SOMATAL DISSENSUS

AND

HERMAPHRODITISM

A Thesis

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by

Raymond Hoffenberg, M.B., Ch.B., M.R.C.P.

Department of Medicine

University of Cape Town.

1957.

TO MARGARET

INDEX

INDEX

INTRODUCTION

INTRODUCTION

This thesis has developed from a study of a series of patients with gonadal dysgenesis. Shortly after the inception of the study, Polani and his co-workers (1954) published a report on the nuclear chromatin pattern in three cases of this syndrome. Their findings provided one of the most illuminating contributions made in the field of endocrinology and have stimulated a new approach to the problem of sexual differentiation.

As a direct result of this work, the present study of gonadal dysgenesis was extended to encompass an investigation into other abnormalities of sexual development. Links between gonadal dysgenesis and other intersexual states became apparent, and an attempt was made to find some more satisfying explanation for these aberrations.

Accordingly, this thesis consists of two main parts. The first concerns the syndrome of gonadal dysgenesis and its interesting ramifications; a series of 23 patients has been studied and their protocols are presented. The second part of the thesis relates gonadal dysgenesis to intersex and includes a new theory to account for several imperfectly explained discrepancies in this complex field.

PART I

GONADAL DYSGENESIS:

A CRITICAL REVIEW

CHAPTER I

THE CONCEPT OF GONADAL DYSGENESIS

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THE CONCEPT OF GONADAL DYSGENESIS

1. GENERAL HISTORICAL BACKGROUND.

Funke, in 1902, was the first to describe the association of sexual infantilism and webbing of the neck (pterygium colli). In a study of certain congenital developmental anomalies, Ullrich (1930; 1949) noted that webbing of the neck was frequently accompanied by other abnormalities; among these were aplasia of muscles, cranial nerve palsies, oedema of the extremities, mammary hypoplasia and shortness of stature. In 1938, Turner published his account of 7 females who showed the triad of sexual infantilism, webbing of the neck and cubitus valgus.

Several papers from American followed which stressed the endocrine aspects of this syndrome. In 1942, Varney et al. and Albright et al. published separately their views on the fundamental cause of the sexual infantilism. These authors found raised levels of urinary gonadotrophin excretion in their patients. This finding reflects excessive pituitary action. When any endocrine gland, which is under pituitary control, fails to respond to the stimulus of its pituitary-produced trophic hormone, then the production of this trophic hormone becomes excessive. Thus, where primary testicular or ovarian failure occurs, an increased amount of gonadotrophin is produced by the pituitary gland, apparently in an attempt to stimulate some response from the gonad - a state of affairs which has been likened to "flogging a dead horse". This gonadotrophin excess is excreted in the urine, where it may be measured.

From the excretion of abnormally high levels of gonadotrophin

by subjects with Turner's syndrome both groups adduced that the basic defect in this syndrome was primary ovarian failure. Wilkins and Fleischmann (1944) were able to support these concepts by laparotomy and necropsy exhibition of undeveloped ovaries. To this syndrome they applied the name "ovarian agenesis".

In the meanwhile, European workers had concentrated on other aspects of the syndrome. Rossi and Caflisch (1951) analysed almost 200 cases of congenital musculo-skeletal anomalies. These shared certain malformational peculiarities, particularly webbing of the neck, axillae, cubital fossae or digits. A proportion of these patients with the "Pterygium Syndrome" displayed shortness of stature and sexual infantilism, conforming to the patients who had been described by Turner. Of significance was the fact that the majority of Rossi and Caflisch's patients appeared to have no evidence of endocrinal disorder.

Lieser et al. in 1947 and del Castillo et al. in the same year added more reports of this syndrome of "ovarian agenesis". Soon a clear picture of the condition emerged, the salient features of which will now be presented.

2. THE "CLASSICAL" SYNDROME

(a) Sexual infantilism

Fundamentally this is due to a failure of gonadal development. These organs are represented by mere streaks of primitive white tissue lying on the posterior aspects of the broad ligaments (Figure 1.01). Histologically these ovarian anlagen contain only rudimentary stroma and no primordial follicles or germinal epithelium (Figure 1.02). Primary amenorrhoea is a reflection of this gonadal failure. A few cases with scanty menstrual bleeds have been reported but a substantial amount of menstruation has not previously been described.

