumour. External pituitary radiation by the implantation of radioactive yttrium and gold and

hypophysectomy have been tried and demonstrate that the attention is again turned to the pituitary gland. Definite conclusions cannot be made at this time. The 'puzzles' of Cushing's syndrome have been discussed in this journal by Wilkins (1962a).

(4) Virilizing and Feminizing Adrenocortical Tumours

Tumours of the adrenal cortex that secrete predominantly excessive amounts of androgenic steroids are rare in children. Wilkins (1957) collected 41 cases in children under 10 years of age. Scarpa-Smith, Thornton, Caffery, and Greenblatt (1959) found published reports of more than 100 cases. Virilizing symptoms may develop at any time after birth and are indistinguishable in males from those produced by congenital adrenal hyperplasia. In females there is normal embryonic sex differentiation without symptoms of pseudohermaphroditism at birth, and virilization beginning after birth in a girl is generally due to an adrenal tumour.

Urinary 17-KS are raised both in patients with adrenocortical tumours and with congenital adrenal hyperplasia. Excretion of large amounts of specific precursors (pregnanetriol) is highly suggestive of CAH.

The most important test for the differential diagnosis is suppression with a glucocorticosteroid. Cortisol quickly suppresses the urinary excretion of 17-KS in patients with CAH, but not in the patient with a virilizing tumour. Cortisol suppresses the increased secretion of ACTH in patients with CAH, while in most patients with adrenocortical tumours there is an autonomy of the neoplastic tissue to suppression or stimulation via ACTH.

Feminizing adrenal tumours are extremely rare in childhood. Wilkins (1948) described a case in a 5-year-old boy causing gynaecomastia.

Adrenocortical tumours may be palpable; radiological evidence can be obtained by pyelography and retroperitoneal pneumography. The treatment is by operation.

(5) Primary and Secondary Hyperaldosteronism

The syndrome of primary hyperaldosteronism has been described by Conn (1954, 1955). The most important symptoms and physical and laboratory findings are hypertension, muscle weakness, polyuria, polydipsia, hypokalaemic alkalosis, and inability to concentrate urine. Usually there is no oedema and no hypernatraemia. Conn, Knopf, and Nesbit (1964) have recently reviewed their experiences with 18 patients, and collected 145 published cases reported up to 1962. Most were in the 30-50 age-group, and most had an adrenal adenoma, usually solitary. Some patients had bilateral adrenal hyperplasia or carcinoma. Production and excretion of aldosterone is raised, while usually excretion of urinary 17-KS and 17-OHCS is normal. Raised production and excretion of glucocorticoids, androgens, and mineralocorticoids is suspicious of adrenal carcinoma.

Very few children with the disorder have been reported. Kretchmer, Dickinson, McNamara, and Karl (1959) described a case of Conn syndrome in a 9-year-old boy. Bongiovanni comments on this paper (1960) and mentions 5 others in children under age 16, none being infants. The youngest patient in the series of Conn *et al.* (1964) was 15.

Primary aldosteronism should be considered in the differential diagnosis of hypertension in childhood. Treatment is by operation.

Secondary hyperaldosteronism can be found in oedematous conditions, such as nephrotic syndrome, cirrhosis of the liver with ascites, severe hypoproteinaemia, and congestive heart failure. High aldosterone production in these disorders is not the primary cause of the salt-water retention, but it certainly increases the sodium retention. Secondary hyperaldosteronism is probably an effort by the organism to maintain the osmolarity of the body fluids, stimulated by hypovolaemia and regulated by the renin-angiotensin system. Secondary hyperaldosteronism plays a part in the water-salt retention in some children with nephrotic syndrome (Muller and Manning, 1963), and spironolactone, a mineralocorticoid-antagonizing substance, is a potent natriuretic agent in nephrotic patients (Genest, 1960; Hill and Burianek, 1963).

IV: Adrenocortical Hypofunction

(1) Adrenal Insufficiency Usually Seen in Infancy (salt-losing syndrome)

a. Defects in the biosynthesis of aldosterone.
   i. Transient?
   ii. Permanent, as hereditary 'inborn error'

—lipoid adrenal hyperplasia (20, 22 desmolase defect?)	with congenital adrenal hyperplasia
—3β-dehydrogenation defect	
—21-hydroxylation defect	
—18-oxidation defect (18-hydroxylation type; 18-dehydrogenation type)	without congenital adrenal hyperplasia

b. Haemorrhage and calcification in the adrenal glands.
c. Congenital adrenal hypoplasia of the adrenal glands.
d. 'Transient adrenocortical insufficiency in infancy (Jaudon, 1948)?'

The presenting symptoms of adrenocortical insufficiency in infancy are those of a salt-losing syndrome: dehydration, poor feeding, failure to gain weight or weight loss, intermittent febrile temperature, and occasional vomiting. There is hyponatraemia, hyperkalaemia, and metabolic acidosis: changes typical of Addison's disease. Hyperpigmentation is often, but not always, present.

A salt-losing syndrome in the newborn period and infancy is most commonly associated with congenital adrenal hyperplasia. The clinical variants and pathogenesis of this syndrome have been discussed earlier (III (1)). In a third of all infants with 21-hydroxylation defects a salt-losing syndrome develops. In all infants with lipoid adrenal hyperplasia and almost all infants with 3β-dehydrogenation defect reported up to now, a salt-losing syndrome was present. There is now strong evidence for severe hypoaldosteronism as the major cause of the salt wasting in patients with the salt-losing variant of the 21-hydroxylation defect (Bryan *et al.*, 1962; New *et al.*, 1964; Degenhart *et al.*, 1965a): see Tables I and II. Although this has not been investigated up to the present, it is very likely that the salt-loss in infants with the 'early' defects in the biosynthesis of adrenocortical steroids is also caused by severe hypoaldosteronism.

