

tion there would be the advantage of having more information about the possible cause of the abnormality in the individual case. It is possible that with new methods of analysis of skeletal development, such as that of Acheson (1954), these diverse elements will be more adequately recognized. Owing to the small number of the endocrine assays (Table I) no attempt will be made to place responsibility for control of two of these factors, and the role of growth hormone and thyroxine can be expected to be deduced from future studies. The figures in Table I may be of interest to others and are for this reason included.

In the case of control of epiphysial closure, certain evidence is available from a study of the shape of the pelvic inlet. It was stated earlier that in 18 cases out of 25 the inlet was triangular in outline, while in the remainder it was either rounded in outline or the shape was indeterminate. This high proportion of so-called android pelvis cannot be due to an increased androgen level, since the 17-ketosteroid level is reduced. It must be concluded, therefore, that the triangular pelvic inlet is not due to any abnormal endocrine stimulus at all. It can be explained thus. The pelvic brim in both sexes is triangular before puberty, and this change persists in the normal male after puberty. In the normal female, however, the pubertal rise in oestrogens causes a change in the pelvic shape which will fit her for future childbirth. In this the pelvis can be compared to the mammary gland, in that both are indifferent to circulating androgens but respond to oestrogens.

In ovarian agenesis this triangular pelvis is almost certainly due to the low oestrogen level. It is suggested that this low level is more likely to be the cause of the marked delay in the closure of the epiphyses than the slight reduction in the androgen level.

Furthermore, such a conclusion is in harmony with the high F.S.H. values, which presumably also indicate low oestrogen levels in females.

### Summary

There is good evidence, derived from animal experiments and from clinical experience, that skeletal development is ultimately controlled by the endocrine system and that this control is multiple.

A study of the radiographs of the hands of 25 cases of ovarian agenesis, together with the films of the pelvic inlets of these cases, led to the conclusion that there are three components in bone growth—namely, (1) assumption of final dimensions, (2) assumption of final shape, and (3) epiphysial closure—and that these three elements are under separate endocrine control. These conclusions were arrived at by estimating both the bone age and the length of the hand skeleton in each case and plotting the results against the normal range for each measurement.

As a result of a study of the pelvic films and of certain endocrine assays which were available, it was also concluded that, in the female, epiphysial closure is controlled by oestrogens.

A new measurement is presented—namely, skeletal hand length, which is referred to simply as hand length throughout this paper. Tables are included which give statistical details for both sexes covering a large number of age-groups.

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## PROBLEMS AND MANAGEMENT OF HERMAPHRODITISM

BY

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The sense of being a complete male or female is happily taken for granted by the vast majority of human beings. To the unfortunate few who are aware that they properly belong to neither sex the problem of intersex is the cause of a great deal of distress and embarrassment, and until recently it has been the cause of considerable confusion in the mind of the medical adviser.

Two main factors appear to enter into the mechanism of the differentiation of sex: firstly, there is the genetic factor which determines the sex of the embryo and of its gonads; and, secondly, there is the influence of the sex hormones produced by these gonads. Harrison (quoted by Gillies and Millard, 1957) says:

"One of the remarkable facts about the development of the reproductive organs, both internal (the gonads) and external (the genitalia), is that young embryos possess organs which at first give no evidence as to whether they will become those of a male or of a female. Thus there can be considered to be a 'neuter' or 'indifferent' stage of the embryo's early development, during which the external genitalia of embryos, destined to be either male or female, look alike. It is as if the forces which will eventually bring about the 'maleness' or 'femaleness' of the embryo

have not yet exerted their influence on the genital organs.

"In this indifferent stage of sexual development the hindgut and the future ducts of the uro-genital system reach the surface of the embryo together at an area known as the *cloacal membrane*. This thin membrane is at first imperforate and is situated on the ventral aspect of the embryo between the area of attachment of the umbilical cord and the degenerating tail. When the embryo is about 6 weeks old . . . the cloacal membrane becomes divided by a septum (uro-rectal), developing from inside the embryo, into a posterior area, the *anal membrane*, through which the gut will open to the exterior, and an anterior area, the *uro-genital membrane*. Around this latter membrane three small protuberances appear. The anterior one, nearest the umbilical cord, is called the *genital tubercle*; the other two flank the uro-genital membrane on each side and are called the *genital swellings*."

Up to this stage in the development of the foetus there has been no sex differentiation. Between the eighth and tenth weeks of intrauterine life changes occur which result in the differentiation of the genital organs into male and female forms, and it seems likely that these changes are brought about by sex hormones. Jost (1957) has shown that male differentiation of the penis, urethra, and scrotum is induced by foetal testicular androgens, and that the effect is quantitative. It is also well known that, in the experimental animal, castration of the early embryo causes it to develop into an anatomical female irrespective of its primary genetic and gonadal sex. Occasionally, and possibly owing to relative hormonal deficiencies, the process of development starting at the eighth to the tenth week is incomplete or else it fails to proceed clearly along one or other path, leading to the condition known as pseudohermaphroditism. Alternatively, and more rarely, the presence of both testicular and ovarian tissue in one foetus results in abnormalities of development at this stage—the condition of true hermaphroditism.

In the normal foetus the further development of the genitals is succinctly described by Harrison (loc. cit.).

