FOETAL ADRENAL HYPERPLASIA

BY

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Ever since its demonstration by Telesius in 1803, there have been reports on the relationship between suprarenal tumour and changes in sex characteristics and configuration.

It was not, however, until the beginning of this century that a serious study of the subject began. As long ago as 1909, Bonin reported the cure of a pseudohermaphrodite by the removal of an adrenal tumour. Since that time attention has been devoted not only to tumour removal, but to surgical interference in conditions with adrenal hyperplasia. A further great impetus to clinical study has been the more recent work in the chemistry of the adrenal cortex. This has demonstrated the extraordinary complexity and variety of steroids which can be isolated, and it has also been possible not only to isolate, but to assay chemically a number of the excretion products of these steroids in the urine. The earlier attempts at biological assay of these excretion products, though useful at the time as a rough indicator, were at best tedious and cumbersome, and in many instances misleading, as we now know that a number of such compounds are biologically inert, and many others have a reduced or modified potency.

Unfortunately, the factor of adrenal tumour formation or adrenal cortical hyperplasia is common to a variety of clinical entities. This fact has led to many endeavours to formulate endocrine entities and syndrome complexes, many of which have the same apparent morbid anatomy, but vary considerably in the admixture of metabolic and sex changes which are seen clinically. In consequence, much confusion in terminology has arisen, and such terms as the adreno-genital syndrome have been used indiscriminately to cover a wide range of clinical entities.

This preliminary confusion was perhaps inevitable at a time when a large amount of clinical material was under preliminary investigation, and when the only common pathological feature discernable was adrenal tumour or hyperplasia. With the advance in knowledge of the chemistry of the adrenal cortex, and the opening of opportunities for more accurate and informative data regarding the nature of the steroid excretion products, it has become of urgent and vital importance to endeavour to make the

nosology of adrenal disorders more precise. Unless this can be done, and the features and, in particular, the natural history of each group can be identified with reasonable certainty, progress, not only in the further elucidation of the adrenal abnormality, but in the pharmacology and metabolism of adrenal steroids as a whole, and the assessment of the present day management and therapy of such conditions, will be indefinitely retarded.

We think that one group of conditions can be sharply differentiated from the heterogenous and complex manifestations of diseases associated with adrenal hyperplasia. This condition gives rise to adrenal hyperplasia during foetal life, and the hyperplasia and excessive cortical activity continues throughout the life span. The excessive activity is localized to the elaboration of substances which have androgenic actions, and the metabolic disturbances produced by excessive corticoid action are absent. Indeed in many cases there is a lack of corticoid secretion of sufficient severity to induce the clinical and chemical manifestation of hypocorticism.

The clinical features of this disease, which we have termed foetal adrenal hyperplasia, are manifold and varied. The presenting features vary according to the age at which the symptoms or signs become manifest. There appear, therefore, to be a number of symptom complexes which occur at different ages according to the severity of the condition, either in respect of over-secretion of androgen or under-production of corticoids by the adrenal. In addition, the virilizing effects of necessity produce differing features in men and women and, curiously, the hypocorticism is either more severe or more hazardous to the woman. The underlying hyperplasia of the adrenal is not limited to early life, and appears to continue indefinitely into adult life. The natural history is thus a long one, and we have endeavoured in the description of the following nine cases to bridge the artificial boundaries of disorders in childhood. We have tried to indicate the progress of a disease which begins in foetal life, and continues its natural course through childhood and adolescence to adult life, though each age group has its own peculiar hazard and features. Many instances of the sex changes have been described (Young, 1937), but

it was not until 1940 that the clinical picture of the hypocorticoidism in infancy was brought to general notice by Dijkhuizen and Behr (1940). A comprehensive general review of the situation was given by Wilkins (1948).

Case Reports

Case 1. This baby, E.S., was born in hospital in September, 1935. She was transferred to the Children's Department at the age of 1 month, because she failed to thrive, and vomited. The parents were healthy and unrelated. The mother's pregnancy had been normal. The labour was uncomplicated and the baby weighed 7 lb. 7 oz. at birth. From the earliest days there was difficulty in getting her to suck, and her weight fell more than $\frac{1}{2}$ lb. during the first week. At the age of 7 days vomiting started; it was not projectile, and it continued almost without interval until the child's death 12 weeks later. No treatment had any effect on the vomiting, except stopping food by mouth and giving 5% glucose in saline intravenously.

