THE PROBLEM OF INTERSEX

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Intersex is not uncommon. Young [24] stated that about one child in every thousand exhibited ambisexual genital configuration. The vast majority of these are pseudo-hermaphrodites. In recent years many advances have been made in the understanding of the problem of intersex, with improvements in diagnostic techniques and in methods of management. In every case the exact reasons for assignment to one or other sex can now be accurately assessed and, indeed, must be so assessed. Vacillation of parents or doctor regarding the sex in which a child should be brought up, with consequent shunting of the patient from male to female and back again, can produce only misery.

Even in those cases in which a definite sex assignment is made—and adhered to—changes at puberty may occur in an unexpected direction. Thus, a 'schoolgirl' may betray her maleness only at puberty, with the growth of facial hair, deepening of the voice and masculine bodily development. If these tragedies are to be avoided, an understanding of the nature of such intersexual states is necessary. It is the purpose of this paper to recount the histories of two patients with pseudo-hermaphroditism, to present some of the current views on intersex, and to describe some of the methods which permit of more accurate diagnosis.

Types of Intersex

Three main categories exist:

1. *True Hermaphrodites.* Gonads of both sexes are present; these may be an ovary on one side with a contralateral testis; or one or both of the gonads may be an ovotestis (i.e. a gonad containing both ovarian and testicular elements).

2. *Female Pseudo-hermaphrodites.* Here both gonads are ovaries, but there is development of some male accessory organs (Wolffian duct derivatives).

3. *Male Pseudo-hermaphrodites.* Both gonads are testes, but female genital ducts and/or external genitalia are found.

TRUE HERMAPHRODITES

These constitute the rarest types of intersex, only about 60 authentic cases having been reported in the literature. Bilateral gonads are present, which may be intra- or extra-abdominal; very rarely a third gonad has been

found. The phallus is variable in size and form; always there is penoscrotal hypospadias. The majority show a bifid scrotum; in some, however, the labio-scrotal folds surround a short phallus and resemble normal labia around a larger than normal clitoris. Almost invariably patients have a normally formed, although small, uterus with one or two fallopian tubes; rare exceptions have been described.[17] Puberty may ensue in either direction. Exploratory laparotomy with bilateral gonadal biopsy is generally needed to confirm the diagnosis.

FEMALE PSEUDO-HERMAPHRODITES

Two forms of this condition are described:

1. The vast majority are the result of intra-uterine adrenocortical overactivity. As a result of this, excessive androgen outpouring leads to more or less evidence of masculinization. This excessive hormonal influence, if not treated, persists throughout life. The external genitals are almost normally female, except for enlargement of the clitoris; in gross instances this may be mistaken for a penis with hypospadiac scrotal development. Rarely a penile urethra is found with a fused, empty, scrotal sac; this variant is usually misdiagnosed as cryptorchidism.

These patients generally have a precocious puberty of male type. More than one member of a family may be affected. Because of the excessive androgen production the urinary 17-ketosteroids are invariably high. This permits certain diagnosis to be made in early post-natal life.

The basic metabolic fault in this condition has been elucidated recently.[4] A block in the synthesis of hydrocortisone has been shown to exist, so that an androgenic precursor is released into the circulation. This substance (hydroxyprogesterone or a related compound) is responsible for the virilization.

Because of the lack of hydrocortisone, episodes of acute adrenal insufficiency of an Addisonian type (with vomiting, diarrhoea and collapse) may occur in the infant. Attacks of this sort in a child of ambiguous sexual development make the diagnosis of adrenogenital syndrome obligatory.

2. Very rarely adrenal overactivity cannot be demonstrated in cases of female pseudo-hermaphroditism.[13] Puberty may then occur in a female direction and reproduction may be possible. In these patients 17-ketosteroid excretion is normal. This form, however, is exceedingly rare and is difficult to distinguish from true hermaphroditism without exploratory laparotomy and gonadal biopsy. No adequate explanation of this type of female pseudo-hermaphroditism has been proposed, although it has been postulated that the female foetus undergoes partial intra-uterine masculinization because of a temporary phase of adrenal androgenic overactivity. At birth this is no longer detectable and the 17-ketosteroid excretion is thus normal. This theory is an ingenious one, but there is no real evidence to support it.

These two forms must be diagnosed early in life, as the adrenocortical type is totally correctable with cortisone therapy and, in both types, reproduction is possible.

