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ARTICLES

INTERSEX*

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Although none of the disorders which may be included under the term "intersex" is very common, yet the consequences of error in diagnosis are disastrous to the emotional stability and even to the life of the affected child. It must therefore be emphasized that the urgent need is for early and complete diagnosis. The true nature of the disorder must be finally established during the first few weeks of life, so that the child may be brought up in the proper role right from the start, without any doubts in the minds of its parents. Yet this diagnosis is not an easy or simple matter, it often requires hospitalization and laboratory tests and occasionally even exploratory surgery. It is seldom possible to say from a simple clinical examination what is the true nature of the condition and the fuller investigation can not be short-circuited.

It is well known that sexual differentiation depends primarily upon the sex chromosomes, XX in the female, XY in the male, (fig. 1). The combination XX produces a distinct chromatin granule which can be recognised in the nucleus of the mature cell, particularly in

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epithelial cells and polymorph leucocytes. Where this granule is present, the nucleus is said to be sex chromatin positive. This chromosomal pattern is not, however, the only factor which influences sexual development, and as will be seen later the complete diagnosis

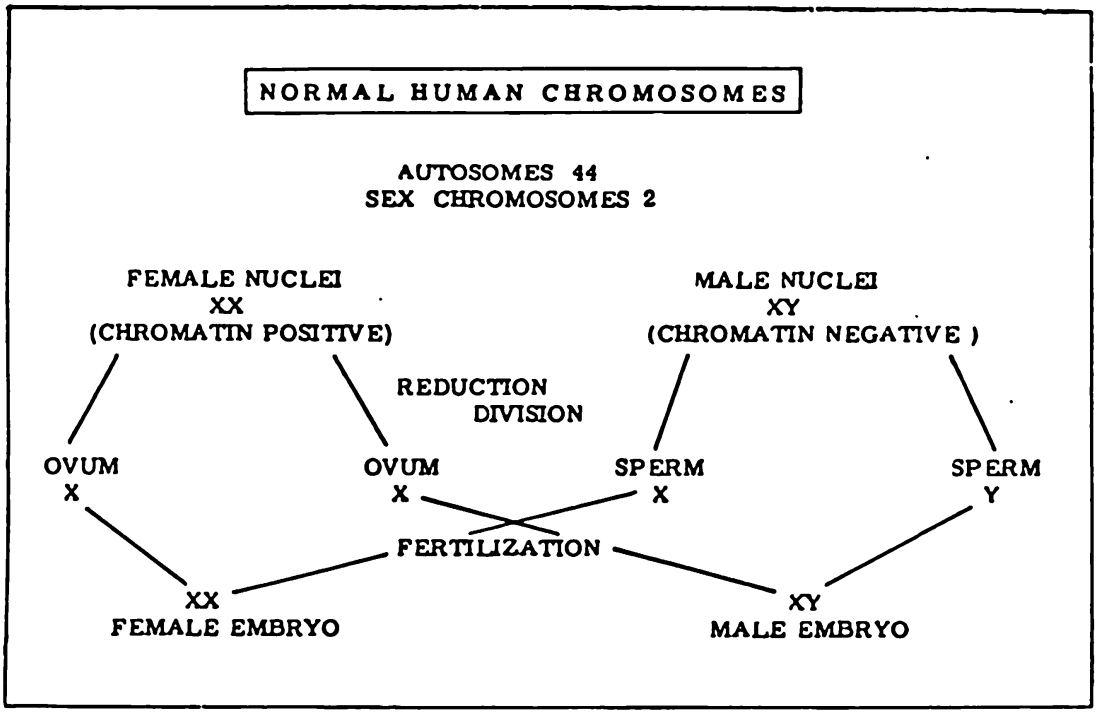

Figure 1.

cannot be made on this cytological finding alone. Hormonal factors, both from the gonads and from other organs, are of vital importance, but many of the causes of intersex disorders remain a mystery. In general, the following table provides a tentative classification of our present knowledge.

1. Variations in the number of sex chromosomes:
   (a) Klinefelter's syndrome
   (b) Turner's syndrome
2. True hermaphroditism:
   Ovaries and testicles present, chromosomes variable
3. Pseudohermaphroditism:
   (a) Male, testicles with feminized genitalia
   (b) Female, ovaries with masculinized genitalia.

Variations in Chromosomal Number

The chromosomal abnormalities will be mentioned only briefly since they do not as a rule present a problem in the diagnosis of sex at birth. Theoretically they can arise from a failure of the disjunction of chromosomes which normally takes place at the reduction

division during the formation of an ovum or sperm. The table below shows a hypothetical case of non-disjunction on the ovum side, (fig. 2). The finding of three X's is very uncommon, but is recorded in mentally deficient female children and infertile adults without any specific anatomical abnormality.