At the age of 1 month, the infant appeared wasted, and weighed 6 lb. 9 oz. She was not cyanosed or breathless. No abnormal physical signs were found, except in the genitalia. The child had been regarded as a boy. There appeared to be a cleft scrotum, not containing testes, and an extreme degree of hypospadias affecting a rather small and malformed penis.

Because of the continued vomiting, a diagnosis of pyloric stenosis was considered, but as no pyloric tumour was felt, this was discarded. It soon became apparent that the baby was subject to syncopal attacks. These occurred at intervals of from two days to a fortnight. They consisted of a sudden onset of limpness, extreme pallor and sweating; during their course the pulse rate increased from its average of 130 to 200 or more a minute, and became weak and feeble. In these attacks the infant became unconscious. The attacks lasted from periods of a few minutes to half an hour. They were not associated with feeds or any other part of the infant's routine.

Investigations showed that haemoglobin was 82%, and later 91%; the blood urea was 20 mg. %; and the Wassermann reaction was negative.

Treatment, for the most part directed towards the digestive disturbance, was unavailing. Vomiting continued, and during the baby's life of 14 weeks she never regained her birth weight.

During the last week of her life, it was decided to give her 0.1 ml. 'eucortone' solution intramuscularly, daily, in an attempt to modify the water metabolism. At that time, 'eucortone' had recently become available, and its use for this purpose was suggested. At the end of a week of such daily injections, the baby suddenly passed into one of her characteristic attacks of limpness and pallor, and in the course of this attack, died. The attack followed very closely on that day's injection of 'eucortone'.

At necropsy, the findings were for the most part those to be expected in a wasted baby. In addition there was considerable enlargement of the suprarenals, the right weighing 10.1 g., the left 8.5 g. They were greyish.

The cut surface showed the cortex thrown into the folds. Very little of the medulla was visible. The infant had a normal uterus, Fallopian tubes and ovaries, and a poorly developed vagina. Externally there was what appeared to be a glans penis, corresponding in size to that seen at about puberty. The prepuce was drawn back. The urethra opened on the under-surface of the glans. Below the 'penis' were two folds of skin, between which was a median raphe, attached to the deeper structures. The folds resembled a scrotum, but no testes were present. There was no vaginal opening.

Case 2. This baby was sent to hospital on December 31, 1941, at the age of 6 weeks, because of wasting and of vomiting attacks. Her weight at this age was 5 lb. 12 oz. During the course of the next eight weeks, before her death in hospital, she gained only a further 15½ oz. Examination when the child was first seen revealed little beyond the fact that she was severely wasted, and had a gross abnormality of the genitalia. This consisted of what appeared to be a divided scrotum with a central urethral meatus at the base of what appeared to be a penis. There was a second meatus in the glans penis, through which no urine passed. The testes were not palpable in the divided scrotum.

The baby had been in hospital for a very short time when she started to have syncopal attacks, similar in all respects to those observed six years earlier in case 1, and a diagnosis of suprarenal hypertrophy with pseudohermaphroditism was made with some assurance. The attacks of pallor, sweating, and limpness continued at intervals, until at the age of 14 weeks one proved mortal.

Treatment was directed primarily to the marasmus, but wartime conditions prevented some of the observations desired to confirm the diagnosis of suprarenal hypertrophy.

Investigations showed that haemoglobin was 78%, and the Wassermann reaction was negative. At necropsy it became apparent that the internal genitalia consisted of a normal uterus, Fallopian tubes, and ovaries. The vagina was represented by a depression about 1 in. deep, lined by keratinized skin, into which the urethra opened. The weight of the two suprarenals together was 16 g. On section, the suprarenals showed an increase in cortical tissue which was nodular in arrangement. Tissue at the neck of the bladder on section showed some resemblance to a prostate, being composed of racemose gland of columnar epithelium, well supplied with interglandular involuntary muscle.

Case 3. This child, E.C., was sent to hospital in December, 1942, at the age of 4 weeks, because of vomiting and failure to thrive. The vomiting was projectile, and an initial diagnosis of pyloric stenosis was discarded in the absence of a palpable pyloric tumour. She had been born at full term, and weighed at birth 6 lb. 2 oz. Four weeks later, in hospital, she weighed 5 lb. 6 oz.

The infant was emaciated, but not dehydrated. The appearances of the genitalia were similar to those already described in Cases 1 and 2. The urethra opened at the base of the penis-like clitoris. Two folds of skin resembled an empty scrotum.

Shortly after admission, the baby collapsed, becoming

cyanosed, limp, unconscious, and in the course of this attack sweated profusely. The attack differed from those observed in the other patients only in the substitution of cyanosis for pallor. The attacks lasted for approximately 30 minutes and occurred almost daily. After 10 days, one such attack proved mortal.