As can be seen in Fig. 3, Part 1, the 18-oxidation enzyme step affects only the biosynthesis of aldosterone between corticosterone and aldosterone. Theoretically one could expect a hereditary 18-oxidation defect with impaired biosynthesis of aldosterone. Clinically a salt-losing syndrome should not show an increased elaboration of androgenic substances by ACTH stimulation. One should find, however, an increased urinary excretion of corticosterone, 11-dehydrocorticosterone, and eventually 11-deoxycorticosterone and their metabolites (see Fig. 3 and 5 of Part 1).

At the European Paediatric Endocrinology Club in Groningen, May 1963, we reported three related patients with a salt-losing syndrome and C_{21}-corticosteroid pattern, highly suggestive of such an 18-oxidation defect (Visser and Cost, 1964a).

Two infants (Patients 2 and 3, Fig. 8) were investigated. They were 5 and 15 weeks old on admission to the local hospitals. There was consanguinity between the parents of each child and the 4 parents of these 2 patients were also related. Another child in the same family, born in 1950 (Patient 1, Fig. 8) was seen at the age of 3 weeks with the same clinical syndrome. The clinical symptoms were those of the salt-losing syndrome. The children never showed hyperpigmentation. Serum sodium was low, serum potassium high. All three patients showed a good response to deoxycorticosterone-acetate (DOCA). External genitalia were normal. Total urinary excretion of 17-KS, 17-KGS, and 17-OHCS was normal. There was no increase in the urinary excretion of pregnanetriol and tetrahydro-S.

Urinary C_{21}-corticosteroid patterns were investigated in the 3 patients using a method described by Cost and Vegter (1962). No aldosterone was detectable in the urine of the 3 patients or in the 2 infants after administration of ACTH and under conditions of hyponatraemia and dehydration. There was a considerable increase in the total 'B' compounds—that is, corticosterone (compound B), and the steroids derived from it, 11-dehydrocorticosterone (compound A), and their tetrahydro-metabolites (THB, THA, allo-THB). Total 'F' compounds were normal for the corresponding age: cortisol (compound F), cortisone (compound E), and their tetrahydro-metabolites (THF, THE, allo-THF). Total 'F'/total 'B' ratios were very low. Small amounts of 11-deoxycorticosterone (DOC) were found in the 2 infants. Some of the results are demonstrated in Fig. 9. Full details of the steroid studies in the patients and in normal control infants, children, and adults are reported elsewhere (Visser and Cost, 1964b).

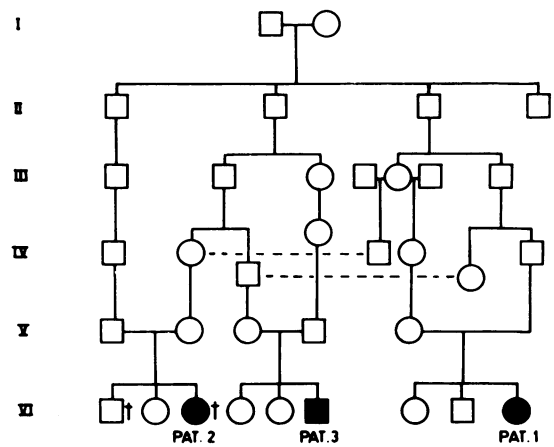

FIG. 8.—*Simplified pedigree of family with hereditary hypoaldosteronism, 18-oxidation defect (Visser and Cost, 1964a, b). See text.*

Both infants with this salt-losing syndrome were able to achieve marginal Na balance with serum Na