MALE PSEUDO-HERMAPHRODITES

This condition exists in several different degrees. It has been shown[11,12] in experimental animals that removal or ablation of the gonads at an early stage of embryonic life (i.e. before differentiation of the genital tract is complete) is followed by the development of the female body-form. If this 'castration' occurs very early, complete feminization ensues, whether the embryo was destined genetically to be male or female. If it occurs slightly later, partial masculine differentiation having already taken place, greater or lesser degrees of intersexual development will be seen. In other words, the earlier the 'castration' occurs, the less obvious are the male features and, in extreme cases, slight enlargement of the clitoris may be the only token of the basic maleness of the animal.

It is suggested that comparable happenings in the human male embryos (i.e. intra-uterine damage to the developing gonads at different stages in different cases) may produce varying degrees of feminization. The genetic maleness of the subject may be determined by use of the skin 'sexing' method (*vide infra*). Pubertal development occurs along normal male lines, but may be partially eunuchoidal.

Another very rare form of male pseudo-hermaphroditism is found where the testes actually produce oestrogens.[13] These patients may have completely normal female genital appearance and they comprise the only members of this group who have a feminizing puberty. Since they live as normal women, this course should not be interrupted. The testes in these individuals may remain intra-abdominal or may present in the groin. Occasionally these patients show the external genital appearance of cryptorchid, hypospadiac males and, in such cases, pubertal feminization reveals their true status.

CASE REPORTS

Case 1

M.E. European 27 years old. This patient, despite original uncertainty, was raised as a girl. When she was 14 years old, a practitioner considered her to be female, amputated a fairly large phallus and removed a gonad which was present in the left labio-scrotal fold; a similar gonad in the right fold was left alone. A year later puberty commenced—along masculine lines. Neither breasts nor menses appeared; instead the voice deepened, facial hair began to grow and soon advanced to a degree which required daily shaving; the body contours assumed a muscular male configuration. Oestrogen therapy was instituted and, in the following few years, some breast development ensued. There was, however, no diminution in the degree of masculinity.

The patient continued to live and work as a female when she left school. She herself entertained doubts about her true sex and, despite being physically attracted towards men, actually attempted mild and 'experimental' sexual relationships with both men and women. About 2 years ago she met a man whom she wishes to marry. Moderate physical intimacy has taken place and it is this friendship which precipitated her admission to Groote Schuur Hospital in the hope that more complete feminization could be established.

On examination, she presented as an attractive but very hirsute female (Fig. 1); axillary and pubic hair was profuse—the latter

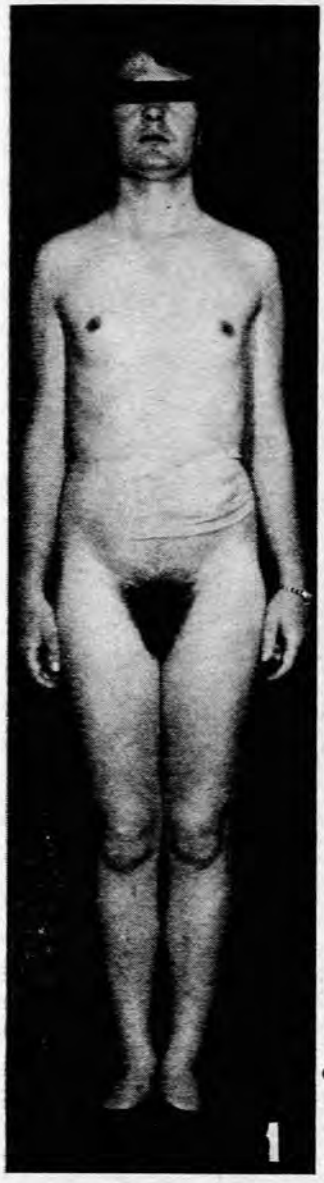

Fig. 1. Case 1 (M.E.).

of typically male distribution. The limbs were muscular and hairy, the breasts poorly developed with dark areolae. External genitalia (Figs. 2 and 3) comprised hypertrophied labio-scrotal folds enclosing a rudimentary vagina and, anteriorly, the scar of the amputated phallus. In the right fold, a bean-sized gonad was felt with an apparent epididymis attached. Further examination showed a small, blind vaginal pouch, but no other evidence of Mullerian derivatives.

17-Ketosteroid estimation was normal and skin biopsy showed a male type of chromatin pattern.

A psychological appraisal was undertaken (Dr. S. Berman, Chief of the Department of Neuropsychiatry). The conclusions reached were that the patient displayed femininity of outlook and it was felt that one should assist her in her desires to become 'normally' female.