"In those embryos destined to become *females* the genital tubercle remains small and becomes the clitoris, the urethra opening through the uro-genital membrane at the base of the clitoris. The uterus and upper part of the vagina develop within the embryo from paired genital ducts (the paramesonephric or Müllerian ducts) and descend to reach the exterior between the urethra and the anal canal. The opening of the vagina to the exterior is at first closed by a membrane, the method of development of which has been the subject of controversy. This membrane partially breaks down and its remnants are known as the hymen. The two genital swellings enlarge and become the labia majora, on either side of the vaginal opening. Medial to them two further folds appear, which also flank the uro-genital opening. They are called the urethral folds and they become the labia minora.

"In those embryos destined to become *males* the genital tubercle elongates and enlarges to become the phallus. The urethral folds fuse together over a groove which appears on the undersurface of the phallus. Thus the opening of the urethra is carried

towards the under aspect of the end of the phallus. Later the end of the phallus enlarges and becomes the glans penis, and the urethral opening is carried to its tip by canalization through the centre of the glans. The genital swellings enlarge, pass towards each other below the penis and fuse to form the scrotum. Just before, or at the time of, birth the testes descend from the abdominal cavity, pass through the inguinal canal and enter the scrotum on each side."

True hermaphrodites are rare and only about 80 cases have been reported in the literature. Three cases, illustrating the three types of the condition, have been reported from Central Africa recently (Hammar and Forbes, 1962). Pseudohermaphroditism is much more common, and there seems to be no marked difference in incidence between the male and the female types. Winkel Smith (1960) reported 31 cases of hermaphroditism investigated in Copenhagen during a period of 11 years: 14 were found to be female and 17 male pseudohermaphrodites, and there were no true hermaphrodites.

Four cases of intersex—a true hermaphrodite, a female pseudohermaphrodite, and two male pseudohermaphrodites of different types—are reported here.

### Case 1

A child was noticed by his mother to have abnormal genitalia at birth. The mother had received no hormone therapy during her pregnancy, and two elder siblings, one boy and one girl, had been perfectly normal. The parents were not sure to which sex the child belonged, but as it grew older they noticed that it behaved more like a boy than a girl and preferred to play with boys, so they decided to regard it as a male.

At the age of 2 years the child was taken to hospital, where the first stage of a hypospadias repair was performed. Further stages were deferred until the child was older.

On March 10, 1961, the patient, aged 7, was admitted for investigation. Clinical examination showed a slight, rather timid child with boyish facial appearance and general body configuration (Fig. 1). Systemic examination was normal except for a firm enlargement of the liver to one fingerbreadth below the right costal margin.

The appearance of the genitalia is shown in Fig. 2. The phallus was approximately 2 in. (5 cm.) in length with a normal-looking glans and prepuce but with no urethral meatus, this being in the perineum about 1 in. (2.5 cm.) posterior to the base of the phallus and flanked on each side by "labio-scrotal" folds. No testes were palpable either in these folds or in the inguinal regions. There was no vaginal opening, but between the urethral opening and the anus was a softish area of perineum. On rectal examination an indefinite thickening was palpable behind the bladder.

A urethrogram was performed and the bladder was outlined. No other organ could be demon-

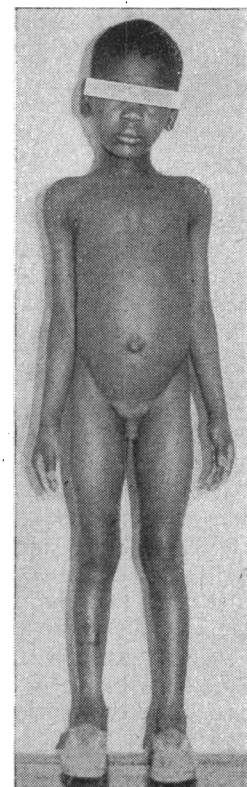


FIG. 1.—Case 1. General body configuration.



strated in communication with the urethra. Excretion of 17-ketosteroids in a 24-hour specimen of urine was found to be normal (less than 1 mg.). Studies of both leucocytes



FIG. 2.—Case 1. Appearance of genitalia.

and buccal mucosal cells gave a positive result for the presence of the sex chromatin body—that is, nuclear sex female (Fig. 3).

On March 23 a lower midline laparotomy was performed (B. H.). A small rudimentary uterus was found with a long

fibrous cervix leading to a broader patent vagina which ended blindly just beneath the perineal skin, accounting for the softish area palpable from without. Bilateral tubes and gonads were present. The left gonad was obviously an ovary, while the right gonad was in two portions—a firm whitish lateral part approximately  $\frac{1}{2}$  in. (1.3 cm.) in length with the macroscopic appearance of

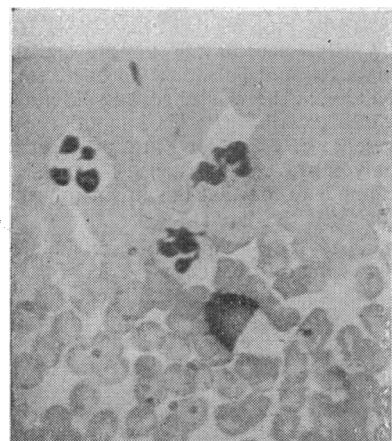


FIG. 3.—Case 1. Photomicrograph of blood smear showing a clubbed poly-morphonuclear leucocyte in centre of field.

ovary, and a softer pinkish medial part about  $\frac{1}{2}$  in. (0.8 cm.) in length appearing more like a testis (Fig. 4).