Secondary sex characters also fail to appear. There is no development of breasts and the nipples are small and surrounded by pale pink areolae. Pubic hair is generally diminished in amount and axillary hair commonly absent. This, together with the reputedly low levels of ketosteroid excretion, was claimed by Albright et al. (1942) as evidence of diminished adrenocortical activity - a view which has been neither confirmed nor refuted. Vaginal smears show absence of oestrogenic effect.

Radiologically the bone age is often slightly retarded and some degree of generalised osteoporosis is commonly found. This has been compared to post-menopausal osteoporosis, in which a similar lack of oestrin obtains.

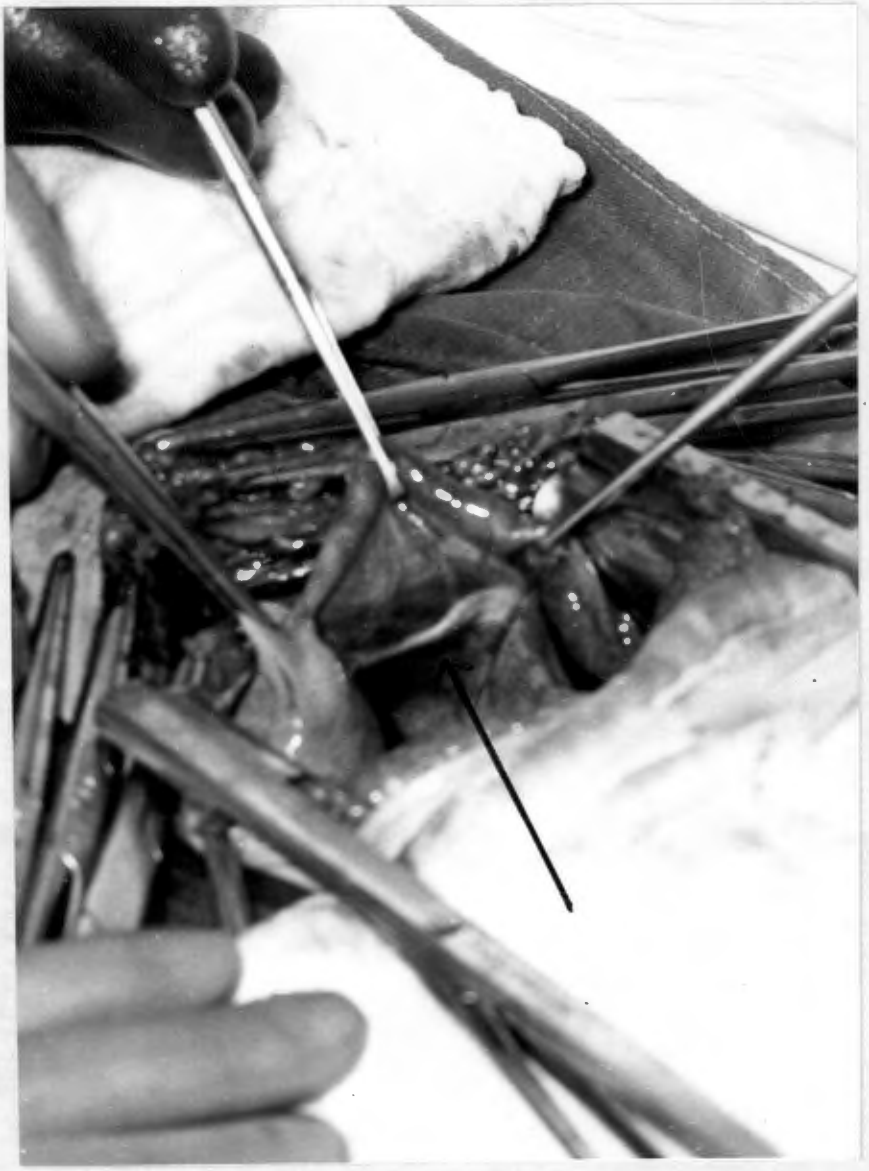

Figure 1.01

Macroscopic gonadal appearance

The arrow points to the typical vestigial "streak" of gonadal dysgenesis lying on the posterior aspect of the broad ligament.