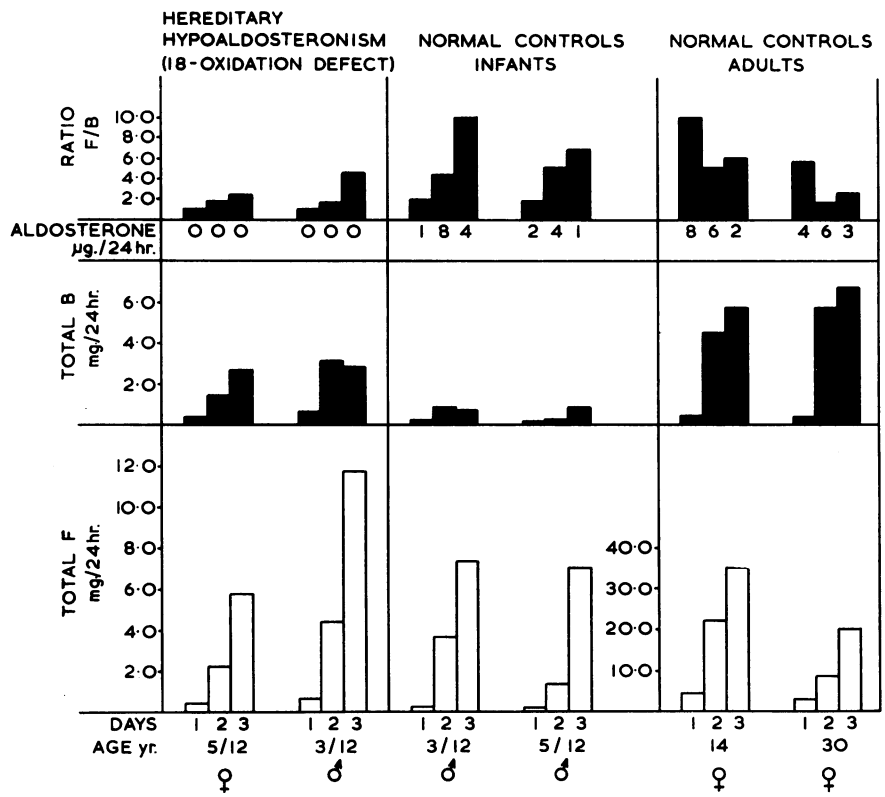

FIG. 9.—*Urinary excretion of C_{21}-corticosteroids before (day 1) and during ACTH administration (days 2 and 3) in two infants with hereditary hypoaldosteronism (18-oxidation defect), two normal control infants, and two normal adults (see text). ACTH (corticotrophin, Organon) intravenously, 25 IU per day during 8 hours (adults). ACTH-gel (corticotrophin-zinc, Organon) intramuscularly 60 IU per day (infants). Total F = F + E + THF + allo-THF + THE. Total B = B + A + THB + allo-THB + THA.*

values between 120-125 and 125-130 mEq/l. respectively, at dietary intakes of 15 and 34 mEq Na/day. The increased production of DOC and corticosterone, both biologically active mineralocorticosteroids (Table II, Part 1), resulted in urinary Na/K ratios of 0·4-0·6 and 0·6-0·8. However, in one infant on a daily intake of less than 1 mEq Na/day, serum Na dropped to 110 mEq/l. and the child became critically ill. The effects of ACTH on Na and K balance were different from those seen in infants with the salt-losing variant of CAH (21-hydroxylation defect). Administration of ACTH was followed by Na retention and K excretion, Na/K ratios were very low. Serum Na became normal. We believe that this was caused by an increased production of DOC and corticosterone. In infants and children with CAH (21-hydroxylation defect) administration of ACTH is normally followed by increased Na excretion and a rise in Na/K ratio. This is seen both in 'salt-losers' on DOCA treatment and in 'non salt-losers'. This effect is probably due to the increased production of 17-hydroxyprogesterone, which has mineralocorticoid-antagonizing activities (Table II).

The pedigree of the family of these 3 patients is remarkable (Fig. 8). Six generations could be traced back: no less than 16 consanguineous marriages in 3 generations were found. The 6 parents of the 3 children with the salt-losing syndrome had the same 2 great-grandparents 5 generations back. This indicates a recessive autosomal heredity of this new defect in the biosynthesis of aldosterone, with its clinical expression in the homozygous state.

Patient 1 is now a well-developed 15-year-old girl with normal pubertal development. DOCA thera-

py was discontinued at 1 year of age and she did well thereafter. She still takes a salt-rich diet. At the age of 13 the same changes in the urinary C_{21}-corticosteroid pattern were still found as in the 2 infants, though they were less pronounced. Patient 3 was treated for about 2 years with DOCA and extra salt; DOCA therapy was then gradually discontinued, and he has developed normally. Patient 2 unfortunately died with an intercurrent viral infection at 7 months. At necropsy the adrenal glands were of normal weight and aspect; microscopically the *zona glomerulosa* showed a tubular and empty aspect of varying width (Visser and Cost, 1964b).

Ulick, Gautier, Vetter, Markello, Yaffe, and Lowe (1964) have studied a male infant with a salt-losing syndrome associated with defective production of aldosterone. They found increased production of corticosterone, 18-hydroxycorticosterone, and deoxycorticosterone, and interpreted the disorder as a biosynthetic block between 18-hydroxycorticosterone and aldosterone (18-dehydrogenation defect). In the 3 patients reported by Visser and Cost (1964a, b), excretion of 18-hydroxycorticosterone could not be estimated, as no reference steroid was available at that time.

Jacobs and Posner (1964) and Posner and Jacobs (1964) described a young male adult with isolated hypoaldosteronism and increased excretion of tetrahydrocorticosterone. They suggested the possibility of a defect in the 18-oxidation enzyme system in their patient. A small number of other adult patients with isolated hypoaldosteronism have been described, but no detailed steroid patterns have been reported and none of these patients demonstrated clinically a salt-losing syndrome (see Lambrew, Carver, Peterson, and Horwith, 1961). It is not known if hypoaldosteronism was present from birth in these adults.

The juxtaglomerular cells in the kidneys are believed to be the source of renin, a substance that initiates the formation of angiotensin, which is a stimulus for aldosterone secretion (Mulrow and Ganong, 1964). In the case of a defect in the biosynthesis of aldosterone with a resulting salt-losing syndrome, a compensatory hypertrophy of the juxtaglomerular areas in the kidneys might be expected. Indeed, in Patient 2 of our family with 18-oxidation defect an increase of cellular elements was found in the juxtaglomerular areas. We were not able to get information about the renin- or angiotensin-like activities in the blood of the patients. Ulick *et al.* (1964) found increased amounts of renin in the plasma of their patients during Na-depletion (personal communication). Hypertrophy of the juxtaglomerular cells was found by Cara and Gardner (1963) in a 5-year-old child with the sodium-losing type of CAH.

It is likely that the increased production and excretion of deoxycorticosterone and corticosterone in patients with a hereditary 18-oxidation defect indicates an increased 21- and 11-hydroxylation of progesterone and DOC, stimulated by the regulatory renin-angiotensin system, as a result of the salt-losing state (Visser and Cost, 1964b). The fall in excretion of 'B' compounds in one of our infants after 4 months of therapy with DOCA, and the fall in production of corticosterone and 18-hydroxycorticosterone in the patients of Ulick *et al.* (1964) on treatment with DOCA and salt, favour this hypothesis. Although the increased production of DOC and corticosterone enables the patient to maintain marginal Na-balance at a relative high intake of Na, the total salt-retaining activity (when calculated in aldosterone equivalent, see Table II of Part 1) is less than under conditions of Na-depletion in a normal infant, with aldosterone production up to 600 μg./24 hr. (see Table I, Part 1).