The left gonad and tube, the uterus, and the vagina were all removed. Biopsies were taken from both portions of the right gonad, which was then mobilized and brought into the right inguinal canal as far as the external ring, where it was anchored. A congenital hernia was found to be present, so the neck of the sac was ligated and the sac partly excised.

Histological examination confirmed that the left gonad was an ovary and that the right gonad consisted of ovarian tissue (laterally) and immature testicular tissue (medially).

### Management

The patient's sex orientation and his predominantly male somatic sex clearly indicated that the sex designated by his parents should be maintained. The fact that his nuclear sex was female was not of great importance in this respect, and the discovery of a rudimentary uterus was not significant, as it could never be a functional organ.

At operation the obviously ovarian left gonad was removed, but it was considered that histological confirmation should be obtained before removing the apparently ovarian portion of the right gonad. Attention has been drawn to the increased incidence of malignancy in intra-abdominal testes, and in male pseudohermaphrodites Morris (1953) has

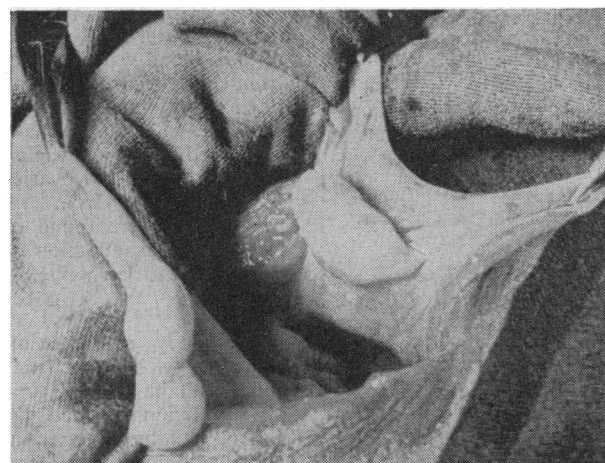


FIG. 4.—Case 1. Laparotomy findings, showing a left ovary and a right ovotestis in two distinct parts.

reported this to be as high as 10%. In view of this, and because it was technically possible, the right gonad was mobilized, brought down, and anchored in the right inguinal canal. Following histological confirmation of the macroscopic appearance, the ovarian portion was excised at a subsequent operation. The correction of the ventral curvature (chordee) was done in 1956. The patient will be returning for the next stage in the repair—the urethroplasty—in due course.

### Case 2

A 12-year-old African "boy" was admitted to hospital on May 17, 1960, with the complaint that his breasts had been enlarging for the past two years. This made him so self-conscious and unhappy that he stopped playing with other boys and at one time wanted to commit suicide. It had been noticed at birth that his penis was rather short and that he did not have testes or a scrotum, but these abnormalities had not worried his parents unduly. His elder brother, a younger brother, and two younger sisters were normal. He gave no history of urethral bleeding.

Clinical examination revealed a very self-conscious child with a rather feminine face, a female body contour, and well-developed breasts (Fig. 5). Axillary and pubic hair was present but scanty. The external genitalia were predominantly female (Fig. 6) with a large clitoris and two pairs of lateral folds corresponding with labia majora and minora. The urethral opening was posterior to the base of the clitoris. No vaginal opening was present, but there was a dimple in the perineal skin posterior to the urethral opening. No testes were palpable in the genital or inguinal regions.

Injection of dye into the urethral opening demonstrated the presence of a urogenital sinus which communicated both with the bladder and with an apparently normal vagina and uterus (Fig. 7). Excretion of ketosteroids (5 mg./24 hours) and of 17-hydrocorticoids (4 mg./24 hours) was normal, while urinary estimation of follicle-stimulating hormone showed no activity at 6 mouse units. Examination of



polymorphs and of squamous cells from the buccal mucosa for the presence of the female sex chromatin body was negative—that is, nuclear sex male.

Sex orientation: the parents had brought the child up as a boy but were agreeable to treatment and surgical procedures to make him into a proper member of whichever sex seemed indicated. The child regarded himself as a boy and agreed to any procedure which would make him a more complete male, but he absolutely refused to be made into a

female no matter what might be found at laparotomy.

Before operation on June 9 (B. H.) an examination under anaesthesia was carried out, and a small amount of dark blood was expressed from the urogenital opening. Laparotomy revealed the presence of normally developed uterus, vagina, fallopian tubes, and ovaries. Biopsies taken from the two gonads were found on histological examination to consist of ovarian tissue.

#### Management

The body configuration, secondary sex characteristics, and genitalia were completely feminine, but the patient had been reared as a boy and his sex orientation was definitely masculine. When, at laparotomy, normal female organs including ovaries were found, it became obvious that he could very easily be made into an anatomically normal female. Furthermore, it seemed that if this were done he should be able in due course to lead a normal marital life and would

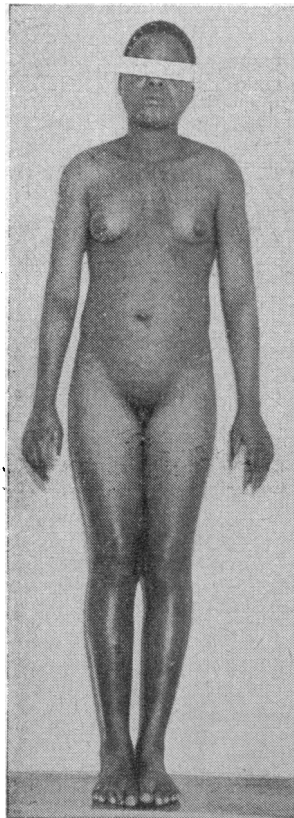


FIG. 5.—Case 2. General body configuration.