At operation, Mr. N. Peterson (Chief of the Plastic Surgery Unit) performed vaginoplasty and excised the remaining gonad. Histology revealed this to be a degenerate testis (a finding probably related to the prolonged oestrogen therapy).

Comment. It is plain that this patient was a male with extreme hypospadias, a bifid scrotum, and testes which had descended into the scrotal folds. (Such normal descent is most uncommon in this sort of case.) This appearance led to the misdiagnosis of her sex with consequent mutilation which forced upon her the choice of continuing life as a male without a penis or a bearded, infertile female. The doctor had removed what he thought to be an enlarged clitoris and also a scrotal testis. This, combined with her strong predilection for femaleness, left us with no option but to assist her surgically and hormonally to attain this goal. Maintenance therapy with oestrogens will, perhaps, further her mammary development, but will not diminish the hirsutes. In this instance, a more total original mutilation would have been preferable, since removal of the other gonad before puberty would probably have prevented the virilization.

It is important to note that there was strongly female psychological orientation in this patient, who was

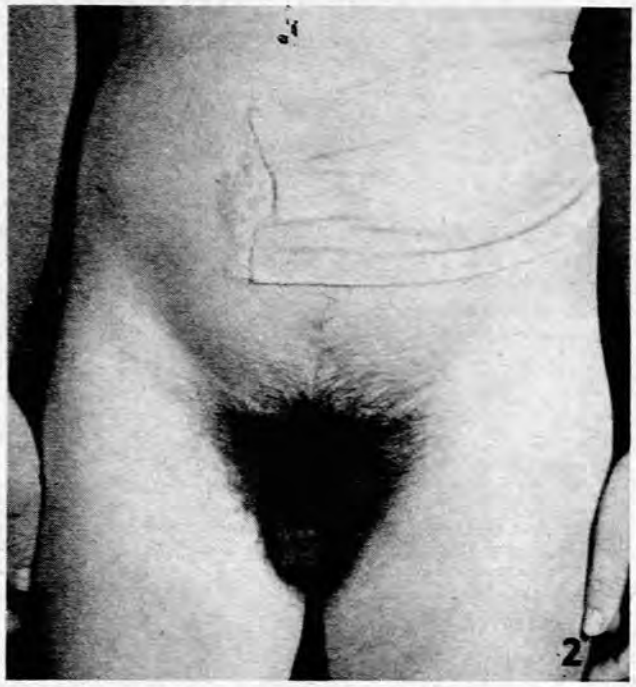

Fig. 2. Case 1 (M.E.). Note right scrotal swelling.

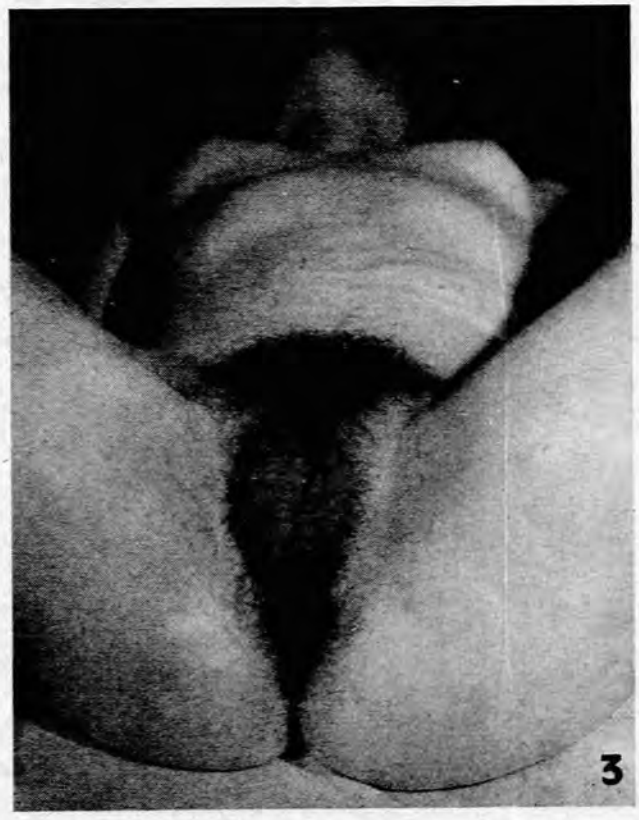

Fig. 3. Case 1 (M.E.). Pubis following amputation of penis and left gonadectomy.

male genetically, hormonally, gonadally and in respect of internal accessory organs of reproduction.