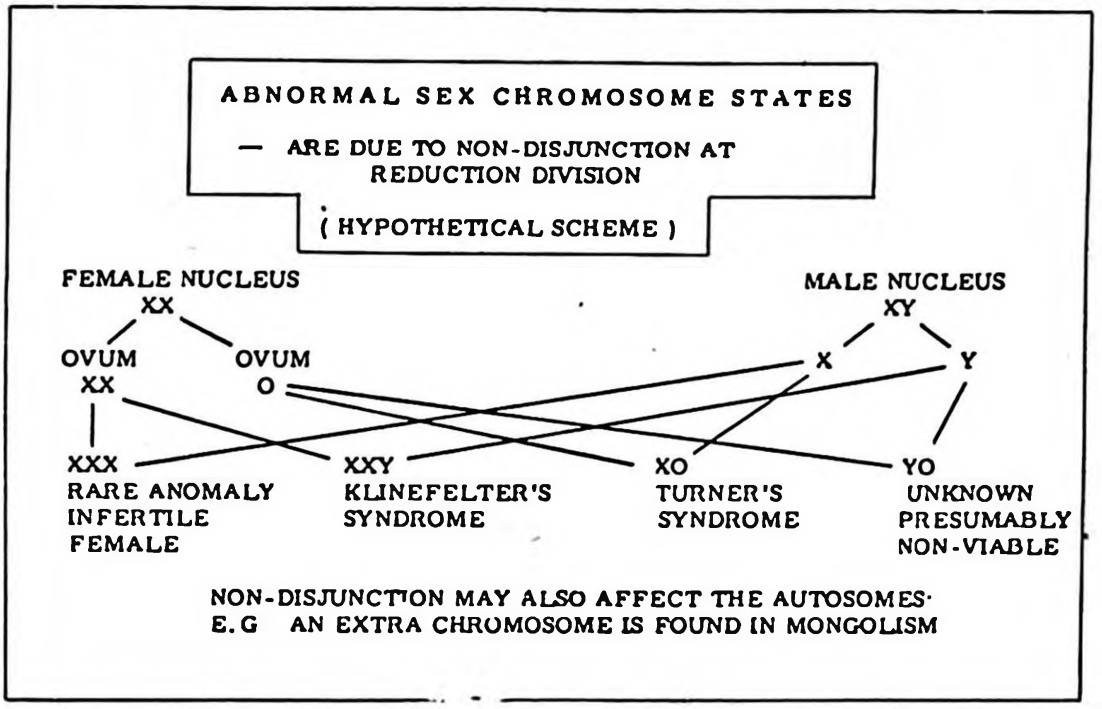

Figure 2.

In Klinefelter's syndrome the chromosome pattern is XXY, and nuclei are therefore chromatin positive. The genitalia are apparently masculine but the testicles are small and firm, being sclerotic histologically and very seldom capable of spermatogenesis. Breast development occurs at puberty, (fig. 3). The growth of the limbs often results in a eunuchoid appearance, and later there may be considerable obesity, but pubic hair and the penis may be normally masculine.

In Turner's syndrome where only a single sex chromatin, X, is present, the individuals are female in type and have normally feminine genital passages, but the gonads are agenetic, represented by a thin ribbon-like structure containing stromal cells only. These girls present dwarfism and certain somatic abnormalities such as webbing of the neck (fig. 4) and other joints, or with amenorrhea during adolescence. The clitoris is sometimes a little enlarged and this is occasionally recognized at birth.

True Hermaphroditism

We now turn to the true hermaphrodites, (fig. 5) in which both ovarian and testicular tissue is present. The chromosomal state has not

been investigated in a sufficiently large number to lay down any definite rules. It is certain that an XX or an XY combination can be present, although an XXY has also been suggested. The examination of epithelial cells may therefore show a chromatin positive or a chromatin negative pattern. The anatomy of the genitalia exhibits wide