Three other reports on isolated hypoaldosteronism in infancy have appeared during recent years, but as detailed steroid studies were not carried out, it is impossible to say if a biosynthetic defect was responsible for the disorder in these patients (Royer, Lestradet, de Menibus, and Vermeil, 1961; Hagge, 1962; Russell, Levin, Sinclair, and Oberholzer, 1963).

Royer *et al.* (1961) described two sibs (boy and girl) with a salt-losing syndrome in infancy. There was a good response to DOCA. Urinary excretion of aldosterone was less than 2 μg./24 hr., even under conditions of Na-depletion. Porter-Silber chromogens increased normally after administration of ACTH. The boy was again investigated at the age of 5 years (Rappaport, 1964). Secretion rates of cortisol and aldosterone were normal, while a normal increase after ACTH and during salt-deprivation was observed.

Russell *et al.* (1963) have reported two infants with a reversible salt-wasting syndrome who responded well to salt-retaining hormones; urinary excretion of 17-KS and 17-KGS was normal. Both infants (a male and a female) had normal external genitalia. A reversibility of the salt-losing state was indicated by the fact that salt and DOCA therapy could be discontinued at the age of 12 months in one infant, and was gradually diminished from the age of 16 months in the other child, ultimately being completely discontinued at $3\frac{1}{2}$ years. At 15 months of age in the first patient a salt deprivation test, involving a salt restriction to 3 mEq Na per day, was performed.

Urinary Na excretion fell from 21 to 2·5 mEq by the fifth day and to 1 mEq by the ninth day, when plasma Na was 130 mEq/l. In one patient aldosterone was measured twice; on the first occasion when the child was 15 months old and on a normal diet without DOCA therapy, no aldosterone could be detected in a 24-hour urine; at the second estimation three months later, less than 1 μg./24 hr. was found. In the other patient aldosterone was not determined.

Jaudon (1946a, 1948) has suggested the existence of transient states of adrenocortical insufficiency in infancy. He has described a series of 14 infants with various symptoms such as attacks of hypoglycaemia, anorexia, listlessness, vomiting, and failure to gain weight. All infants had a marked tendency to dehydration. In some cases serum electrolyte values are reported and indicate hyponatraemia and hyperkalaemia. All infants responded well to daily doses of DOCA and 'whole adrenal extract' available at that time. It was possible after various periods to stop treatment without any recurrence of symptoms. Several of them are described as hyperpigmented; in some, steroid determinations indicated increased excretion of pregnanediol. One infant was reported as a male with hypospadia and undescended testicles. In our opinion some of such infants have been cases of congenital adrenal hyperplasia with salt loss. In other cases, the clinical and laboratory findings do not satisfy the diagnostic criteria of Addison's disease. However, it is possible that some of these cases represent transient insufficient production of salt-retaining steroids by the adrenal cortex.

It is possible that two types of isolated hypoaldosteronism in infancy exist: *permanent* hereditary hypoaldosteronism, as a result of an 'inborn error of metabolism' in the 18-oxidation enzyme system (Visser and Cost, 1964a, b; Ulick *et al.*, 1964), and *transient* hypoaldosteronism, caused by delayed maturation of the zona glomerulosa after birth, which may mean delayed biochemical maturation of the 18-oxidation enzyme system. This transient hypoaldosteronism may be of hereditary nature as in the family of Royer *et al.* (1961).

Five infants, all males with a salt-losing syndrome, who did not respond to salt-retaining hormones, have been reported during recent years (Cheek and Perry, 1958; Donnell, Litman, and Roldan, 1959; Lelong, Alagille, Philippe, Gentil, and Gabilan, 1960; Raine and Roy, 1962; Royer, Bonnette, Mathieu, Gabilan, Klutchko, and Zittoun, 1963). This syndrome has been ascribed to a renal tubular insensitivity to salt-retaining hormones. In 2 cases a doubtful family history is mentioned; in the case described by Royer *et al.* (1963) the parents were consanguineous. Adrenocortical function appeared to be normal both by clinical and laboratory investigations in all 5 cases. Aldosterone excretion was determined in 3 of them. If the salt-losing syndrome were due to a renal tubular insensitivity to salt-retaining hormones, aldosterone excretion would be expected to be increased: this was so in the 3 cases (Donnell *et al.*, 1959; Lelong *et al.*, 1960; Royer *et al.*, 1963). In the cases described by Donnell and Royer, excretion of aldosterone on a normal Na intake was 335 μg. and 140 μg./24 hr., respectively. Addition of salt to the diet reduced the urinary excretion of aldosterone, salt restriction caused a rise in urinary aldosterone.

By increasing the dietary intake of salt, serum electrolytes were corrected in all 5 cases and the general condition was controlled. The child described by Donnell *et al.* (1959) was able to maintain electrolyte balance on a standard diet after 15 months, but could not tolerate salt deprivation. The infant described by Royer *et al.* (1963) had a salt-losing syndrome at the age of 20 months, when on a diet supplemented with 5 g. NaCl. Administration of extra salt was discontinued for the other children after 15-24 months.

A most interesting phenomenon is the improvement of the different salt-losing syndromes, which takes place with age. An amelioration of the salt-losing symptoms with age is well known in children with the salt-losing type of CAH; though these children usually do not require further DOCA therapy after 1 year of age, they are still unable to conserve Na and get into difficulties when salt intake is restricted. It is remarkable that the same process has been observed in our children with the 18-oxidation defect, and also in some of the children with a salt-losing syndrome caused by insensitivity of the renal tubules to salt-retaining hormones. It is not known how this age-dependent adaptation to the Na-losing tendency in the different salt-losing syndromes is mediated.