At necropsy, a gross patency of the interauricular septum was found. The suprarenals were recorded as being extremely large and atypical, but no record of their weight has survived in the notes.

The infant had a normal uterus, Fallopian tubes, and ovaries. The vagina was missing, and was represented by a dimple 0.5 cm. deep in the midline. The clitoris was enlarged, and resembled a penis of a size natural for a male of this age.

especially round the genitalia and nipples, but this was never sufficiently marked to be convincing to all observers.

Almost from the moment of her birth, she showed signs of distress. This first took the form of cyanotic attacks, coming on at intervals of less than 24 hours, and lasting up to two or three hours. During the attacks the respiration became feeble and irregular. Later, the cyanotic attacks were replaced by less frequent attacks of pallor, limpness, and sweating. These occurred at infrequent intervals from the age of 14 days until she was over 2 months old. Since then, none has been observed.

Vomiting was a troublesome and persistent symptom from the age of 3 weeks until the end of the third month, then it became much less frequent.

FIG. 1

FIG. 1a

Figs. 1 and 1a.—Photographs of B.B. (Case 4).

Case 4. This child, B.B., was born in November, 1950. She was the first baby of healthy parents. The mother's pregnancy and labour had been uncomplicated. The baby's birth weight was 8 lb. 14½ oz. An abnormality of the genitalia was observed at birth. This was similar to those described in the foregoing cases, and consisted of a large clitoris resembling a penis, with the opening of the urethra at its base. The labia majora were large and fused, and resembled an empty scrotum. The baby appeared large, and she had rather a dusky colour (Figs. 1 and 1a). Later it was thought by some that there was an increased pigmentation of the skin,

Her weight fell more than 16 oz. soon after birth, and it was not until she was 2 months old that she regained her birth weight. Thereafter there was a steady increase, apparently as a result of treatment. At the age of 3 months she weighed 10 lb., and by the time she was 5 months old her weight had increased to 12 lb.

Investigations gave R.B.C. 7,480,000 per c.mm. four days after birth, falling a week later to 7,000,000 per c.mm. The haemoglobin was 132 and 134% at those times, falling later to 106%; when she had reached the age of 6 weeks her haemoglobin was 64%.

Within a week of birth, the urinary chlorides were

2.9 g. per litre. Later their quantity rose, especially after the child had been put on additional salt by mouth. At the age of 3 weeks, she was passing 19.5 g. per litre; this appears to have been a high rating, for three days later the figure was 11.7 g. per litre; and at the age of 5 weeks it was 5.3 g. per litre. A week later this had risen to 9 g. per litre. When daily observations were made between the ages of 6 weeks and 3 months, the urinary

chlorides varied at first from 3 to 7 g. per litre, and at the end of that time they had risen to 10 g. per litre. In all this latter period the child had additional sodium chloride by mouth.

Two days after she was born, the serum chloride level was 632 mg. per 100 ml., and the serum sodium 353 mg. per 100 ml. When she was 6 weeks old, the serum chloride level was 765 mg. per 100 ml., and the serum

FIG. 2

FIG. 2a

Figs. 2 and 2a—Photographs of Case 5 at the age of 3 years.

sodium 350 mg. per 100 ml. The serum potassium level at that time was 23 mg. per 100 ml. The blood urea at the age of 6 weeks was 88 mg. per 100 ml., and blood sugar was 93 mg. per 100 ml.

An estimation of urinary 17-ketosteroids was made when the baby was 4 days old, and again at 6 days. On the first occasion, the figure, corrected for interfering chromogens, was 2.4 mg. per 100 ml. urine, and on the second specimen, 0.9 mg. No gross abnormalities were found in the skiagram of the chest and abdomen, nor in an electrocardiograph tracing.

The infant was helped through her early days of cyanotic attacks with oxygen and stimulants. For a period she was fed by tube. From the age of 2 weeks, sodium chloride, 7 g. a day, was given with the feeds in divided doses. At the age of 10 weeks, the amount of

of the child improved. She was sent from hospital when she was just over 3 months old, and was seen at the age of 4½ and again at 5½ months. Her weight had increased, and she herself was developing in most respects as a normal baby.