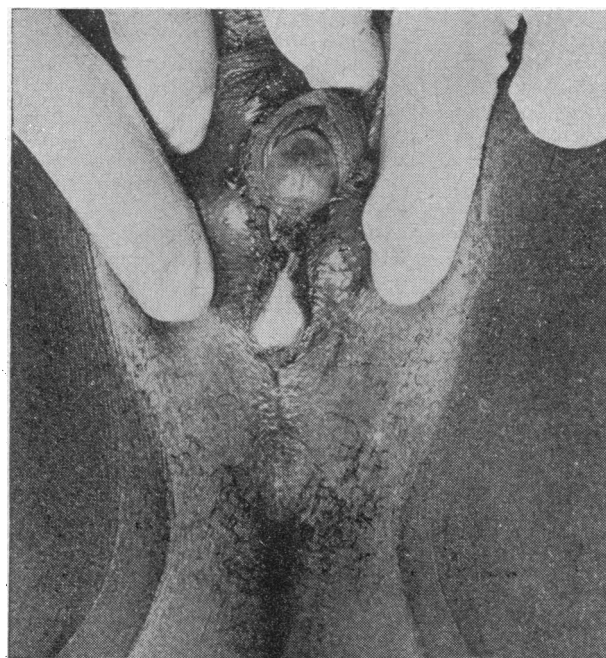


FIG. 6.—Case 2. Appearance of genitalia.

possibly even be fertile. Cases of successful pregnancy in female pseudohermaphrodites have been reported recently (Stuart Mason, 1961; Swyer and Bonham, 1961), but, unlike the present subject, their patients were adrenal pseudohermaphrodites.

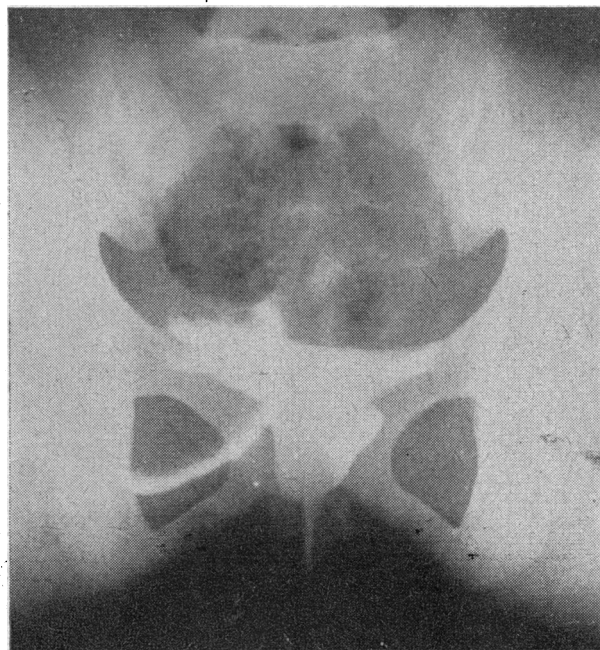


FIG. 7.—Case 2. X-ray of pelvis with radio-opaque dye injected into urethral opening, showing bladder and an apparently normal uterus.

Our patient, however, had expressly refused to become female. Compliance with his wishes would have meant removal of completely normal ovaries, tubes, uterus, and vagina, and as we could not confidently do this at the time, the abdomen was closed after biopsies had been taken. The position was carefully explained to the patient and his parents, and it was suggested that he should go home for a period of three months to see if he would feel any differently by the end of that time, knowing that his internal organs were female. The presence of dark blood in the urogenital sinus before laparotomy suggested that menstruation might be about to commence and we felt that this might influence his attitude towards his sex.

We now consider this to have been a mistake and feel that the patient's wish should have been carried out, to make him a male, albeit an artificial one. The definitely inferior status of the female in African social life is of significance in this respect. The patient did not return at the end of three months as requested, so we are attempting to contact him, and we propose to offer to remove the unwanted female organs and to attempt to masculinize his external genitalia. Androgenic therapy will obviously be necessary.

#### Case 3

Martin was born in Umtali in about 1940, and was the only child of his mother but had two stepbrothers and one stepsister, all of whom were normal. The abnormality of the genitalia was noticed at birth by the parents, but they thought that the child was probably a girl and called her Marion. At the age of about 1 year they sought medical advice but were told to wait until the child was 12 years of age. Marion was dressed and brought up as a girl and played with girls, but always felt that she was different and longed to take part in boys' activities. At school she reluctantly did domestic science and sewing but drew the line at knitting and was allowed by an understanding teacher to read during the knitting class. She excelled at sport, being the best sprinter and high jumper among the girls and



the best netball player. She greatly enjoyed netball, but often longed to play football with the boys. From about the age of 12 she began to experience libido and to have occasional erections when in the company of girls. From the age of about 15 there was slight growth of hair on her upper lip. She had always known of a lump in each groin and she suspected that these lumps might be testes. She did well at her schoolwork and was always near the top of the class. At the age of 17 she passed standard six, being third in a class of 56. She then left school and became an unpaid social worker.