Acute adrenal insufficiency in infancy has been described as a result of congenital hypoplasia of the adrenal glands. This may occur either in combination with congenital hypoplasia or absence of the pituitary gland (Blizzard and Alberts, 1956; Mosier, 1956; Ehrlich, 1957; Brewer, 1957; Reid, 1960), or as an isolated congenital adrenal hypoplasia (Šikl, 1948; Deamer and Silver, 1950; Welsh and Mehlin, 1954; MacMahon and Wagner, 1956; Williams and Robinson, 1956; Harlem and Myhre, 1957; MacMahon, Wagner, and Weiner, 1957; Mitchell and Rhaney, 1959; Boyd and MacDonald, 1960).

Mitchell and Rhaney (1959) observed two male

sibs. Vomiting, dehydration, and weakness, with severe hyponatraemia and hyperkalaemia, occurred about 3 weeks after birth. The first patient died at the age of 2 months. At necropsy the adrenal glands together weighed 0·72 g. The cortical cells were abnormally large and irregularly arranged, without differentiation into glomerular and fasciculate zones. The large cells resembled the giant cells occasionally found in the foetal adrenal cortex. This appearance differs from that found in association with anencephaly and pituitary hypoplasia (Harlem and Myhre, 1957; MacMahon *et al.*, 1957). The second patient was treated successfully with 9α-fluorocortisol. His urinary 17-KS and 17-KGS were low, and there was no significant increase in urinary steroids after giving ACTH for several days.

Adrenal cortical hypoplasia in two male sibs, who both died in the neonatal period, is also reported by Boyd and MacDonald (1960).

Acute adrenal insufficiency in infancy may occur as a result of haemorrhage and calcification in the adrenal glands. Important causes of adrenal haemorrhage in the newborn infant are trauma due to difficult delivery, anoxia, shock, prematurity, haemorrhagic diseases, and infections. Small bilateral adrenal haemorrhages may occur with rapid subsequent calcification (Snelling and Erb, 1935; Rack and Eiben, 1951; Stevens and Tomsykoski, 1954; Gardner, 1957; Jarvis and Seaman, 1959; Stevenson, MacGregor, and Connelly, 1961), while massive haemorrhage with rupture into the peritoneal cavity has been described (Hill and Williams, 1959).

In some cases large haemorrhagic adrenal cysts have been found, which may be several times the size of the normal gland and cause compression of other organs. Moore and Cermak (1950) have reported a case of congenital adrenal insufficiency with hyponatraemia and hyperkalaemia, in which bilateral adrenal cysts were found at necropsy. The patient was treated with DOCA for 7 months. Sudden death followed a minor infection.

The differential diagnosis of the salt-losing syndrome in infancy is illustrated in Table III. It can be seen that almost always the diagnosis can be made without much difficulty. The differential diagnosis between lipoid adrenal hyperplasia and congenital adrenal hypoplasia may not be possible in girls, however, as specific steroid studies are not yet carried out.

(2) Chronic Adrenocortical Insufficiency Usually Seen in Older Children

a. Classical Addison's disease
   i. 'Idiopathic' type, often familial
   ii. Familial type with hypoparathyroidism and moniliasis

b. Hypopituitarism with secondary adrenocortical insufficiency.

c. Iatrogenic chronic adrenocortical insufficiency after stopping corticosteroid therapy.

Chronic adrenal insufficiency, *Addison's disease*, is a rare condition in childhood. 'Addison's disease' is a clinical and not a pathological entity, and can be

TABLE

Differential Diagnosis of Salt-

	External Genitalia		Sex Chromatin*		Urinary	
	Boys	Girls	Boys	Girls	17-KS	17-OHCS (Appleby)
Biosynthetic defects (permanent)						
Lipoid adrenal hyperplasia	Male pseudo-hermaphrodite	Normal or slight virilization	−	+	(Small increase)	(Small increase
3β-dehydrogenation	Male pseudo-hermaphrodite	Normal or slight virilization	−	+	Small increase	Small increase
21-hydroxylation	Normal	Female pseudo-hermaphrodite	−	+	Increase	Increase
18-oxidation	Normal	Normal	−	+	Normal	Normal
Congenital adrenal hypoplasia	Normal	Normal	−	+	Low	Low
Haemorrhage and calcification in adrenal glands	Normal	Normal	−	+	Low	Low
Transient adrenocortical insufficiency (?)	Normal	Normal	−	+	(Normal)	(Normal)
Delay in maturation zona glomerulosa or 18-oxidation system(?)						
Insensitivity of renal tubules to mineralocorticoids	Normal	Normal	−	+	Normal	Normal
Other renal diseases (nephropathies)	Normal	Normal	−	+	Normal	Normal

* − negative; + positive.

applied to any disorder that ultimately leads to destruction or atrophy of the adrenal cortex with the clinical symptoms of insufficient glucocorticoid and mineralocorticoid activity. Defined in this way, it is seen in infants as a result of congenital hypoplasia of the adrenal glands, or of haemorrhage and calcification in the adrenals as already discussed. Symptoms may only appear later. Thus White and Sutton (1950) described a case of Addison's disease in a 2½-year-old girl, who apparently had had partial destruction of the adrenal glands by septicaemia and haemorrhage at the age of 1 month, and who did well until an acute adrenal crisis was precipitated by acute infection at the age of 2½ years. In our opinion, *partial* adrenocortical insufficiency, such as isolated hypoaldosteronism (see IV (1) or isolated glucocorticoid insufficiency (Shepard, Landing, and Mason, 1959), should not be termed Addison's disease.