Case 5. J.L. was born in March, 1944, and was first seen at the age of 11 months, because the parents were in doubt about the baby's sex. She had been christened as a girl, but during the next nine or ten months, because of the changes in her genitalia, the parents were unable to be certain whether she was a girl or a boy. At this time she weighed 28½ lb. The appearance of the genitalia was such that she appeared to be a boy with a urethra opening at the base of a penis, with a web of tissue joining the penis-like clitoris to a cleft in what appeared to be a scrotum. The opinion that she was a boy was accepted

FIG. 3.—Section of adrenal gland of Case 5 showing extensive convolution and hyperplasia.

salt was reduced to 5 g., and it has been continued at that level during the first five months of the baby's life. Daily injections of 'eucortone' started when she was a fortnight old and they were given first for a week at 2 ml. and thereafter continued at 4 ml. for the next three weeks; for a further week the injections were 5 ml. daily. No material change in the child's condition was noticed during this period. When the child was 7 weeks old the 'eucortone' was stopped, and daily intramuscular injections of desoxycorticosterone acetate were started. For the first five days only 1 mg. a day was given. This was increased to 3 mg., and continued at that level for a further eight days. The dose was then increased again to 5 mg. daily. At this time the child was 2 months old, and this dosage was continued up to the age of 5½ months, when it was halved. A material improvement in the child's condition took place at the time when the desoxycorticosterone acetate was increased to 5 mg. Her weight started to increase and the general condition

quite readily by the plastic surgeon to whom she was referred, and plans were made for plastic operations when she was 5 years old. She was admitted to hospital at the age of 1 year 2 months for investigation. At that time the 17-ketosteroids were found to be 4 mg. in a 24 hour specimen. A skiagram of the skull was normal, but no other part of her skeleton was then radiographed. When she left hospital at the age of 1 year 4 months, having had measles in hospital, she weighed 32½ lb.

During the next year and a half, the child grew very rapidly. She was seen again at the age of 3. Her bodily configuration had changed, and the muscles of her legs and shoulders were relatively very well developed. Her weight was 52½ lb. and her height 45 in. She had a greasy skin with an acne-like eruption on the face and chest. Her voice was deep. Pubic hair was present, with a feminine distribution. The clitoris had still further enlarged (Figs. 2 and 2a). The 17-ketosteroids

in a 24 hour specimen of urine measured 50 mg. The plasma chlorides were 585 mg. per 100 ml.

Skiagrams revealed a skeletal age considerably in advance of her chronological age, the olecranon epiphysis

FIG. 4

was present, and the epiphyseal discs of the vertebrae were visible. An intravenous pyelogram suggested that the left kidney might be displaced slightly downwards.

In spite of the absence of palpable tumours in the loins, and the relatively normal pyelogram, it appeared

likely that the child had hypertrophy of the suprarenal cortex, and Sir James Paterson Ross undertook to explore the child's loins. The operation was carried out in March, 1947. Both suprarenal glands were found to be grossly enlarged, the right more than the left. They were a deep purplish red. The right suprarenal was removed, and measured approximately 2 in. across in each direction. It weighed 21 g. On section macroscopically there was no tumour. Microscopically, the layers of the cortex appeared to be present in the normal proportions, and the only unusual feature was an increase in the cellularity of the zona glomerulosa. The child survived the immediate effects of the operation, but died of pneumonia three days later.

At necropsy further information became available. It then became apparent that the thyroid weighed 5 g., the thymus 25 g. The liver appeared normal, as did the spleen. The left suprarenal weighed 17 g., and, on section, showed that the zona glomerulosa was more prominent because the cells appeared to be more closely packed. The cortex as a whole was thickened. The cells of the zona fasciculata and reticularis showed no histological abnormality.

Both ovaries were present, and, on section, showed round, reddish cystic areas. The Fallopian tubes and uterus were present. There was a vagina, but this had no opening in the perineum.

The kidneys looked normal to the naked eye, but on section showed small areas of calcification in the walls and lumina of the tubules.

Case 6. This child, C.R., was brought to hospital at the age of 6½ because of his precocious development. The child was born of normal parents; pregnancy was uneventful; delivery normal; he was breast fed for eight months; and there was no history of difficulty during that time. His mother had noticed that he was always bigger than babies of comparable age, and that he talked earlier than other babies of his age. For the last four years he had been subject to recurrent attacks of severe vomiting at intervals of about three months, though these attacks had declined in frequency during the last year. Apart from his excessive growth, the mother had noticed that at least a year before his visit to hospital, he had developed a considerable growth of pubic hair, and when he was admitted to another hospital eight months previously for treatment of jaundice it was noticed that he had a marked precocious genital development, and it was on this account that he was brought to hospital.