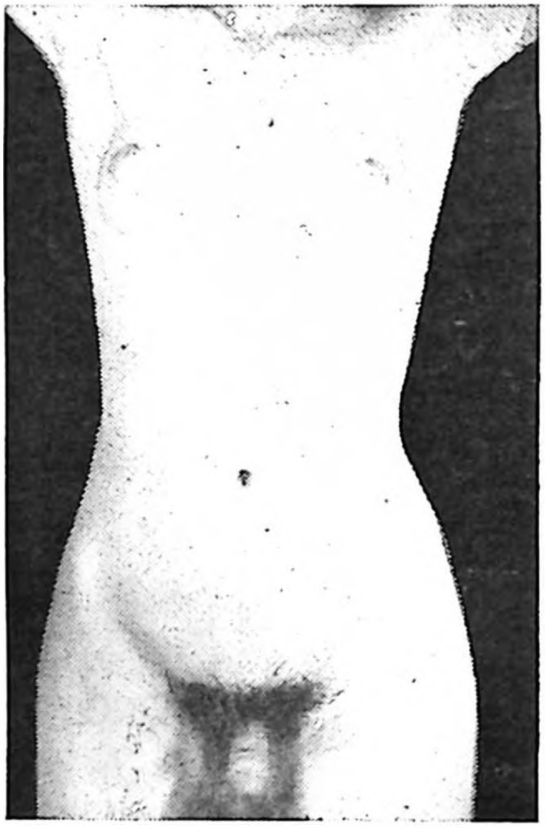

Fig. 3. — Breast development in a boy of 15, with chromatin positive nuclei (Klinefelter's Syndrome).

Fig. 4. — Webbing of the neck in an infant with Turner's syndrome.

variations, there is usually a penis with some degree of hypospadias, though a complete urethra has been observed. A vagina is almost always present, though its orifice may be hidden in the depths of the urethra. The testicular and ovarian tissue may be present in the same organ (an ovo-testis), or in separate organs on the same or opposite sides. A testis or ovo-testis may be descended into the scrotum, but the ovary remains within the abdomen.The importance of this abnormality is in the developments at puberty, when menstruation and breast development occur at the same time as a deepening of the voice, the appearance of facial hair and penile erections. This is of course a psychologically disastrous situation which should never be allowed to occur. Its avoidance entails full diagnosis during the earlier part of childhood, the removal of the inappropriate gonad and correction

of the genital passages. The problem of diagnosis will be discussed later.

Pseudohermaphroditism

In the female pseudohermaphrodite the individuals have ovaries and chromatin positive nuclei, but the genitalia are to some degree virilized. Conversely the male pseudohermaphrodite has testicles

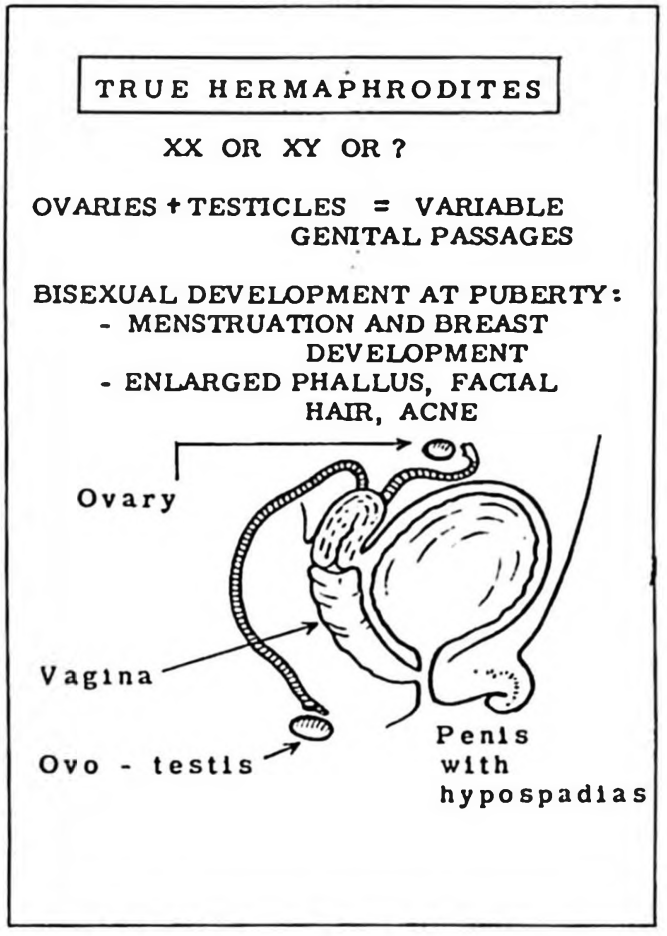

Figure 5.

and chromatin negative nuclei but feminized genitalia. Even these categories must be further sub-divided, however, as shown in table 1.