The presenting symptoms of chronic adrenal insufficiency in children are general weakness, anorexia, weight loss with dehydration, and gastro-intestinal symptoms such as nausea, vomiting, and diarrhoea. Recurrent convulsions, probably of hypoglycaemic origin, may occur. Pigmentation of mucous membranes and skin is usually present, particularly of areolae, genitalia, and scars, though cases without it have been described (Fellows, Buchanan, Peterson, and Stokes, 1962).

Jaudon (1946a) reviewed critically the published reports up to 1946. Of 100 reported cases 62 were classified as 'proved'; 35 male and 24 female children were under 15 years of age; only 3 patients were under 5 years of age, and 9 were between 6 and 10 years old. Most cases were of tuberculous origin. A 6½-month-old girl with a salt-losing syndrome was reported by Jaudon (1946b) as the youngest patient with Addison's disease at that time; she probably had tuberculous involvement of the adrenals. Additional cases of Addison's disease in childhood have been reported since 1946 (Malloy and Woodruff, 1958), but tuberculosis was an aetiological factor in only a few of them. Nowadays, however, the aetiology of Addison's disease is rarely tuberculosis, but usually seems to be an idiopathic atrophy or degeneration of the adrenals. Several cases of familial Addison's disease have been described in recent years (Briggs, Goodwin, and Wilson, 1951; Berlin, 1952; Brøchner-Mortensen, 1956; Hewitt, 1957; Meakin, Nelson, and Thorn, 1959), the familial occurrence of the disorder having been recognized in 1900 by Fleming and Miller.

A number of familial syndromes involving Addison's disease are known. Frequently the disease is associated with hypoparathyroidism and/or moniliasis. Children with idiopathic Addison's disease should be carefully watched for the development of hypoparathyroidism, and the reverse is true. The subject was discussed by Di George and Paschkis (1957). Addison's disease has been reported in combination with Hashimoto's disease (Anderson, Goudie, Gray, and Timbury, 1957) and diabetes mellitus (McNicol and McNicol, 1960). Anderson *et al.* (1957) reported the presence of circulating auto-antibodies against the adrenal gland in patients with Addison's disease, and the concept

III

losing Syndrome in Infancy

Peroids			Response to ACTH		Response to Mineralo-corticoids	Other Symptoms
17-OHCS (Porter-Silber)	Aldosterone	Specific Pre-cursors (metab.)	17-OHCS (Appleby)	17-OHCS (Porter-Silber)		
(Low)	(Low)	(+)	(Small increase)	(No increase)	+	
Low	(Low)	+	(Small increase)	(No increase)	+	
Low	Low	+	Increase	No increase	+	
Normal	Low	+	Increase	Increase	+	No pigmentation
Low	Low	–	No increase	No increase	+	
Low	Low	–	No increase	No increase	+	X-ray calcification in adrenals
(Normal)	(Low)	(+ ?)	(Increase)	(Increase)	+	
Normal	Increase	–	Increase	Increase	–	
Normal	Normal	–	Increase	Increase	–	Renal pathology

Between parentheses: hypothetical data, exact data not known.

that the disease may be of autoimmune origin was supported by the findings of Blizzard, Chandler, Kyle, and Hung (1962). These investigators found adrenal antibodies in the sera of 16 of 30 patients with Addison's disease, but none were found in sera from 15 patients with CAH or Cushing's syndrome. Of the 16 patients with adrenal antibodies, 7 also had thyroid antibodies, and 7 of 22 patients with idiopathic hypoparathyroidism had adrenal antibodies; 3 of these had associated Addison's disease. The combination of Addison's disease, pernicious anaemia, and superficial moniliasis was reported by Hung, Migeon, and Parrott (1963) in a 10½-year-old girl. In this child and in a sib, circulating adrenal antibodies were present. Berlin (1952) reported the occurrence of familial Addison's disease and pernicious anaemia. Antibodies to gastric mucosa and thyroid have been found in patients with diabetes mellitus or Addison's disease (Moore and Neilson, 1963). These findings taken together lend some support to the idea of an autoimmune basis for Addison's disease and the other disorders with which it is sometimes associated.

Other familial syndromes in childhood are those of Addison's disease in combination with spastic paraplegia (Harris-Jones and Nixon, 1955) and cerebral sclerosis (Fanconi, Prader, Isler, Lüthy, and Siebenmann, 1963).

There are two reports on familial glucocorticoid deficiency without hypoaldosteronism. Shepard *et al.* (1959) described two sisters: one died aged 30 months, after the onset of hyperpigmentation, weakness, and convulsions. At necropsy all cells of the zona fasciculata and reticularis were absent; occasional clumps of cortical cells remained in the zona glomerulosa. The sister had all the signs of cortisol deficiency; at the age of 3½ years she could withstand a Na-free diet for 6 days by decreasing urinary Na to 2 mEq/l., while urinary aldosterone excretion increased. Stempfel and Engel (1960) described a syndrome of 'familial, congenital selective cortisol deficiency'. One male sib died shortly after birth and no identifiable adrenal tissue was found at necropsy. A 4-year-old brother had signs of complete absence of cortisol production from birth on; at 3½ years of age aldosterone excretion was normal on free sodium intake though he had episodes when there was decreased serum sodium concentration.

These two reports on familial adrenal hypoplasia, involving primarily those glandular elements responsible for the production of glucocorticoids, are of considerable interest. Such cases may represent partial adrenocortical insufficiency, secondary to familial absence of ACTH, though other signs of pituitary insufficiency were lacking.