There was no family history of any abnormality; the parents were both normal, and investigation of their ketosteroids showed an excretion in the mother of 11 mg. and 20 mg. in the father. A second boy had been born to these parents two years and nine months after the patient. Again pregnancy and delivery were normal. This child was breast-fed for six weeks, and then weaned because of 'feeding' difficulties. At 12 weeks, the child was extremely ill without any firm diagnosis, and collapsed suddenly and died, and according to the report from the hospital at that time no obvious cause was found for death.

On examination the patient was 4 ft. 7 in. in height and

his weight 5 st. 5 lb. Muscular development was remarkable for his age but his mental development was in proportion to his true age. There was a profuse growth of pubic hair of the so called 'female distribution'; the penis was adult in size, the scrotum and testes were

vomiting, the child appears quite healthy and has remained so since the time of his first observation.

The skin showed no abnormality, the blood pressure was normal, the glucose tolerance was normal, there was no excessive hair growth on the body.

FIG. 5

FIG. 5a

FIGS. 5 and 5a.—Photographs of C.R.J. (Case 7) at the age of 13.

equivalent to his true age, and there was no hair growth on the perineum or on the scrotum (Fig. 4). The radiograph of his skeleton showed an epiphyseal development corresponding to the age of 13 or 14 years, and estimation of 17-ketosteroids in the urine showed an average excretion over a week of 35 mg. a day. Apart from the precocious development and the recurrent

Case 7. This patient, C.R.J., was referred for investigation at the age of 13. The child was born of normal parents, pregnancy and delivery had been uneventful, and there was no history of any difficulties in early life. The sex of the child was in doubt at birth, but later the child was thought to be a boy and had been brought up as a boy, and during his life had had multiple

FIG. 6

FIG. 6.—Skiagram showing extensive calcification of rib cartilages in C.R.J. (Case 7).

FIG. 7a.—Skiagram showing extensive calcification of rib cartilages in R.R.J. (Case 8).

FIG. 7a

FIG. 7

operations for the repair of the so-called hypospadias. During early life, skeletal growth had been rapid and until the age of 8, the child was above average in height; after the age of 8, growth in height had ceased so that the height at the age of 13 was 4 ft. 7 in. and the weight 6 st. 7 lb. Apart from the physical abnormality there had been no story of ill-health throughout the child's life. The family history showed that both parents were normal and had apparently developed normally, but a child had been born to the father's parents whose sex was impossible to determine at birth, and who collapsed and died suddenly within the first few weeks of life. The patient was the second child of his parents, and the first child is a boy who developed precocious puberty and is described as Case 8.

On physical examination (Figs. 5 and 5a) the shortness of stature was rather striking, but the muscular development was masculine and adult; there was a profuse growth of pubic hair which in the last few years had spread much more profusely over the labial area and the perineum; there was a grossly enlarged clitoris and a partial apparent hypospadias which had been in the process of repair by multiple operation; the skin was normal, axillary hair was marked with no facial hair, and no excessive hair growth on the body. Blood pressure and glucose tolerance were normal. X-ray examination of the skeleton showed that all epiphyses had united and there was extensive calcification in the rib cartilages (Fig. 6). 17-Ketosteroid output in the urine showed an average excretion of 54 mg. a day. While the patient was under observation during the course of the next year, he began to develop rhythmic abdominal pain in the hypogastrium occurring almost regularly every three to four weeks. In consequence the abdomen was explored, and this exploration showed the presence of a small, but otherwise normal, uterus with normal Fallopian tubes and immature ovaries. In the absence of any evidence of a vagina, and the history of upbringing, the uterus and ovaries were removed. The patient made an uneventful recovery after this operation. He has been under observation for four years since, and his health has remained good throughout that time.

Case 8. R. R. J., the brother of case 7, was aged 17. This patient was seen because he was worried by his short stature. Pregnancy, delivery, and infant life had apparently been uneventful, although even during the first year of life precocious genital development had been noted. By the age of 5, the growth was obviously excessive, the genital development had become even more marked, and there had been a considerable growth of pubic hair. From the ages of 6 to 8, he had grown rapidly to his present height, and by the age of 8, his genital development was adult in type. Since that time he had not grown appreciably in height; his present height is 5 ft. (Fig. 7), and his weight 8 st. 1 lb. At the age of 8, although penile development was adult, there had been no development of the scrotum or testes. Between the ages of 13 and 14, testicular development began, hair growth proceeded on the perineum and scrotum, he began to develop facial hair growth, and his voice deepened. Apart from this physical change his health had remained good.