In February, 1960, she came to Harari Hospital, where clinical examination showed a young adult female with male characteristics and a rather gruff voice. The patient's build was slim and muscular, more masculine than feminine, and small but definite breasts were present. There were a few hairs on the chin, and the pubic hair was of male distribution. The scrotum was well formed, and the right testis was palpable in the neck of the scrotal sac. The left testis was incompletely descended but palpable in the inguinal canal, and there was an associated inguinal hernia. The penis was small but well formed (Fig. 8). The urethra opened at the base of the penis and there was no narrowing of its meatus, which easily admitted a No. 18 Jacques catheter. There was a well-marked curvature of the ventral surface of the penis (chordee) caused by failure of development of this surface.

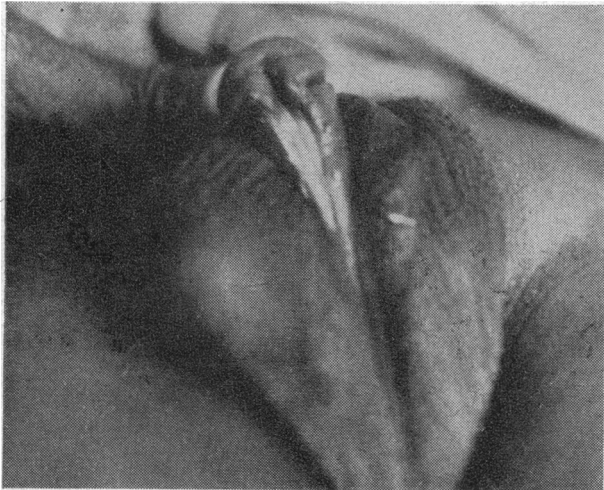


FIG. 8.—Case 3. Appearance of genitalia.

Marion was admitted to the female ward. The presence of a fully descended testis excluded the possibility of female pseudohermaphroditism and it seemed likely that the patient was a male pseudohermaphrodite or possibly a true hermaphrodite. Examination of blood polymorphs and oral squamous cells showed complete absence of the sex chromatin nodule (nuclear sex male). 17-Ketosteroid excretion was found to be 6 mg. in 24 hours.

On March 14 bilateral herniorrhaphy was performed and biopsies were taken from the gonads, which had the macroscopic appearance of testes. Arising from the upper pole of each was a fleshy mass, and each of these was amputated and submitted for histology. The left gonad was brought down into the scrotum and ligated to the left thigh. The two biopsy specimens were found histologically to be portions of cryptorchid testicle with sclerotic seminiferous tubules and hyperplastic interstitial cells. The fleshy masses removed from the upper poles of the testes were found to consist of rather large cavernous epithelium-lined spaces and were thought to be rete testes.

#### Management

Marion had been brought up as a girl for the first 20 years of life, but it was clear that physically she was predominantly masculine and that mentally and emotionally she had

rebelled against her sex of rearing and was orientated towards being a male. The absence of sex chromatin from her cells, the predominantly male genitalia and secondary sex characteristics, the histological confirmation that both gonads were testes, and above all the patient's own inclination indicated that treatment should be directed towards making her into as complete a male as possible.

The first operation was that of breast reduction. Through a small incision below each gland the necessary amount of breast tissue was removed. Histologically it was found to consist of dense fibrous tissue with scattered ducts but no breast acini.

Two weeks later the first stage in the correction of the hypospadias was carried out (G. E. C.). In order to correct the ventral curvature all the tissues which prevented adequate straightening were divided and freed, and the urethra was mobilized and pushed back towards the base of the penis, allowing it to straighten easily. The resultant raw area on the ventral surface was closed by means of a small Z plastic. The ventral surface had adequate skin cover, and sufficient covering was provided for the subsequent epithelial inlay.

At this stage it was felt that the patient could no longer stay in the female ward, and it was decided to make the change suddenly and with as little upset as possible. Accordingly, Marion left the female ward, and was admitted as Martin to a side-room in the male ward. There was a certain amount of psychological disturbance, manifested chiefly in insomnia and depression. During his attacks of depression he was helped considerably by reassurance and explanation that he would, with further operations, become increasingly masculine.

After about three weeks he was sent home to await the next stage. When he returned the change in his appearance and in his mental outlook was remarkable. He arrived smartly dressed in flannels and a sports coat with a camera hanging from his shoulder. He had decided to become a social welfare officer.

In June a urethroplasty was carried out, using McIndoe's method, an adaptation of the Nové-Josserard operation. This was completed with a No. 18 Jacques catheter inserted in the epithelial inlay and, as is usual, this was left in place for six months.

The last stage of the repair, the anastomosis of the epithelial inlay with the urethra, was carried out in March, 1961. Function of the urethra was satisfactory and it easily admitted a No. 18 cystoscope. The ability to pass urine through the penis has been of tremendous psychological value to the patient and has helped considerably in assuring him of his masculinity.

#### Case 4

This patient, aged 28, was admitted to hospital on June 8, 1961, for bilateral herniorrhaphy. (Most of the significant data concerning this case were obtained after operation.) She had become aware of a swelling in the left groin one year previously, and a week later a similar swelling had appeared in the right groin. She was one of a family of four; her twin brother was married, was in good health, and had one son; her two younger sisters were both well and unmarried. None of these siblings had ever had a hernia.