Some hypopituitary dwarfs also show a deficient cortisol production which is secondary to decreased ACTH. They are subject to hypoglycaemic attacks and are extremely insulin-sensitive. Despite their deficient cortisol production, they usually respond normally to a salt-deprivation test, with decrease in urinary Na and increase in urinary aldosterone excretion.

Perhaps the most frequent and important cause of chronic adrenocortical insufficiency in childhood is the iatrogenic chronic adrenocortical insufficiency in the patient who has been treated with glucocorticoids and who has recently stopped taking them. Administration of glucocorticoids results in suppression of pituitary ACTH release, suppression of cortisol production, and ultimately adrenocortical atrophy. There is considerable clinical and experimental evidence that short periods of glucocorticoid therapy may lead to a severe degree of adrenocortical atrophy. Christy, Wallace, and Jailer (1956) studied the response of plasma 17-OHCS to an intravenous infusion of ACTH in patients without adrenocortical disease, before and after one week of prednisone therapy. The diminished response after this short period of therapy was comparable to that in patients with chronic hypopituitarism. The response to a standard dose of ACTH has been studied in several groups of patients treated for some period with glucocorticoids (Vermeulen, 1958; Sandberg, Eik-Nes, Migeon, and Koepf, 1957), and Bierich, Kersten, and Maruektad (1959) studied this in children. The longer the course of therapy had lasted, the less was the response to ACTH. After 2 or 3 weeks of therapy the response to ACTH was already diminished. Treadwell, Savage, Sever, and Copeman (1963) studied the ACTH response in patients with rheumatoid disease treated with glucocorticoids: even after 10 years of therapy there was a positive response. Thus, though adrenal atrophy occurs to some extent during steroid treatment, it seems that the adrenal glands never atrophy completely.

Intermittent administration of ACTH during chronic steroid therapy has been recommended to prevent this adrenocortical atrophy, and the adrenal response to ACTH can be maintained in this way (Bondy, Hollingsworth, D'Esopo, and Upton, 1958). However, there is ample evidence that during steroid therapy the ACTH-releasing mechanism at the hypothalamic or pituitary level has been disturbed, and the response of this mechanism to low endogenous production of cortisol may be impaired for some time after steroid therapy has been stopped.

TABLE IV

Treatment of Chronic Adrenocortical Insufficiency

	Maintenance Dose (mg./day)	Stress Dose (mg./day)
Cortisol (alcoholic, *not* acetate) orally, in 3 doses Prednisone, orally in 3 doses	10-50 2-10	2-5 times maintenance dose
Cortisone acetate, intramuscularly, necessary only for parenteral treatment and before and during surgery	5-25	2-5 times maintenance dose
Deoxycorticosterone-acetate (DOCA), intramuscularly DOC-trimethylacetate (Percorten-M, CIBA), intramuscularly	1-3 10-30 mg./1-4 wk.	

Kyle, Meyer, and Canary (1957) studied ACTH release in two patients with Cushing's syndrome after removal of the adrenal tumours. Although the remaining adrenals responded well to exogenous ACTH, pituitary ACTH release was disturbed up to two years after the operation. Evidence for a disturbed ACTH-releasing mechanism in long-term steroid-treated patients has also been given by Meakin, Tantongco, Crabbé, Bayles, and Nelson (1960) and Holub, Wallace, and Jailer (1960), both groups using the metyrapone test. Meakin *et al.* (1960) found that pituitary function might recover more rapidly than adrenocortical function and recommended periodic ACTH administration to patients receiving long-term steroid treatment. Holub *et al.* (1960) described one patient who responded well to administered ACTH but was totally unresponsive to metyrapone. Treadwell *et al.* (1963), using metyrapone, found no negative response up to 15 months of treatment and no positive tests after 30 months of treatment.

Although conclusions cannot be positive at this time, the author favours frequent intermittent administration of ACTH in children receiving long-term steroids. This will at least prevent severe adrenal atrophy and will promote rapid recovery of adrenocortical function after stopping therapy. Because ACTH release may be disturbed for some time after stopping therapy, for at least 24 months after discontinuing prolonged therapy stress doses of cortisol should be given for infection, trauma, or surgery. Stress doses of cortisol should be high, 2·5 mg./kg. 24 hr. (Table IV, and Table I of Part 1) or 2-5 times the maintenance dose.

(3) Acute Adrenal Crisis in Infants and Children

(a) As the first symptoms of adrenocortical insufficiency in infants and children with the diseases discussed in Section IV.

(b) In the course of acute stress (surgery, infections) in patients treated for chronic adrenocortical insufficiency or congenital adrenal hyperplasia.

(c) In the course of acute stress in patients on long-term steroid treatment, or in patients after stopping long-term steroid treatment.

(d) In the course of meningitis and other overwhelming infections (Waterhouse-Friderichsen syndrome).

Acute adrenal crises are common in patients with adrenocortical insufficiency and are precipitated by acute infections. The patient becomes very ill, with signs of circulatory failure. Blood pressure falls, the size of the heart is decreased. The patient may be comatose or delirious, and looks pallid and cyanotic. Frequently there is severe abdominal pain, suggesting acute abdominal disease. Vomiting and diarrhoea are often present. Serum Na and Cl are decreased, and K is increased. There is haemoconcentration and metabolic acidosis.

Patients treated for chronic adrenocortical insufficiency should receive maintenance doses of cortisol which are not in excess of the physiological production of cortisol. Major stress situations such as surgery, injuries, and infections should be managed by a two- to fivefold increase in the maintenance dose for the duration of the critical situation. If the patient is not vomiting and is fully conscious the treatment can be given orally.