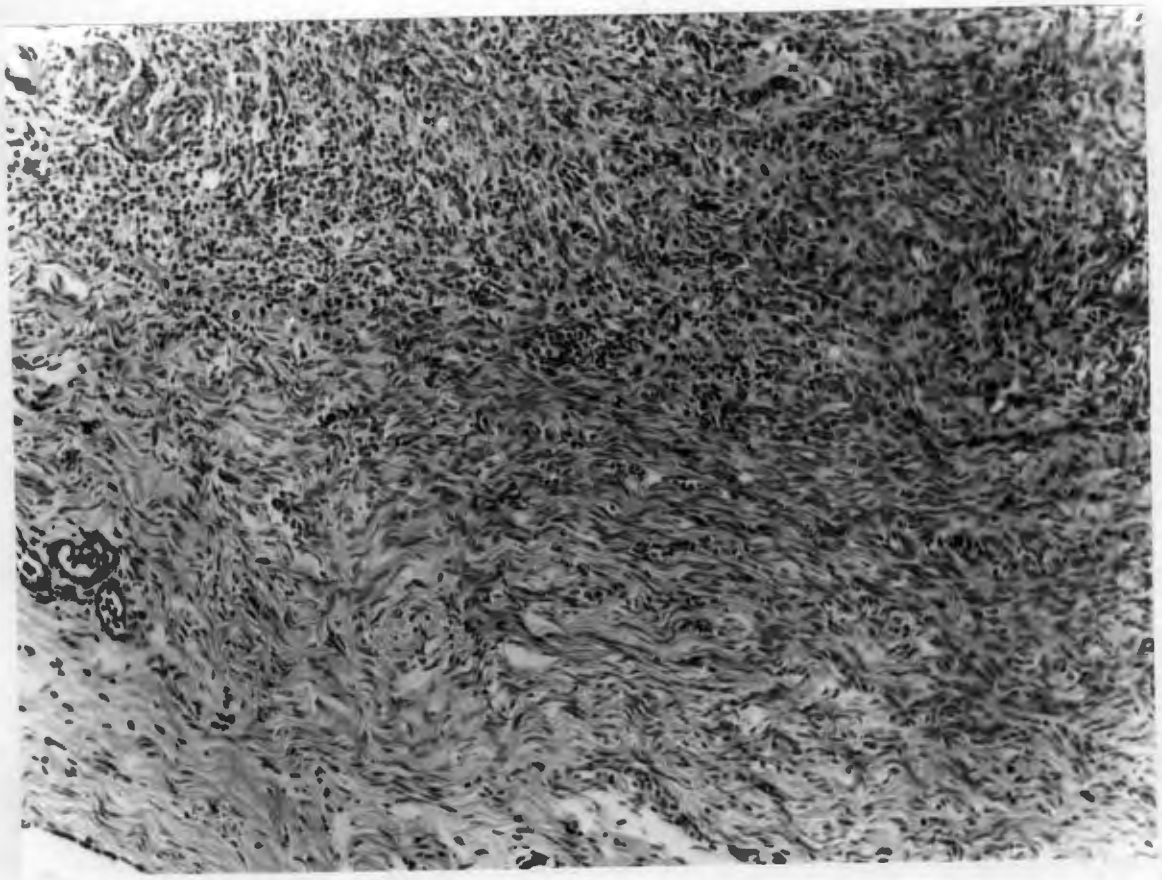

Figure 1.02

Microscopic gonadal appearance

This illustrates the absence of germinal elements and the wavy gonadal stroma.

As expected in primary gonadal failure, the urinary excretion of pituitary gonadotrophin (follicle-stimulating hormone)[4] is raised. This provides an important diagnostic criterion. A few patients have been described in whom this F.S.H. excretion was not raised. In these coincidental hypopituitarism has been postulated (Dorff et al. 1947).

(b) Shortness of Stature

This is present in the vast majority of cases, the height, as a rule, being between 4' 6" and 4'10". Scanty reports of taller patients have appeared.

In most subjects with gonadal failure, a tall eunuchoid stature is found; this is attributed to continued growth of long bones due to lack of closure of the epiphyses - the latter process normally being hastened by sex hormones. The shortness of stature in gonadal dysgenesis is unexpected, since sex hormone is obviously deficient in this syndrome. Most authorities, therefore, regard the shortness as a separate genetic anomaly, chromosomally connected with the gonadal dysgenesis and skeletal defects. (Albright et al. 1942).