She said her menarche had taken place at the age of 10 years and her menstrual cycle had been regular and of a 6/30-day type. She said she had two children of her own. The first, a girl, was born in 1955 after labour lasting four days. Lactation became established two days after delivery, and she breast-fed the baby for six months, after which she became pregnant again. Her second baby, a boy, was born in 1956 after labour lasting 12 hours. After the birth of the second child she never had another menstrual period, but during the year before admission she noticed that the swellings in her groins increased in size and became

painful for six days in each month. There was no significant past medical history, and she never had a surgical operation. Her husband had been married previously and there were two children, both girls, from that marriage. His first wife had died during her third pregnancy. The patient had not previously been married.

Attempts to interview the husband were frustrated, it seemed deliberately, by the patient. However, we were able to interview her father, who said she had been married three times and that she had had one child by each of the first two husbands and none by the third. He had been in Nyasaland when these two children were born and had no personal knowledge of their births.

Clinical examination revealed a normal-looking female with rather pendulous breasts and with scanty axillary and pubic hair. The external genitalia were of normal female type and a vagina was present, but no cervix was palpable on vaginal examination.

Examination of buccal mucosal cells showed no sex chromatin bodies at all, and blood smears showed only three doubtful structures in 1,500 polymorphs (nuclear sex male).

Bilateral herniorrhaphy was performed on June 12 and each hernial sac was found to contain a gonad with the macroscopic appearance of a testis with an epididymis attached (Fig. 9). A lower midline laparotomy revealed that the vasa deferentia passed from the gonads to enter the pelvis through the internal ring on each side and ran medially towards the base of the bladder, where they merged with a thickened transverse peritoneal fold. No uterus, fallopian tubes, or ovaries were present. Both gonads were excised, and histological examination showed them to consist of cryptorchid testicular tissue with exceptionally prominent interstitial cells, there being in one of the testes a small adenoma of interstitial cells.

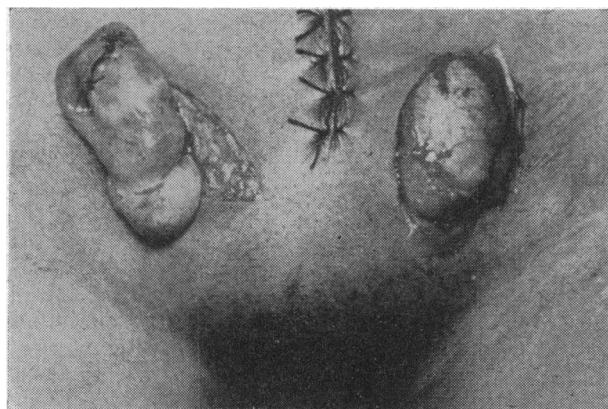


FIG. 9.—Case 4. Oestrogen-producing testes found in inguinal canals when bilateral herniorrhaphy was performed.

#### Management

This was clearly a case of male pseudohermaphroditism with oestrogen-producing testes, presenting in the classical way, and as the patient was not prepubertal it was obvious that the testes should be removed. The patient was not told anything about the operative findings or procedure except that her hernia had been repaired, and care was taken to avoid showing any doubt about the veracity of her obstetrical history. Fertility is of great importance among the more primitive Africans, and a wife is unsatisfactory if she cannot produce children. According to tribal law, under which the great majority of Africans are married, a husband can obtain a divorce from a barren wife simply by taking her back to her father, who may either return the lobola (marriage payment) to the dissatisfied husband or offer another of his daughters as a substitute. In this case the wife had in some way contrived to obtain two children and was bringing them up as her own, with or without her

husband's knowledge as to their origins. We considered that it was in the interests of the patient, her marriage, and the children to draw as little attention as possible to the abnormalities we found.

#### Discussion

The condition of hermaphroditism can be classified simply as follows:

##### A. True hermaphrodites.

B. Pseudohermaphrodites. 1. Female: (a) congenital adrenal hyperplasia; (b) non-adrenal; (c) maternal endocrine disturbance. 2. Male: (a) male-type external genitalia; (b) female-type external genitalia.

#### The True Hermaphrodite

In the true hermaphrodite both ovarian and testicular tissue are present in the same individual. Three types have been described according to the sites of the gonadal tissue: (1) bilateral, with an ovary and a testis on both sides or with bilateral ovotestes; (2) unilateral, with testis and ovary (separate or united) on one side and either an ovary or a testis on the other—Case 1 was an example of this type; and (3) lateral, with a testis on one side and an ovary on the other.

The anatomical variations are multiple, but as a rule the external genitalia and secondary sex characteristics show a mixture of male and female features. In the majority of cases a uterus and tubes are present. It has been suggested that regression of the Müllerian ducts, which normally occurs in the male, may be brought about by foetal testicular androgen. The persistence of Müllerian-duct derivatives may therefore be due to inadequacy of this hormone in the true hermaphrodite.

Considerable interest has been aroused recently in the possibility that true hermaphroditism may be associated with an abnormal complement of sex chromosomes, especially since it has been shown that deviations from the normal chromosome number (46) may occur in some cases of Klinefelter's syndrome (chromatin-positive cases having 47 chromosomes—the XXY pattern) and in some cases of Turner's syndrome (chromatin-negative cases having only 45 chromosomes—the XO pattern). However, in those cases of true hermaphroditism in which a chromosomal analysis has so far been carried out the complement has been found to be normal.