Adreno-cortical Hyperplasia

The majority of these are hormonal in origin and result from the overproduction of androgens in the hyperplastic adrenal cortex. This disorder has its first effects in later fetal life, after the ovaries, tubes and uterus have taken their definitive shape; under androgenic influence the phallus enlarges and the vaginal orifice remains high in the urogenital sinus; the labial folds become prominent and rugose as in the scrotum. At birth a single urogenital opening is found in

TABLE 1.
CHARACTERISTICS OF MALE AND FEMALE PSEUDOHERMAPHRODITES

FEMALE PSEUDOHERMAPHRODITES	MALE PSEUDOHERMAPHRODITES
Chromatin positive	Chromatin negative
Chromosomes : XX	Chromosomes : XY
Ovaries	Testicles
Masculinized genitalia	Feminized genitalia
1. Hormonal	1. Testicular feminization syndrome
a. Endogenous : adrenal hypoplasia	
b. Exogenous	
2. Non-hormonal	2. Perineal hypospadias, with undescended testicles and vagina present
With other congenital anomalies	

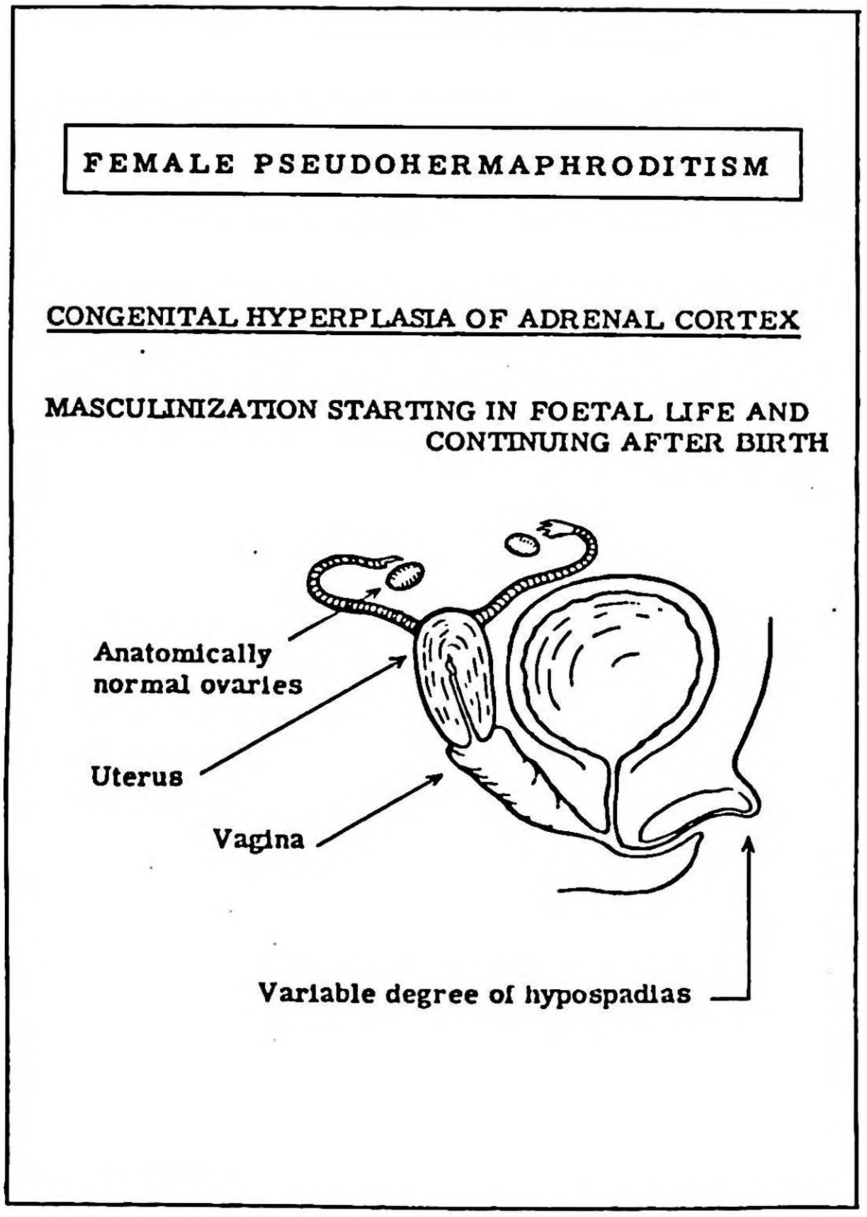

Figure 6.

the position of a hypospadias, and the phallus has the appearance of a penis with a well marked chordee (fig. 6). No gonads are, of

course, palpable in the groin. The activity of the hypertrophied adrenal continues after birth and androgenic output affects both somatic and sexual development. General bodily growth is more rapid than normal, centers of ossification appear early and fusion of epiphyses is correspondingly premature. At the age of four or five these children are therefore much bigger than their contemporaries but, as growth ceases early, they are in adult life shorter than normal. The phallus continues to enlarge and exhibits frequent erections; breast development does occur at the age of puberty and menstruation is absent. In earlier childhood the behavior of these children is often a difficult problem.