Case 2

L.R. European 28 years old. Despite the ambiguous nature of the external genitalia at birth, this patient was raised as a female. Throughout early childhood her inclinations were towards male pursuits. She preferred to climb trees and play male games, showed little interest in dolls or clothes and always felt strongly that she should have been a boy. At 16 years her voice became deeper, male sex hair appeared and the limb musculature began to develop in a male fashion. Menstruation did not appear and the breasts failed to enlarge.

She continued to live as a female, but still showed a preference for male company socially and females sexually. Her associates constantly suggested to her that she had been assigned to the wrong sex and advised her to undergo a 'change'. Recently the patient has become interested in a young girl and is considering marriage. This has stimulated her to come to Cape Town for 'rectification' of her sexual state.

On examination (Figs. 4 and 5), the scalp hair was seen to be cropped short in male style and there was moderate temporal hair recession; facial and body hair was profuse, with a typical male pubic escutcheon. The limbs were hairy and muscular; the breasts were almost non-existent. External genitalia consisted of a single urogenital sinus with a large phallus, but the perineal opening was so small that neither digital examination nor a hysterogram was possible. Cystoscopy was performed under anaesthesia (Mr. R. B. Watson) and a small vaginal opening was seen; dye displayed a small uterus (Fig. 6). No gonads were palpable.

A psychological appraisal was undertaken by Dr. W. A. Saffery and her orientation was regarded as strikingly male.

The diagnosis at this time was male pseudo-hermaphroditism. Taking into account her marked virilization (even to the extent of incipient baldness) and, particularly, her strongly male psychological orientation, the decision was made to convert her to full masculinity. The 17-ketosteroid excretion was then reported to be 134 mg. in 24 hours—a figure some 10 times normal. This finding completely refuted our previous diagnosis and indicated female pseudo-hermaphroditism (adrenogenital variety). Nevertheless, in view of her age and complete male orientation, the sexual conversion was proceeded with.

Fig. 4. Case 2 (L.R.). Note masculine habitus.

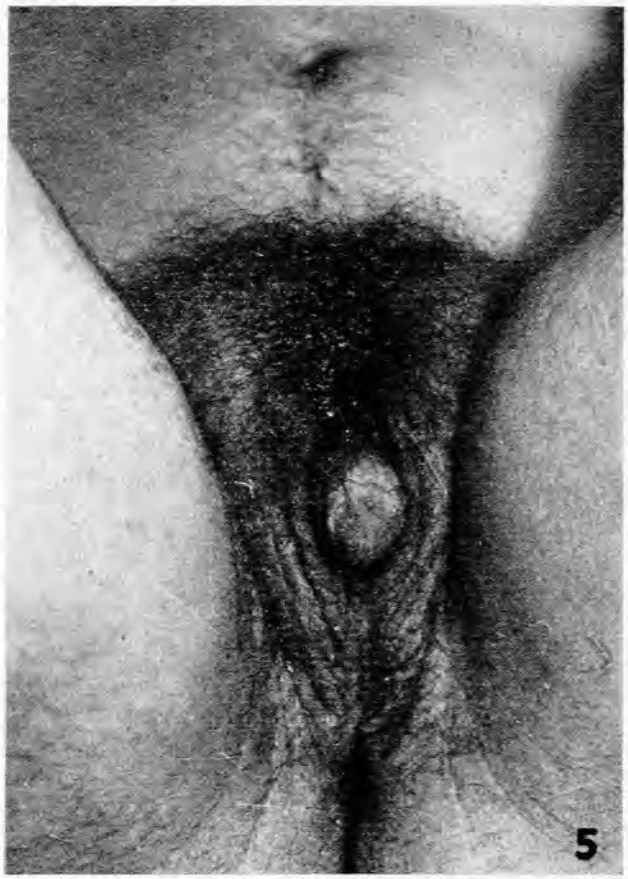

Fig. 5. Case 2 (L.R.). Appearance of external genitalia showing enlarged clitoris.

Professor James Louw and Mr. R. B. Watson found a very small uterus, well-developed fallopian tubes and gonads which, macroscopically, were not readily identifiable. Total hysterectomy and bilateral salpingogonadectomy was performed. Histology showed that the gonads were ovaries. Plastic masculinization with canalization of the phallus (to enable the patient to urinate standing) has been performed by Mr. N. Peterson.