On physical examination, apart from the shortness of stature, there was no obvious abnormality to be found. A radiograph of the skeleton showed complete fusion of all epiphyses, and his ketosteroid excretion averaged 112 mg. per day. He has remained well under observation during the last four years.

Case 9. H.C., aged 44, was referred to hospital with multiple anxiety symptoms, largely with reference to her physical abnormality. Her health had been good throughout her life, but her sex had been doubtful at birth, and she had been brought up as a girl, although her inclinations and outlook were entirely masculine. She had grown rapidly during her early life, and had reached her present height of 4 ft. 9 in. by the age of 10, since when growth in height had ceased. She had always noticed an excessive muscular development, and she had been told that she had developed precociously at an early age, but more details of her early life were not available as she was estranged from her family.

On physical examination she showed the typical changes of a pseudohermaphrodite (Figs. 8 and 8a); the radiographs of her skeleton showed complete fusion of epiphyses, and extensive calcification in the rib cartilages. The blood pressure was normal, and her ketosteroid excretion averaged 55 mg. a day. Owing to the circumstances, it proved impossible to investigate the family history completely, but one sister, three years younger, a pseudohermaphrodite, was investigated, and showed an average excretion of 45 mg. a day of ketosteroid.

Aetiology

The aetiology of this condition remains obscure. The disease has been frequently reported in siblings, but there has been little attention in the literature to the mode of inheritance, and there is little information available on extensive family histories. In Case 6 the history of a second boy, born two years after the first, suggests the possibility of hypoadrenalism as a cause of his sudden death at the age of 4½ months. In one of the families reported (Cases 7 and 8) inheritance seems definitely to be through the father, and in Case 9, there is definite evidence of a familial incidence, and it is unfortunate that in this case it has proved impossible to obtain an accurate family history. Further exploration of this factor is desirable in order not only to elucidate the mode of inheritance, but to assess the inheritance chance in affected families. It is also important to remember that the effects in boys may be relatively trivial, and once adolescence has been reached there is little to reveal the true state of affairs except a body height below average, unless detailed investigation of early development and the urinary changes are undertaken.

Natural History and Discussion

In the female the child is born a pseudohermaphrodite, while the male may show at birth unusual genital development, but more frequently the

FIG. 8

FIG. 8a

FIGS. 8 and 8a.—Photographs of H.C. (Case 9) at the age of 44.

overgrowth is not sufficient at this age to cause undue comment. In both male and female children the initial weeks or months of life are rendered hazardous by the lack of corticoid excretion. Gain in weight is slow, and their life is punctuated by episodes of recurrent syncope and frequent and intractable vomiting. This phase is not always present, and if it should either be absent or the child survive the first year, the manifestations of corticoid lack tend to recede and growth to proceed.

The patients observed by us in the early months of their life have all been of the group with Addisonian crises. Either the syncopal attacks themselves or the associated vomiting has led to their admission. Symptoms and signs in this group vary little from patient to patient. Vomiting, which is present from a few days after birth, becomes increasingly severe

during the next three weeks, so that an initial diagnosis of congenital hypertrophic pyloric stenosis is understandable. In none of our cases was the vomiting with the resulting dehydration alone sufficiently severe to lead to the patient's death. The syncopal attacks, in their fully developed form, start as a rule within three weeks of birth, although they may be preceded by less well-defined periods of distress. The attacks in themselves are so characteristic that, having once been seen, they immediately suggest the diagnosis when they are observed in another patient. In fact, an experienced ward sister can make a diagnosis of the true condition on observing an attack, even though the patient has been sent into hospital labelled with another diagnosis.

Three out of the four patients we observed died during one of these Addisonian crises. In the

fourth, they diminished in frequency after the third month of life, apparently as a result of treatment. It still remains to be shown whether, as time progresses, the attacks will recur when treatment is stopped. From the appearance of the patient and her general growth and behaviour, it seems unlikely that they will in fact return.

The observation in Case 5 that there was calcification in the walls and lumina of the renal tubules together with fatty change in some areas is in accord with the report by France and Neill (1951) in one of their cases. We have not observed this calcification in the infants who have died in the first few weeks of life. This finding is of considerable interest, as the condition must have developed together with, if not because of, prolonged sodium deficiency as a result of hypocorticism. It is possible that these observations may throw some light on the aetiology of nephrocalcinosis in infants in whom the administration of sodium citrate has often produced such striking improvement, and lends credence to the suggestion of Jaudon (1946) that hypocorticism without adrenal destruction may occur in infancy, and may not, of necessity, be the result of foetal adrenal hyperplasia. The stunting of growth in chronic nephrocalcinosis with sodium deficiency is in striking contrast to the excessive growth of the patient with adrenal hyperplasia, and presumably represents a lack of suprarenal androgen together with a failure of corticoid formation. Perhaps even more remarkable is the rapid skeletal growth with foetal adrenal hyperplasia in children who must, for long periods, be on the verge of sodium deficiency, and in whom acute sodium deficiency with hypocorticism may develop rapidly and fatally either spontaneously, or more usually precipitated by infection. This growth is presumably brought about by the remarkable economy in foodstuff which is induced by the action of the androgens. Those patients, seen later in life because of their physical abnormalities, appear from their own accounts to have had an uneventful early infancy.