#### The Female Pseudohermaphrodite

Female pseudohermaphroditism is usually due to the adrenogenital syndrome, being caused *in utero* by an excess of male sex hormone produced by bilaterally hypertrophied adrenal cortices. It has been suggested that there may be a deficiency of the enzyme concerned with the conversion of cholesterol to cortisone, and that androgens are produced instead (Jailer, 1953; Mason and Morris, 1953). Of the 14 cases of female pseudohermaphroditism reported by Winkel Smith (1960), 13 suffered from the adrenogenital syndrome.

These patients may present in either of two ways. The genital abnormality may be noticed at birth, when they appear to be females but have a large phallus and usually some degree of fusion of the labio-scrotal folds. The urethra is in the female position (perineal hypospadias) and a uterus and vagina are present, usually opening into the posterior urethra. Alternatively, the



baby may fail to thrive and may present with repeated attacks of vomiting and collapse with severe hypotension. These episodes are in fact Addisonian crises, and early diagnosis is therefore of great importance.

Once the diagnosis is considered it is not difficult to confirm, because the urinary 17-ketosteroid excretion is always high. In Winkel Smith's cases it varied between 5 and 12 mg./24 hours (normal less than 1 mg./24 hours in children below the age of 2 years). A high family incidence has been noted in cases with the adrenogenital syndrome.

More rarely, female pseudohermaphroditism may occur apart from the adrenogenital syndrome. Wilkins (1957) has pointed out that androgen therapy given to the mother during pregnancy may account for some of these cases, and an arrhenoblastoma may act in the same way. In others, such as our Case 2, no such cause can be found. The non-adrenal female pseudohermaphrodite is the rarest type of intersex, and Wilkins *et al.* (1955) were able to find only 15 such cases in a review of a total of 394 cases of intersex; of this total, 188 were cases due to adrenal hyperplasia. Two of these were reported in infants by Papadatos and Klein (1954).

Our Case 2 is of particular interest because nuclear sexing showed a chromatin-negative pattern, indicating that genetically the child was male. So far as we are aware, this has not previously been described and the combination of male genetic sex and bilateral ovaries is difficult to explain. It appears to be generally accepted that the finding of a male skin pattern excludes female pseudohermaphroditism, and vice versa (Hoffenberg and Jackson, 1956). In this case a chromosomal analysis would be most interesting, and it is hoped to arrange this as well as an independent repeat of nuclear sexing if the patient can be traced.

#### The Male Pseudohermaphrodite

Male pseudohermaphrodites have testes, either descended or abdominal, and they show varying degrees of feminization of the external genitalia and persistence of Müllerian ducts. They may be broadly divided into those having a predominantly female appearance and those having a predominantly male appearance. The first group includes the syndrome of "oestrogen-producing testes," as illustrated by our Case 4. These patients appear to be normal girls and the condition is diagnosed only when the patient presents with primary amenorrhoea. There is female body configuration with good breast development and a normal vagina, but axillary hair is absent, pubic hair is either absent or very scanty, and there is no uterus. The sex chromatin pattern is male. Occasionally the condition is diagnosed before puberty, when the "girl" presents with a hernia and the surgeon finds a testis in the hernial sac at operation. (The frequent occurrence of congenital inguinal hernia in hermaphrodites has been pointed out by a number of writers and was present in three of our four cases.) As a general rule these patients should continue to live as females. They have good libido, so normal marital relations are possible (Jackson, 1959). It is probably wise to remove intra-abdominal gonads because of the danger of malignant change and to remove inguinal gonads because of the discomfort they produce, but the removal should be deferred until puberty has been passed. Rathbun, Plunkett, and Barr (1958) point out a definite familial incidence in this type

of male pseudohermaphroditism. As these cases are all chromatin-negative, nuclear sexing will help to distinguish male pseudohermaphrodites with moderate feminization from female pseudohermaphrodites.

The group of male pseudohermaphrodites with predominantly male appearance may present a management problem at puberty when marked virilism occurs in a child who has been reared as a girl. Case 3 was an example of this type of case. The general consensus of opinion seems to be that most of these patients should remain in their sex of upbringing, and that the gonads should be removed and any necessary plastic procedures undertaken. This is because, whatever the type of intersexuality, it is exceptional for an individual later to desire to be of the sex opposite to that in which he has been reared. As a rule the psyche develops in accordance with the assigned sex and the sex of rearing, rather than the structure of the internal or external genitals or the gonadal or chromosomal sex (Hoffenberg and Jackson, 1956). Case 3 was an exception to this rule.

#### Careful Appraisal

The investigation of a case of intersex must include an appraisal of all the factors concerned in the patient's sexual structure. (1) The somatic sex must be judged by the general body configuration and secondary sex characteristics, by the appearance of the external genitalia, and by the evidence of internal genital organs as revealed by clinical and radiological examination. (2) A psychological appraisal is of great importance to determine the patient's own sex orientation, which may not correspond with his sex of rearing. (3) The genetic sex is determined by examination of mucosal cells and leucocytes for the presence of sex chromatin body, and where possible by a chromosome analysis. (4) Hormone studies are positively diagnostic of female pseudohermaphrodites with the adrenogenital syndrome, as only in this condition is 17-ketosteroid excretion increased. (5) With the exception of cases with the adrenogenital syndrome, laparotomy and gonadal biopsy should be performed.