- Classically -

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[4]Footnote: The terms "gonadotrophin" and "follicle-stimulating hormone (F.S.H.)" are used interchangeably in this thesis to represent that excretory product which produces changes in mouse uterine or rat ovarian size. Attempts to separate F.S.H. from I.C.S.H. (Interstitial-cell-stimulating hormone) have not yet proved practicable except in very specialised laboratories.

Classically, the body-build is stocky with a broad "shield-like" chest.

(c) Associated Congenital Anomalies

There is a multiplicity of abnormalities which might affect almost any tissue or organ of the body. Turner originally described webbing of the neck (pterygium colli) and cubitus valgus, but many other defects have been added. The extremities might show syndactylism, wrist deformities, pes cavus, laxity of the joints, dystrophic nails, e.g., koilonychia, or curving 5th fingers. Peculiar oedematous swellings (to be discussed later) affect bizarre situations in an intermittent fashion. Various types of chondro-dystrophy have been described, as have osteogenesis imperfecta tarda, spina bifida occulta, abnormal ribs and fused vertebrae. The eyes might manifest squints, ptosis, cataract or prominent epicanthic folds. Coarctation of the aorta is a well-known association, the significance of which is to be discussed below. Hypertension is found - sometimes without demonstrable coarctation. Mental defects, deaf-mutism and cranial nerve palsies are seen in some. The skin frequently shows numerous pigmented moles or naevi; aplasia of muscles sometimes occurs. Renal lesions have been demonstrated by pyelography in 5 of 8 patients (Hartling, 1955).

Ocular defects, asymmetry, a hypoplastic mandible and triangular-shaped mouth combine to give the face a characteristic appearance in many cases - a physiognomy described as "bec de lievre" or "gueule de loup" (hare beak or wolf jaw).

Rossi and Cafliesch (1951) published a paper entitled "The Pterygium Syndrome". Their cases showed multiple malformations including pterygium formation (webbing). They subdivided this syndrome into several groups, according to the type and distribution of the lesions. One of these groups was Turner's syndrome, which, in addition to webbing of the neck, showed sexual infantilism as a necessary criterion.

These malformational anomalies generally do not occur together. Individual patients tend to show varying combinations - and, in fact, cases of proved gonadal dysgenesis have been noted without obvious congenital abnormalities of this type.

3. NUCLEAR "SEXING"

In 1949, Barr and Bertram published a report describing a morphological distinction between neurones of the male and female cat. This finding did not arouse much interest, until in 1953 Moore et al. demonstrated a similar sex difference in the skin cell nuclei of man, and proposed certain clinical applications of the test.

In female skin-cells these authors were able to show small, dark masses situated at the periphery of the nuclei (Figure 1.03). These masses were not seen in every cell; but, in 50 normal females, they were observed in 52 - 83% of the nuclei; in 50 normal males, on the other hand, similar masses were seen in 1 - 14% of nuclei. It was inferred that these heterochromatic masses represented the visible sex chromatin of the cells (from their staining characteristics they were shown to consist of deoxyribonucleic acid). This was the first indication of a discernible difference between the resting or interphase nuclei of male and female cells. The visibility of the female chromatin mass was attributed to its larger size - due to the presence of the XX chromosome pair. The lack of visibility of male sex chromatin was thought to be due to its smallness - the size of Y chromosomes being negligible compared to that of X.

Barr, himself, (1956) recommends caution in ascribing this heterochromatic nuclear mass to sex chromatin or direct attributes of XX chromosomes. Nevertheless, indirect evidence for this is strong and it appears reasonable to equate the presence of this mass in

a high proportion of cells with "genetic femaleness"; whereas absence or paucity of these masses implies "genetic maleness". Support for this concept is derived from the unfailing demonstration of the expected nuclear pattern in normal individuals. Only in subjects with abnormal sexual development has a discrepancy been found between "clinical sex" and "genetic sex" as determined by this chromatin-counting method.