From the age of 1 year skeletal growth becomes excessive, although the phase of maximum growth may not appear until the age of 4 to 5. By the age of 10, skeletal growth and bodily configuration approximate a stage of late adolescence. Radiologically, throughout these years, acceleration of epiphyseal growth and skeletal maturation are apparent, and after the age of 10 many epiphyses become united and skeletal growth ceases, so that the earlier phase of excessive growth and skeletal maturation only results in a height equivalent to normal early adolescence, growth ceasing owing to the epiphyseal closure. The adult body height seldom exceeds 5 ft. It is interesting to observe that

calcification of cartilage proceeds rapidly at the phase of epiphyseal closure, and at the age of 12 to 13 years extensive calcification in rib cartilage is equivalent to that which is seen in late adult life.

By the age of 1 year, in many instances, evidence of the development of male secondary sex characteristics arises in both male and female, though this is usually incomplete. Axillary hair, and pubic hair of so-called female distribution, develop, and muscular contours become masculine in type. Facial hair growth is not usually striking, and when present, it is sparse. The voice may deepen, although this development is irregular and may not occur even after many years of progressive virilization have elapsed. The mental development of such children is not precocious, it is normal for their age, develops normally with their age, and is strikingly disproportionate to their apparent age.

In the male the precocious development is progressive, and between the ages of 5 and 8 years penile development is adult in proportion and erection of the penis may occur frequently. Usually no sex urge is apparent, though the possibility frequently causes parental concern and alarm.

The testes do not take part in this development, and remain of normal size for the child's age; the scrotum, similarly, shows no remarkable changes in proportion.

Growth, both somatic and genital, proceeds rapidly in this manner until about the tenth year of life. Then epiphyseal closure occurs, and skeletal growth ceases, leaving a permanent stunting, but with muscular development well marked and adult in type, the costal cartilages at this time begin to undergo a remarkable and extensive calcification, so that within a few months to a year the appearances of the radiographs of the ribs resemble the changes seen in adult or late adult life. Hair growth in the scalp is normal, and hair development in the limbs is not remarkable even after many years have elapsed.

A normal puberty develops between the ages of 13 to 15, the testes develop in size, the epididymis becomes enlarged, the scrotum develops and pigments; hair growth on the scrotum begins to develop. In one instance, the hair growth in the pubis which had been present since before the age of 5, but had remained so-called 'female' in distribution, accorded, after puberty, with the so-called 'male' pattern, and the voice broke. No breast development occurred, though the nipples became pigmented. At this stage, the male is of short stature, but is otherwise indistinguishable from normal, unless the excessive calcification in ribs is observed, and the urine is examined for excess of androgen by estimation of the 17-ketosteroids.

In the female somatic development and the

changes in cartilage proceed exactly as in the male, although body height as a rule remains several inches less than the male.

The clitoris becomes progressively enlarged, and the scrotal labia more rugose. This enlargement becomes maximal between the ages of 8 to 10, and does not seem materially to alter after this time, although the perineum and scrotal labia become more pigmented, and perineal hair growth more abundant during the next few years. The enlarged clitoris is erectile, and orgasm and ejaculation may occur. The ejaculate is sparse.

No development of the breasts occurs, and even at the age of 40, although the nipples have pigmented, there is no sign of breast growth. Menstruation has not occurred in the patients we have seen, and the uterus remains infantile in size.

In none of these cases of either sex has there been any evidence of obesity. There has been no glycosuria, and in the cases observed after infancy the glucose tolerance has been normal.

The skin has not shown any atrophic change or pigmentation and no cutaneous striae have been observed. In one case, Case 5, the skin showed excessive greasiness, and an early acneiform eruption on face and shoulders developed, but no other cases have shown any skin abnormality.

Hypertension has not developed in any of the cases seen, nor has there been any evidence of arterial degeneration.