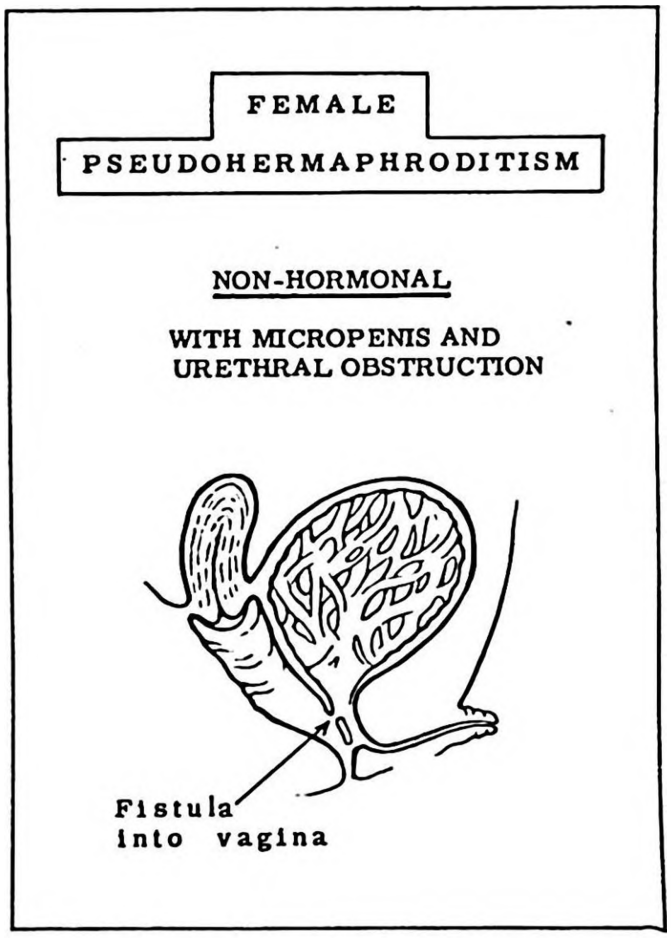

Figure 7.

Psychological orientation of untreated adolescents depends very largely upon their upbringing. Those raised as boys have usually been content to remain as such, those brought up as girls go through great difficulties since the virilizing influence of the adrenal androgens affects not only the body but the mind as well.

The androgenic excess is not the only abnormality of the adrenal cortex and in early infancy these children show an electrolyte dis-

turbance of the Addisonian type. Many of them are admitted to hospital with acute collapse, vomiting and dehydration with severe loss of sodium and chloride and a high serum potassium. In later years there is less tendency towards electrolyte disturbance but a few of the children develop hypertension. The androgen output is measured by 24-hour estimations of 17-ketosteroids and the excess can be determined from very early infancy. Urinary pregnanetriol is also consistently raised. Cortisone has a remarkable effect in these children. It causes a rapid fall in the output of androgens and, given over a long period, it will halt or reverse the virilization, and allow breast development and menstruation to start in the post-pubertal child. It has been postulated that the primary defect in the adrenal is a failure of the complete synthesis of hydrocortisone, which stops short at the 17-hydroxyprogesterone stage. This substance is excreted as

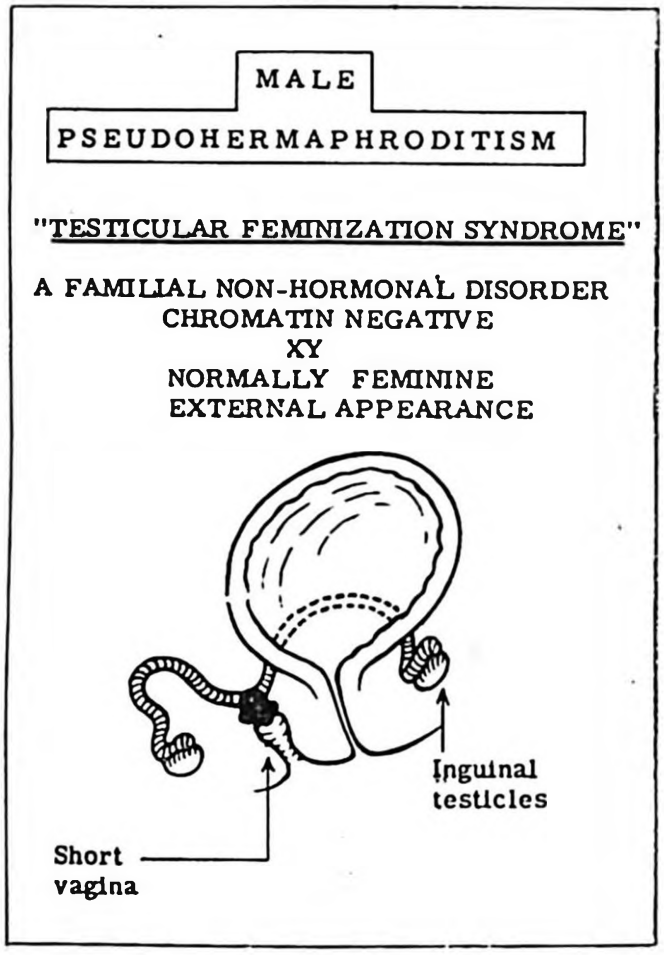

Figure 8.