Since these original observations many workers have confirmed this sex difference, utilising skin biopsy or other techniques. Thus, distinctive chromatin masses have been noted in oral or vaginal mucosal cells, in polymorphonuclear leucocytes (Figure 1.04) and, even, in the epithelial cells obtained from a centrifuged urinary deposit ! (Hunter et al. 1954; Emery and McMillan, 1954; Marberger and Nelson, 1954; Marberger et al. 1955; Carpentier et al. 1955 and 1956; Davidson and Smith, 1954; Moore and Barr, 1955; Herrmann and Davis, 1956; Dixon and Torr, 1956; Sun and Rakoff, 1956; Briggs and Kuppermann, 1956; Greenblatt et al. 1956). Excellent reviews of the techniques and applications of nuclear sexing have been published by Lennox, 1956, Davidson and Smith, 1956, and Nelson, 1956. These and other authors testify to the importance of these "sexing" methods in the study of conditions of abnormal sexual development.

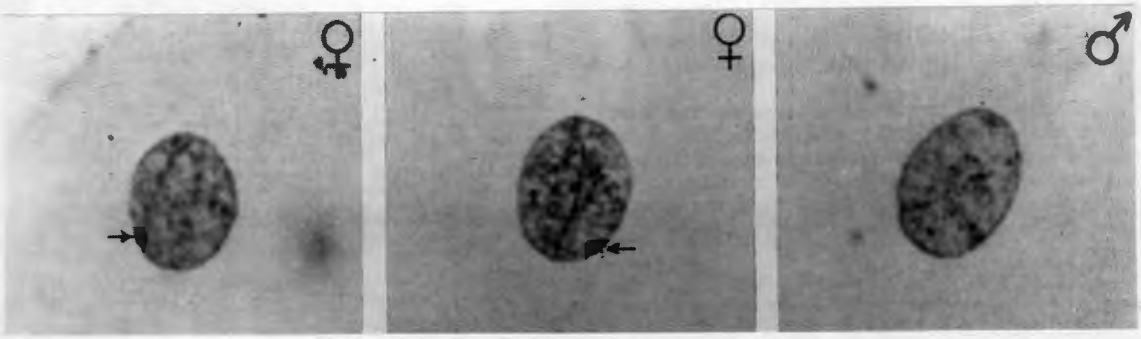


Figure 1.03

Sex Chromatin in Epithelial Nuclei

The arrows point to the peripheral nuclear masses in female cells. These are not seen in the male nucleus.

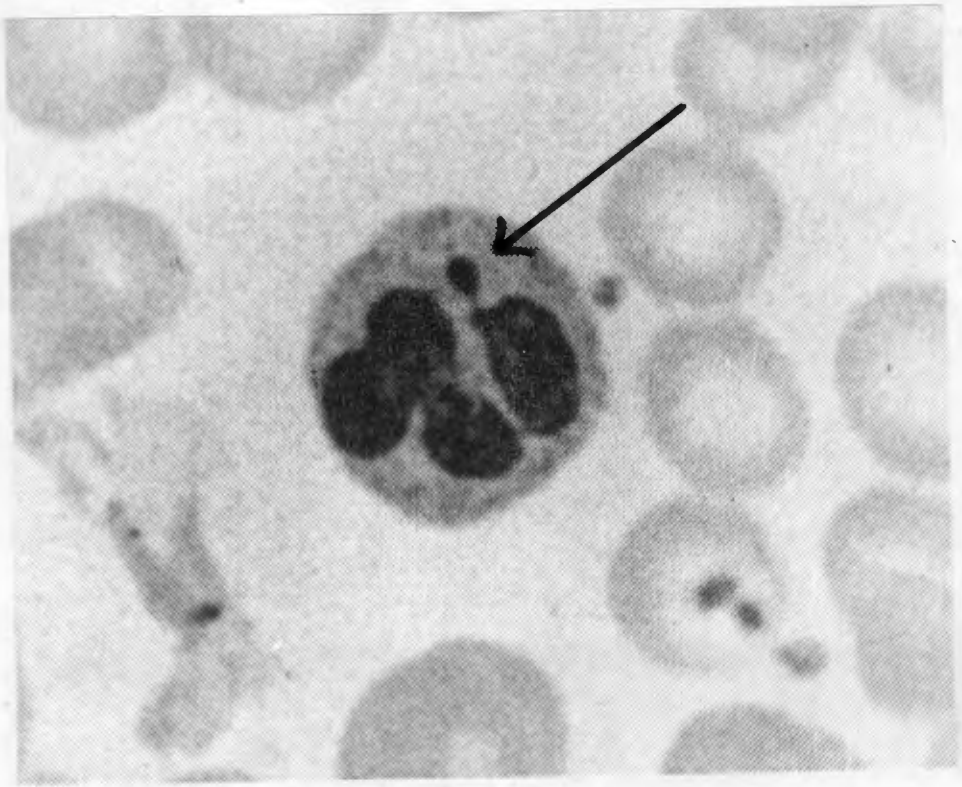


Figure 1.04

Sex Chromatin in a Polymorphonuclear Leucocyte

The arrow points to the typical "drumstick" projection from a female polymorphonuclear leucocyte.