Ketosteroid Excretion

Reports on ketosteroid excretion in this condition are few, and we felt it worth while to report on these patients in some detail.

The androgen excretion as measured by the estimation of the 17-ketosteroid in the urine is always raised.

The estimation in the new born baby (Case 4) was easily measurable in the fourth day of life, and showed a total 24 hour excretion of 2.4 mg., and 0.9 mg. on the fifth day. In normal babies, by these methods, it is difficult to detect appreciable quantities of 17-ketosteroids at this age, and these figures probably represent a tenfold increase at least.

At the age of 1 year and 2 months (Case 5) there was a ketosteroid output of 4 mg. in 24 hours, and in the same case the excretion had risen to 50 mg. by the age of 3 years. During this time, skeletal growth was rapid, the body height had reached 45 in. and a gain in weight of 20 lb. had occurred.

Case 6 at the age of 6½ years showed an average excretion of 35 mg. a day of 17-ketosteroids. The ketosteroid excretion of the mother of this patient was 11 mg. a day, and of the father 20 mg. a day.

Case 7 at the age of 14 years showed an excretion of 54 mg. a day, and Case 8 at age of 17½ years showed a daily excretion of 112 mg.

Case 9 at the age of 44 years showed an excretion of 55 mg. a day, and a sister pseudohermaphrodite three years younger showed a figure of 45 mg. a day.

The excretion of 17-ketosteroids in this condition is increased at birth and continues to rise during the early months of life. It rises more steeply during the third year of life, and appears to reach its maximum within a few months or years of this age and remains at this maximum indefinitely through adolescence, early and mid-adult life.

Investigation of the nature of the compounds excreted has been undertaken, and will be reported in detail elsewhere, but it is of considerable interest that it has not been possible to identify any appreciable excretion of dehydro-isoandrosterone in the excretion products, even in the highest excretions we have found in this condition. Indeed the total β -ketosteroid is not increased in proportion to the α -ketosteroids.

Treatment

Treatment is first concerned with helping patients who have Addisonian crises in earlier infancy to survive to the calmer waters which may be reached in the second half of their first year. It would be unwise to generalize about treatment in these cases, which must be directed towards rehydration and reversal of the excessive loss of sodium in the urine. It is suggested that, in addition to sodium chloride by mouth or parenterally in quantities at least sufficient to balance the urinary output of the chlorides, desoxycorticosterone acetate may avert the worse effects of the syncopal attacks, provided it is given in sufficient quantities. In our surviving case of this type, 3 mg. of desoxycorticosterone acetate daily was not a sufficient dose, whereas the exhibition of 5 mg. daily was followed by a dramatic change in the child's condition, and an almost complete cessation of the syncopal attacks.

The dangers of substitution therapy with DOCA have been stressed (Jacobsen, Koepf, Talbot, and Wilkins, 1949). We think that it is equally dangerous to under-estimate the advantages which may accrue from its use; it may be the only means of saving the child's life. If the initial dose is not excessive, and the maintenance is arrived at by cautious trial and error with constant vigilance for early signs of systemic or pulmonary oedema, the benefits obtained far outweigh the dangers. In addition, an adequate and regular intake of carbohydrate will ensure against the possible development of hypoglycaemia which may from time to time complicate the use of DOCA in all forms of adrenal failure.

A curious feature of this phase of the disease is the gravity of its manifestations in pseudohermaphrodites as compared with male children. All the recorded instances of survival of infancy in children showing hypocorticism at this stage are boys. In one case in our series, Case 4, a pseudohermaphrodite has survived eight months with substitution therapy with DOCA, and appears to be progressing well, but we fully realize the hazards which still lie before her.

It is possible that the use of cortisone may revolutionize the treatment at this stage, as initial trials would suggest that the excessive androgenic activity of the cortex may be overcome, and more adequate replacement therapy be obtained by its administration (Wilkins, Lewis, Klein and Rosenberg, 1950),

At present the treatment after infancy is in the male, a matter of the management of precocious puberty the basis of which is intelligent cooperation and handling from the parents. In the female the chief endeavour must be to lighten the burden of a life handicapped heavily and irreparably by the physical abnormality. In most instances, the configuration and inclination to lead a male

existence should be encouraged, as these patients seem to be much happier in such circumstances.

Operative interference should not be attempted. Surgical procedures are extremely hazardous in these patients, and even if successful, achieve nothing.

Whether or not amelioration of the condition in infancy would be brought about by the suppression of corticoid activity with cortisone is still on trial, but this method seems hopeful, though a reversion of the intrauterine change in the development of the female genital tract seems improbable.

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