pregnanetriol. The lack of circulating hydrocortisone results in increased pituitary activity which by the excretion of ACTH stimulates the adrenal glands to hypertrophy, and androgens are then produced in excess. Administered cortisone suppresses ACTH output and therefore allows production to fall back to normal.

External Hormonal Influence

Androgens derived from the maternal circulation can affect the developing female fetus: testosterone and progesterone given to the mother to prevent abortion are both capable of having an androgenic effect which results in an enlargement of the clitoris at birth. Often this is of a mild degree only, but occasionally a complete phallic urethra is formed. No abnormalities are found in the child's hormone excretion and some tendency to return to normal is observed in the months following birth.

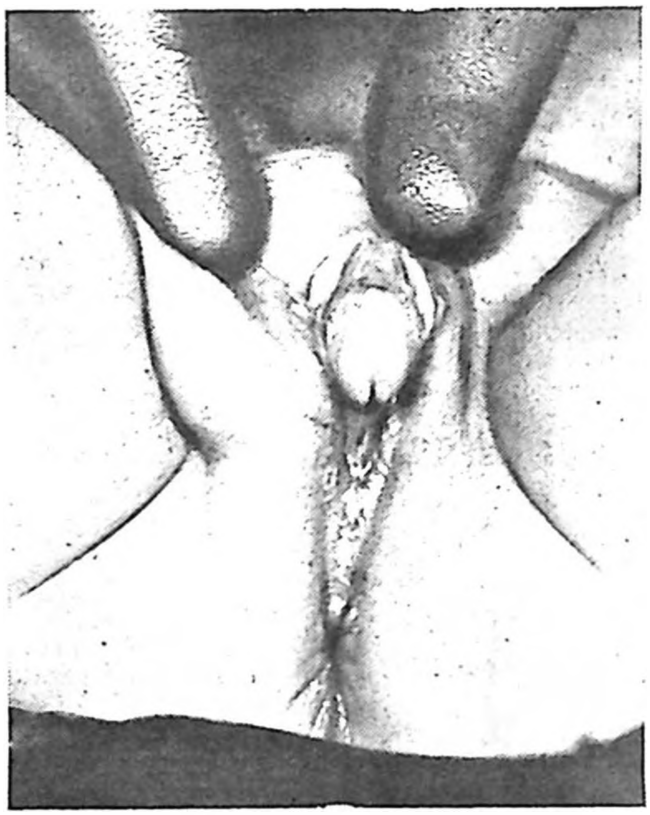

Fig. 9. — External genitalia in a case of testicular feminization age 18 months.

Non-hormonal Cases

Occasionally a female pseudohermaphrodite has no evidence of an endocrine disturbance. There is one particular form of pseudohermaphroditism in which there is a micropenis consisting only of skin and subcutaneous tissue with a very narrow urethra, as shown in the diagram, (fig. 7). This is often associated with severe urinary obstruction.

Male Pseudohermaphrodites: Chromatin Negative XY

1. Testicular Feminization Syndrome. This type of male intersex abnormality is familial and all cases present a very similar appearance (figs. 8, 9). The individuals are always reared as little girls and on external inspection there is nothing to suggest that an intersex abnormality exists. The clitoris, urethra and vulva are typically feminine. The vagina is short, however, and ends in a mass of