4. THE APPLICATION OF NUCLEAR "SEXING" TO GONADAL DYSGENESIS

Polani and his co-workers were impressed by the frequent association of coaretation of the aorta with cases of Turner's syndrome. This cardio-vascular anomaly is generally stated to occur predominantly in males. They "sexed" the skin of 3 patients with Turner's syndrome and coaretation of the aorta, and found the male nuclear pattern. (Polani et al. 1954.) Confirmation of their findings was reported shortly afterwards by Wilkins et al. (1954).

This extraordinary observation evoked renewed interest in the subject of genetic sex and sex differentiation. It became necessary to explain why these genetic males developed the physical properties of females. Reference to the experimental work of Jost and others appeared to provide an explanation. (Jost 1953)

Normally in growing embryos the gonads are identical in both sexes up to the 6th week. If the embryo is to become male, the gonads begin to differentiate into testes in the 7th week; if the sex is to be female, ovarian differentiation starts in the 10th week. In the undifferentiated stage, two pairs of genital ducts run from the gonad to the urogenital sinus - the Wolffian or mesonephric ducts and the Müllerian ducts or oviducts. These ducts themselves are not ambisexual. The Wolffian ducts are capable of differentiating into the epididymis, vas deferens and seminal vesicles in the male, the Müllerian ducts into the fallopian tubes, uterus and vagina in the female. Normally, at the stage of genital duct differentiation (early in the third month), the

Müllerian duct begins to degenerate, while the Wolffian duct derivatives are developed; conversely, in the female, the Wolffian duct disappears and Müllerian duct elements become prominent.

In 1953, Jost reported the results of his own and other workers' experiments, during which surgical removal or X-Ray ablation of foetal gonads had been accomplished at varying stages of embryonic development in different animal species. In genetic females, these operations were followed by normal or near-normal female development, i.e. persistence of the Müllerian duct derivatives and retrogression of the Wolffian duct; the external genitalia become female in type.

In male foetuses the results were startling and informative. If the operation were performed before genital tract differentiation had occurred, the foetus assumed a completely female form - retrogression of the Wolffian duct, persistence of the Müllerian duct and feminisation of the external genitalia. If the operations were performed a day or two later, forms of "pseudohermaphroditism" were produced, with partial feminisation, some prostatic development and hypospadias. Castration at a still later stage was attended by normal or near-normal male differentiation.

Thus, it appeared that genital differentiation along normal male lines was dependent upon the presence of functioning testes. Without this, feminisation occurred, whether the foetus was destined genetically to be male or female.

This appeared to provide an interpretation of Polani's curious findings. The "female" cases of Turner's syndrome who showed male nuclear patterns, were, in fact, genetic males. Some form of "castration" or failure of testicular development had occurred at a stage of embryonic life before the genital tract had differentiated. In consequence these subjects assumed the female, or neuter, form and their true genetic sex was exposed by the skin test of Barr.

Polani's observations and their explanation in the light of these experiments suggested that gonadal dysgenesis was, in fact, a form of intersexual development. The term "ovarian agenesis" could no longer be applied to the syndrome, since many of these patients actually had "testicular agenesis" - "gonadal agenesis" seemed a more suitable designation. Grumbach et al. (1955) objected even to this term and pointed out that, since some rudimentary mesonephric elements of the gonad might appear in the genital ridge, "dysgenesis" was a more correct description than "agenesis". The condition originally called "Turner's syndrome" has thus become known as "gonadal dysgenesis" and the investigations of Barr, Polani and Jost have led to a clearer understanding of its pathogenesis.