Comment. It is most unusual for patients with the adrenogenital syndrome who are reared as females to show such striking male feelings. Money *et al.*[14] found in 38 hyperadrenocortical patients only one who exhibited bisexual interests. The overwhelming majority of patients adopt the gender role which is in accord with their assigned sex and sex of rearing (see later discussion).

If such a patient is diagnosed correctly at birth, treatment with cortisone will prevent all virilization and permit of a normal female existence, even including reproduction in later years. In this patient, at this stage, cortisone would serve no useful purpose and

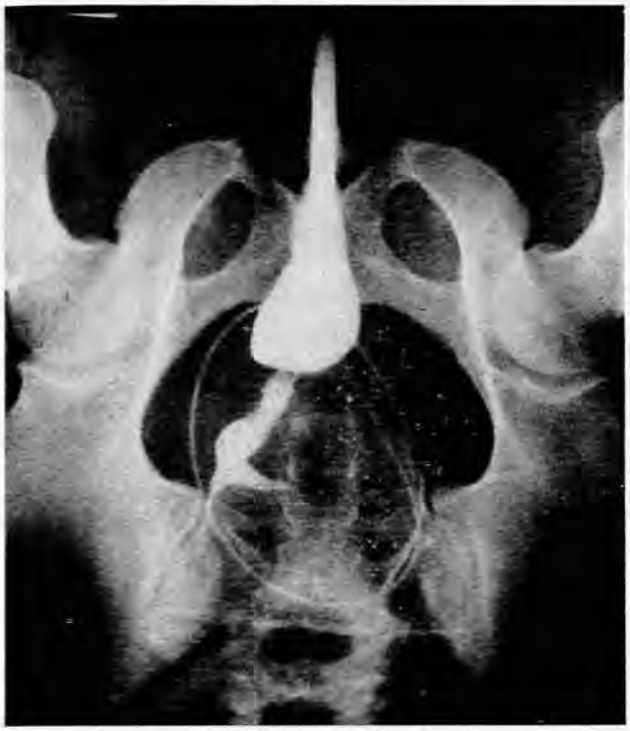

Fig. 6. Case 2 (L.R.). Injection of dye displays uterus and left fallopian tube.

future therapy must be aimed at consolidating her increased masculinity.

DISCUSSION

The Diagnosis in Hermaphroditism

There is no place for 'snap' diagnoses in the consideration of the ambisexual patient; those who appear to be members of one sex are often shown to belong to the other. Each patient requires careful examination of the external genitalia with roentgenological visualization of any orifice in the phallus or in the perineum; 17-ketosteroid excretion must be estimated; and where doubt is still present, laparotomy with bilateral gonadal biopsy may be necessary to establish the diagnosis with certainty.

Recently another valuable diagnostic tool has become available. Barr and his associates[1,2,15,16] have demonstrated that the nuclei of skin cells differ in males and females. In the latter the XX chromosome (or some attribute of it) is visible in 25-60% of cell nuclei as a small dark dot; in males such a mass is visible in less than 5% of cells. The same phenomenon may be seen in cells of the oral or vaginal mucosa and in polymorphonuclear neutrophil leucocytes.[6,7,15]

By means of this examination one may determine the genetic sex of the patient. Whatever the external appearance of the patient, one can ascertain whether the individual was destined genetically to be male or female. Thus, female pseudo-hermaphrodites with hyperadrenocorticism show female-type nuclear chromatin patterns regardless of the degree of virilization. Male pseudo-hermaphrodites show the male pattern, whilst true hermaphrodites may show one or the other. In practice the finding of a male skin-pattern excludes female pseudo-hermaphroditism and *vice versa*.

Correct Sex Assignment in the Neonatal Period

It has been shown that children begin to show gender awareness at approximately 18 months of age. By $2\frac{1}{2}$ years a child has assimilated his role as a boy or a girl so thoroughly that a change of sex should not be made lightly.[13] It is therefore of prime importance to diagnose the type of ambisexual development early in life and to assign the child to that sex in which it will be least incapacitated.

It is a mistake to assume that the child must be raised in the sex which corresponds to its gonads. For instance, the most extreme form of male pseudo-hermaphroditism is completely female in body-build and external and internal genital development. It is patently ridiculous to rear such a patient as a male.

Where possible there should be an attempt to forecast the changes which will ensue at puberty. Case M.E. above illustrates the results of failure to consider this factor—the unhappy sequelae of pubertal virilization in this patient might have been avoided. A forecast of this nature requires accurate diagnosis of the underlying aberration and justifies procedures such as laparotomy and gonadal biopsy.