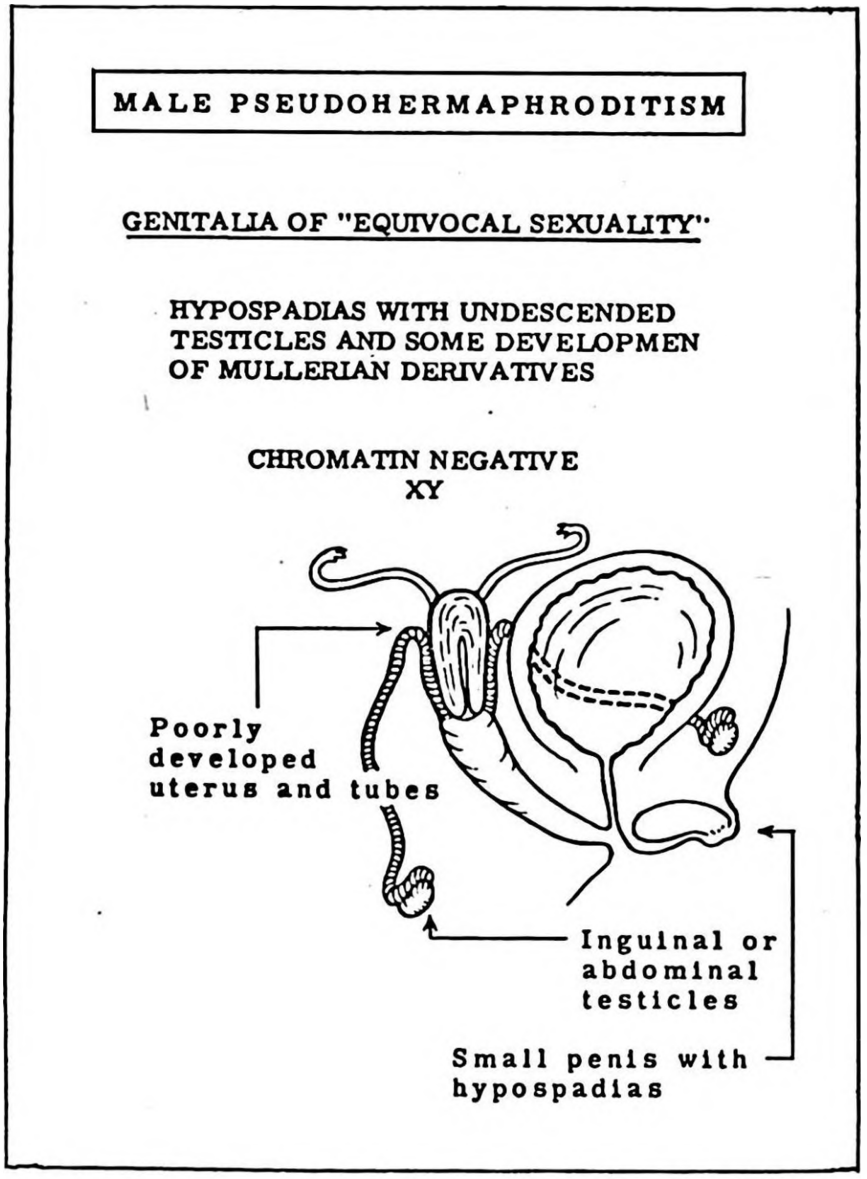

Figure 10.

fibro-muscular tissue, from which two vasa deferentia run to the testes, which are inguinal or abdominal in position. These anomalies are often discovered at puberty when there is complete amenorrhea. Breast development is slight at this time and pubic and axillary hair is absent. Discomfort in the groin caused by the inguinal testes is another reason for presentation. Many of these individuals have

married and had sexual intercourse in the female role, though it is apt to be unsatisfactory. No fundamental treatment of this condition is possible, though castration is sometimes undertaken to relieve the inguinal discomfort, and hormonal replacement therapy with estrogens is advisable.

2. Male Intersex with Equivocal Genitalia. This is much the largest group of intersex males, but a heterogeneous one. The least severe cases differ only in degree from simple perineal hypospadias. A boy with a very small penis and undescended testicles is often mistaken for a girl, but careful clinical examination sometimes reveals the presence of both testicles in the groin. In more severe cases, however, a vaginal canal is present opening either exteriorly or into the urethra. There may be a uterus, often asymmetrical, with fallopian tubes (figs. 10, 11). The testicle is then retained within the abdomen and often is completely absent on one side. The uterus in these conditions does not exhibit menstrual changes, though infection and bleeding from the genital tract occur. The general bodily development is masculine but may be modified by hypogonadism. The psychological orientation depends very largely on the upbringing, but where children have been reared as girls they may have severe emotional disturbances in adolescence.

Diagnosis

It has already been emphasized that clinical examination is seldom adequate for diagnosis. Only where two testicles can be palpated beyond doubt can the diagnosis be made from clinical signs alone. In the newborn child with genitalia of equivocal sex, the first step in examination must be cytological study of the epithelial cells, either buccal smears or skin biopsies, for sex chromatin, together with estimation of the 17-ketosteroid output in the urine. The collection of 24-hour specimens presents some difficulty, but stick-on cellophane bags are usually sufficient.