Patients with congenital adrenal hyperplasia should be maintained on glucocorticoids in the same dosage range as patients with chronic adrenal insufficiency. They cannot increase their production of cortisol sufficiently during stress, and they therefore have then to be managed in the same way as patients with chronic adrenocortical insufficiency.

Patients on long-term steroid treatment should never discontinue the steroid during stressful situations. If the dose has been decreased before, it should be increased again as high as stress doses, and given parenterally, if there is vomiting. Ambulant patients on long-term steroid therapy should carry a card with them containing information of the treatment. In the child that acquires varicella, the dose should be *decreased* to the maintenance dose (Haggerty and Eley, 1956).

Waterhouse-Friderichsen syndrome. The clinical syndrome of overwhelming sepsis with extensive purpura and circulatory collapse ('Water

house-Friderichsen' syndrome) is mostly seen in children and young adults. Most cases are due to massive invasion with meningococci, though other micro-organisms may produce the sepsis.

The earliest reports of the syndrome came from Great Britain around 1900, and the authors recognized the association of the fulminating, rapidly fatal syndrome with bilateral adrenal haemorrhage (Voelcker, 1894; Batten, 1898; Talbot, 1900; Little, 1901). Waterhouse reviewed the then available published material in 1911, and Friderichsen in 1918. Bernhard and Jordan (1944), Thomison and Shapiro (1957), and many others have reviewed the later reports.

Acute meningococcaemia, with purpura and vascular collapse, may also occur without the adrenals showing any obvious disease. The term 'Waterhouse-Friderichsen syndrome' should be restricted to cases in which bilateral adrenal haemorrhage is found at necropsy: in the absence of adrenal pathology the term 'fulminant meningococcaemia' should be used.

This question is relevant in regard to the role of corticosteroid therapy in the treatment of the syndrome. It has been found that plasma 17-OHCS and cortisol production are increased in patients with severe overwhelming infections (Melby and Spink, 1958; Kenny, Hung, Voorhess, and Migeon, 1964), but these patients survived and probably did not have severe adrenal pathology. On the other hand in patients with the fulminating, fatal form of the syndrome, in which severe bilateral adrenal haemorrhage was present at necropsy, plasma 17-OHCS were not detectable (Kenny *et al.*, 1964). It may be true that adrenocortical insufficiency is not usually the cause of the shock in the Waterhouse-Friderichsen syndrome, and that there is little reason to administer steroids to patients with the syndrome, if they have increased blood corticoid levels and are able to increase these levels after administration of ACTH (Melby and Spink, 1958). At the same time, the writer sees no contraindication to attempting to raise the very low plasma corticoid levels known to exist in some of these patients. Treatment, of course, has to be decided before any laboratory results are available.

May (1960) has strongly opposed the use of steroids in the treatment of fulminant meningococcal infection. Animal experiments have demonstrated that the generalized Sanarelli-Shwartzman reaction, which normally occurs after repeated intravenous injections of endotoxin, can be elicited after only one injection of endotoxin when the animal is pretreated with cortisone. Margaretten and McAdams (1958) reported 3 fatal cases of meningococcaemia treated with steroids, with necropsy findings of renal cortical necrosis, a characteristic finding in the generalized Shwartzman reaction. Stuber and Hitzig (1961) studied 13 patients with the syndrome, all of whom died within 24 hours, with severe circulatory collapse and very low blood pressure. Necropsy showed massive haemorrhagic adrenal lesions in 12 patients. Fibrin deposits in the capillaries in the parenchymatous organs were similar to those seen in the experimental Sanarelli-Shwartzman reaction. These authors suggest administration of heparin to prevent the formation of fibrin deposits, and warn against the use of steroids.

The role of steroids in the treatment of Waterhouse-Friderichsen syndrome thus remains controversial. While the writer would not recommend the use of steroids for all patients with meningococcaemia in order to *prevent* circulatory collapse, there is inadequate evidence to warrant withholding stress doses of cortisol from patients with circulatory collapse and low blood pressure. Maintenance of normal blood pressure partly depends upon the presence of cortisol, since cortisol potentiates the effects of noradrenaline. In the absence of cortisol, responses to the adrenalines are progressively lost, while the symptoms of adrenal insufficiency are progressively exhibited (Ramey and Goldstein, 1957). We conclude that until the contrary is proven, children with Waterhouse-Friderichsen syndrome, circulatory failure, and low blood pressure, should be treated with adequate doses of noradrenaline and cortisol.

Full details of therapy of chronic adrenocortical insufficiency and acute adrenal crisis in infants and children are easily available in the paediatric literature. Excellent reviews are given by Bongiovanni (1959) and Aceto, Blizzard, and Migeon (1962). The chapters on replacement therapy and complications of steroid therapy in the recent book by Cope (1965) are recommended.

For the convenience of the reader, a short outline of treatment, as used by the author, is given in Table V.

TABLE V

Treatment of Acute Adrenocortical Insufficiency

Intravenous fluid (isotonic saline in 10% glucose, approx. 100 ml./kg. during first 24 hr., if necessary plasma)
Cortisol hemisuccinate, intravenously, 1·0-2·0 mg./kg. at once, 25-250 mg. during first 24 hr.
Adrenaline, noradrenaline, or aramine (Sharp-Dohme) for treatment of shock; vasopressor substance is diluted in 250 ml. 5% glucose, and a slow rate of i.v. drip maintained, under careful control of blood-pressure
Aldosterone (Organon), i.v., 1·0 mg. at once, if necessary repeated during first 24 hr.
DOCA, i.m., 3·0 mg. at once, 2-4 mg. per day thereafter
Antibiotics and other supportive treatment

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