A very important consideration is the structure of the external genitalia. If these are so strongly male or female in type as to defy surgical reconstruction, then the child should be assigned to the sex which it resembles. Future therapy must be aimed at furtherance of development in the direction of the assigned sex. Where no such marked predominance is found, other factors may be considered, e.g. gonadal type or hormonal preponderance.

The outstanding exception to the above precepts is the condition of hyperadrenocorticism producing female pseudo-hermaphroditism. This state can usually be diagnosed with certainty in very early life and Wilkins[23] has shown the remarkable restoration to normal femininity which follows cortisone therapy.

Considerations in Older Patients

Many patients are seen in later life after they have already been reared in one or other sex. In this group the gender role* has become well established, although ambivalence may exist. Here, generally, psychological considerations are the most important. Full and careful psychological appraisal is necessary before any decision can be taken.

Case L.R. above illustrates this point well. This patient was female genetically, gonadally and by up-

* By gender role is meant 'all those things that a person says or does to disclose himself or herself as having the status of a boy or man, girl or woman, respectively. It includes, but is not restricted to, sexuality in the sense of eroticism. A gender role is not established at birth, but is built up cumulatively through experiences encountered and transacted . . .'[13]

bringing; yet her psyche was developed in a very strong male direction. This was the consideration which prevailed upon us to alter her status to that of a male.

In the vast majority of hermaphrodites the psyche has been shown to develop in accordance with the assigned sex and sex of rearing, rather than the structure of the internal or external genitals, or the gonadal or chromosomal sex. It is therefore exceptional to find a hermaphroditic subject reared in one sex whose psychological orientation is that of the opposite sex. Money *et al.*[14] found only 4 of a series of 76 hermaphrodites in whom psychological ambivalence was detected. The remaining 72 all developed mentally in accordance with the sex to which they had been assigned. This small percentage of patients showing lack of psychosexual concordance is, perhaps, no higher than the percentage of 'normal' people who are found to show psychosexual ambivalence.

CONCLUSIONS

The incidence of bisexual anomalies at birth is high. Differentiation of the underlying defect is usually difficult and the 'spot' diagnosis is frequently incorrect. At a very early age every attempt must be made to establish the correct diagnosis; at the same time a firm decision must be made with regard to assignment of the child to one or other sex; such assignment should generally be made on the basis of external genital anatomy. Where this is completely ambiguous, other factors may be considered. Once this decision has been made, artificial devices may be employed to further development in the 'chosen' sex, e.g. gonadectomy or hormonal therapy.

It is of the utmost importance that the true facts should be withheld from both patients and parents in those instances where the choice of sex differs from genetic or gonadal sex. In case 1, for example, the disclosure of the patient's true sex could only occasion distress.

The psychological state of affairs in older patients must be very carefully appraised before any decision is taken about allocation to one or other sex.

In the consideration of intersexual subjects, the following aphorisms may be of value:

1. A fully-descended gonad is a testis or an ovotestis; it is never an ovary. Female pseudo-hermaphroditism may thus be ruled out.

2. A male skin-chromatin pattern also rules out female pseudo-hermaphroditism; a female pattern excludes male pseudo-hermaphroditism.

3. Hence, female skin-sex with a descended gonad indicates true hermaphroditism.

4. Female pseudo-hermaphrodites with the adrenogenital syndrome—and *only* these—always have a raised output of 17-ketosteroids.

5. Female pseudo-hermaphrodites, if treated, may well be fertile; male or true hermaphrodites cannot become parents.

6. Precocious puberty of male type in an intersexual individual indicates hyperadrenocorticism with respect to androgen (i.e. female pseudo-hermaphroditism).

7. Those intersexuals who exhibit neonatal episodes suggesting Addisonian crises are female pseudo-hermaphrodites with adrenocortical overactivity.

8. Every 'male' without palpable testes must be suspect, *whatever the state of his genitals.*

9. Every 'female' who does not have a menarche must likewise be suspect.

SUMMARY

The current views on intersexual states are briefly summarized. Two case-reports are presented to illustrate some of the difficulties in diagnosis and to emphasize the unfortunate sequelae of incorrect diagnosis and sex assignment. A plea is made for thorough investigation of cases at an early age and for firm decisions with regard to rearing. Some of the important factors which should influence one's decisions are reviewed.

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