All intersex females are chromatin positive, but all chromatin positive cases are not necessarily females, they may be true hermaphrodites or examples of Klinefelter's syndrome. Sex chromatin, therefore, gives an important lead but not a complete diagnosis. The adrenal hyperplasia cases have raised 17-ketosteroids and raised pregnanetriol output, and this together with chromatin positive nuclei provides a conclusive diagnosis. Chromatin positive cases without evidence of adrenal disease may have a history of an androgen influence during pregnancy; if

so, it is often sufficient to watch development, since some regression of the enlargement of the clitoris may be observed. Where, however, the urogenital sinus is present, the differentiation from true hermaphroditism is important and can only be accomplished by laparotomy and biopsy of the gonads. There should be no hesitation in undertaking this procedure even in infancy, since as already emphasized, the final and complete diagnosis must be reached at the earliest possible moment.

In the chromatin negative cases, if a urethroscopy reveals a normal verumontanum it may be safely assumed that the condition

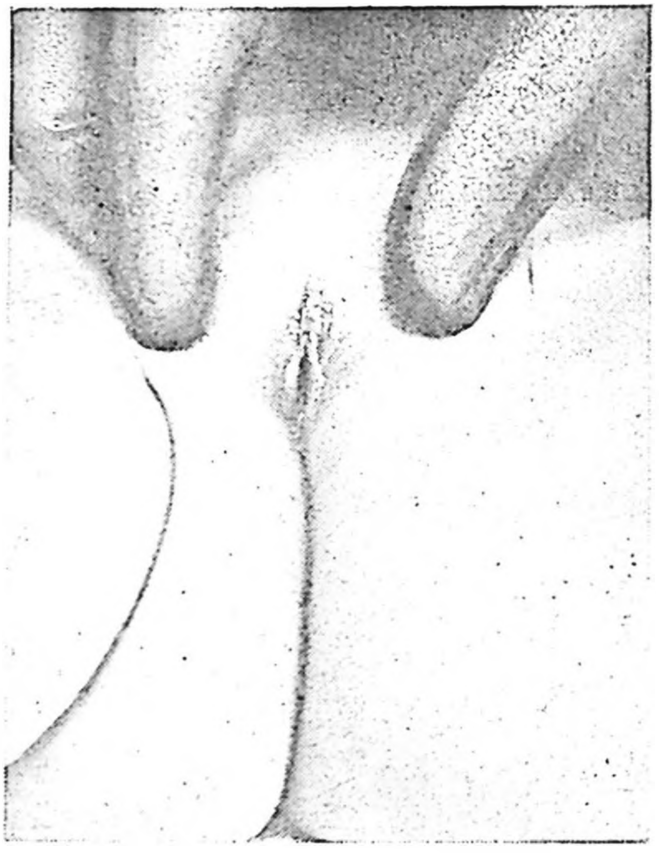

Fig. 11. — Male pseudohermaphrodite with external genitalia of equivocal sex.

is one of male pseudohermaphroditism, but if there is also evidence of a vaginal canal the possibility of true hermaphroditism again arises and once more laparotomy is advisable.

In later childhood the diagnostic problems are in a somewhat different form: the apparent males with hypospadias who present in infancy acute collapse and salt loss may well be intersex females with adrenal hyperplasia, and the same goes for apparent males with sexual precocity without palpable testes. The "boy" with

a micropenis and absent testes may be a non-hormonal female pseudohermaphrodite, while the adolescent boy who develops breasts is normally an example of Klinefelter's syndrome or true hermaphroditism. The "girl" with palpable gonads in the groin and a short vagina is probably a male pseudohermaphrodite (testicular feminization syndrome).

UNDER THE PATRONAGE

OF THE PRESIDENT OF TURKEY

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THE SECOND

MIDDLE EASTERN - MEDITERRANEAN PEDIATRIC CONGRESS WILL BE HELD AT HACETTEPE, ANKARA

from September 6-9, 1961

Pre-Congress Seminars

1. The Newborn — Full term and Premature
2. Fluids and Electrolytes.
3. Pediatric Hematology
4. Pediatric Cardiology
5. Genetics of Interest to the Pediatrician
6. Pediatric Allergy
7. Working with Parents of Children with Emotional Problems
8. Social Pediatrics
9. Pediatric Neuro - Surgery
10. Pediatric Thoracic (including Cardiovascular) Surgery

Post - Congress Activities

A one day clinical session will be arranged in İstanbul under the auspices of The Turkish Pediatric Association on Monday, September 11. Another Post-Congress Pediatric Day will be organized in İzmir by the Aegean Chapter of The National Society of Pediatrics and Child Health of Turkey.

Tours to Boğazkale, Ephesus, Pergama, Troy, Gordium, Kayseri, İstanbul and other spots of interest in Turkey have been arranged.

Program for the Ladies' Entertainment

A luncheon, fashion show, visit to the Atatürk Mausoleum, Hittite Museum and the Temple of Augustus, a concert and a banquet will be features of the entertainment planned for wives of the members. No extra fee, other than the associate membership fee, will be charged.