Only when all aspects of the case have been carefully considered can a decision be reached on the correct method of management. In most patients the gender in which the child is reared is the predominant factor in determining future sex orientation, and, according to Wilkins (1957), change of sex after the age of 18 months to 2 years should rarely, if ever, be considered. This view seems to be borne out in our Case 2, the patient who had female anatomy but had been reared as a male. We are now of the opinion that our advice that he consider becoming a female was unwise. There can, however, be no absolute rules. In Case 3 the patient had undoubtedly undergone a psychological change in sex orientation many years before presenting for medical advice as a result of a progressive build-up of genetic, gonadal, somatic, and hormonal factors which made continued life as a female wellnigh intolerable. Armstrong (1955) describes a similar case in a 13-year-old child brought up as a girl and then converted into a male.

Treatment of hermaphroditism may include the removal of unwanted gonads, the administration of hormones, and the carrying out of plastic procedures. The indications for removal of gonads are usually clear. Ovotestes may be made up of macroscopically distinct though contiguous portions as in our Case 1. Some-

times the ovarian and testicular tissues may merge, making removal of the unwanted part more difficult.

There are several indications for hormone therapy. Androgens may be necessary for their virilizing effects; oestrogen may be of great psychological value in producing artificial menstrual periods and in promoting breast development; in the adrenal type of female pseudohermaphroditism corticosteroid administration suppresses excessive androgen production by the adrenal glands, and when started soon after birth it enables these girls to develop into normal women, to menstruate, and to give birth to children. Swyer and Bonham (1961) reported a successful pregnancy in a patient of this type in whom cortisone therapy was not started until the age of 24 years.

In most cases of hermaphroditism reconstructive surgery is necessary, and in no part of plastic surgery is the need for adequate function more compelling than in that of the sex organs. As in any multiple-stage reconstruction, the whole procedure must be carefully planned in advance, because each stage lays the foundation for the next. As illustrated by Case 3, this is particularly true in the choice of method for correcting the ventral curvature of the penis (chordee), and it must be ensured that the method chosen will be adaptable to the subsequent type of urethroplasty.

### Summary

Four cases of intersex—a true hermaphrodite, a female pseudohermaphrodite, and two male pseudohermaphrodites of different types—are reported and the main features of these conditions described. True hermaphrodites are rare, and only about 80 cases have been reported in the literature. The great majority of cases of female pseudohermaphroditism are of the adrenogenital type. The non-adrenal female pseudohermaphrodite is the rarest type of intersex. Case 2, an example of this group, is of particular interest on account of a chromatin-negative nuclear sex pattern—a finding which is usually taken to exclude female pseudohermaphroditism. Male pseudohermaphrodites may be broadly divided into those having a predominantly female appearance (including the syndrome of "oestrogen-producing testes") and those having a predominantly male appearance.

The investigation of a case of intersex entails the appraisal of all the factors concerned in the patient's sexual structure, including the somatic sex, the genetic sex, and especially the patient's own sex orientation. Hormone studies are positively diagnostic of female pseudohermaphroditism of the adrenogenital type, and, except in this group, laparotomy and gonadal biopsy should be performed. Such investigations should be carried out as early in life as possible so that a definite decision on the sex of rearing may be made. In older patients the two most important considerations are the patient's own sex orientation and the sex of upbringing. As these are nearly always in accordance, a change of sex after the first two years of life should rarely be considered. In exceptional cases, however, the patient's sex orientation may change, and it may then be that the psychological upheaval of sex reversal is to be preferred to the unhappy state of continued rebellion against the sex of rearing.

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## INFANTILISM TO FATHERHOOD IN THE MALABSORPTION SYNDROME

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The literature on the malabsorption syndrome is voluminous, and has naturally been concerned with the aetiology, the pathology, and the treatment with gluten-free diet, which indeed was a major discovery in the treatment of what at one time was a condition with a bleak prognosis. The introduction of the gluten-free diet (Dicke, Weijers, and van de Kamer, 1953) not only corrected the steatorrhoea in cases of coeliac disease but has ensured that children with this disease grow at an optimal rate (Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952; Sheldon and Lawson, 1952). Gerrard, Ross, Astley, French, and Smellie (1955) found in a series of 32 children and adolescents who had not been treated with a gluten-free diet that steatorrhoea, stunted growth, and anaemia were the commonest residual clinical findings.

Little has been written, however, on the long-term follow-up of these cases. One study of value is that of Gerrard, Ross, and Smellie (1955), who reported an account of the late treatment of older children and adolescents in response to a diet free from wheat gluten. In particular they described the effect of this treatment on the growth and development of 18 children and adolescents who had been diagnosed as having coeliac disease 3 to 14 years previously. However, their follow-up of the benefits of this diet on growth covered a period of only 4 to 25 months; the results were striking. Sheldon (1955) found that there was an initial spurt of growth during the first six months on a gluten-free diet, and that some children with coeliac disease continued to grow satisfactorily when gluten was reintroduced in the diet. His follow-up unfortunately ceased at 12 years. Lindsay, Nordin, and Norman (1956) reassessed 25 young adults who had coeliac disease in childhood, 15 years after their initial assessment by Hardwick (1939). They found that these