C H A P T E R XI

REPORT OF A SERIES OF

CASES OF GONADAL DYSGENESIS

CHAPTER IX

REPORT OF A SERIES OF

CASES OF GONADAL DYSGENESIS

The following case-reports describe patients who have been seen at the Endocrine Clinic, Groote Schuur Hospital, in the past three years. Not all cases of primary amenorrhoea have been seen at this Clinic; it is likely that some patients have presented to other clinics, where they have been treated. The number of patients in this series testifies to the frequency of occurrence of gonadal dysgenesis. Three cases have been included despite lack of proof of the diagnosis; reasons for considering these patients to have gonadal dysgenesis are discussed in Part I, Chapter VI; their inclusion is partly motivated by the desire to illustrate some of the difficulties in establishing the diagnosis.

Case I : S. L. White female aged 18 years. (Figure 2.01)

The patient complained of primary amenorrhoea and shortness of stature. She was short and dumpy with flat breasts, pin-point nipples and moderate pubic and axillary hair. There was webbing of the neck, asymmetry of the eyes, a congenitally blocked naso-lachrymal duct, low nuchal hair-line (Figure 2.02), asymmetrical 12th ribs and a Scheuermann type of vertebral abnormality. The skin sex pattern was male.

Urine F.S.H. was positive at 96 mouse units. (Normal up to 24 m.u.)

Treatment with stilboestrol achieved excellent results. (Figure 2.03). The breasts enlarged, the contours feminised and regular vaginal bleeds ensued. A timid, retiring girl with little interest in her appearance now began to curl her hair, apply cosmetics, and behave in a female manner. On a recent visit, she brought with her a newly-acquired husband, with whom she appears to be leading a normal married life, with good libido and enjoyment of the sexual act.

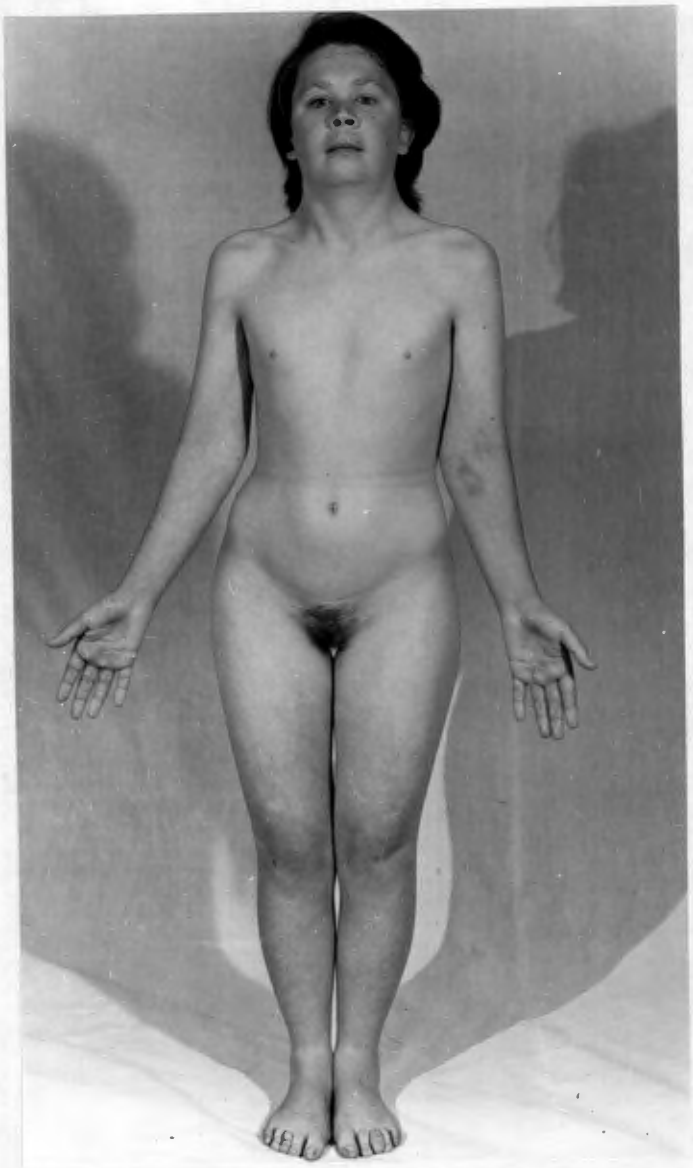


Figure 2.01

Case 1 : S. L.

Note flat breasts, small nipples, moderate amount of pubic hair and webbing of the neck.

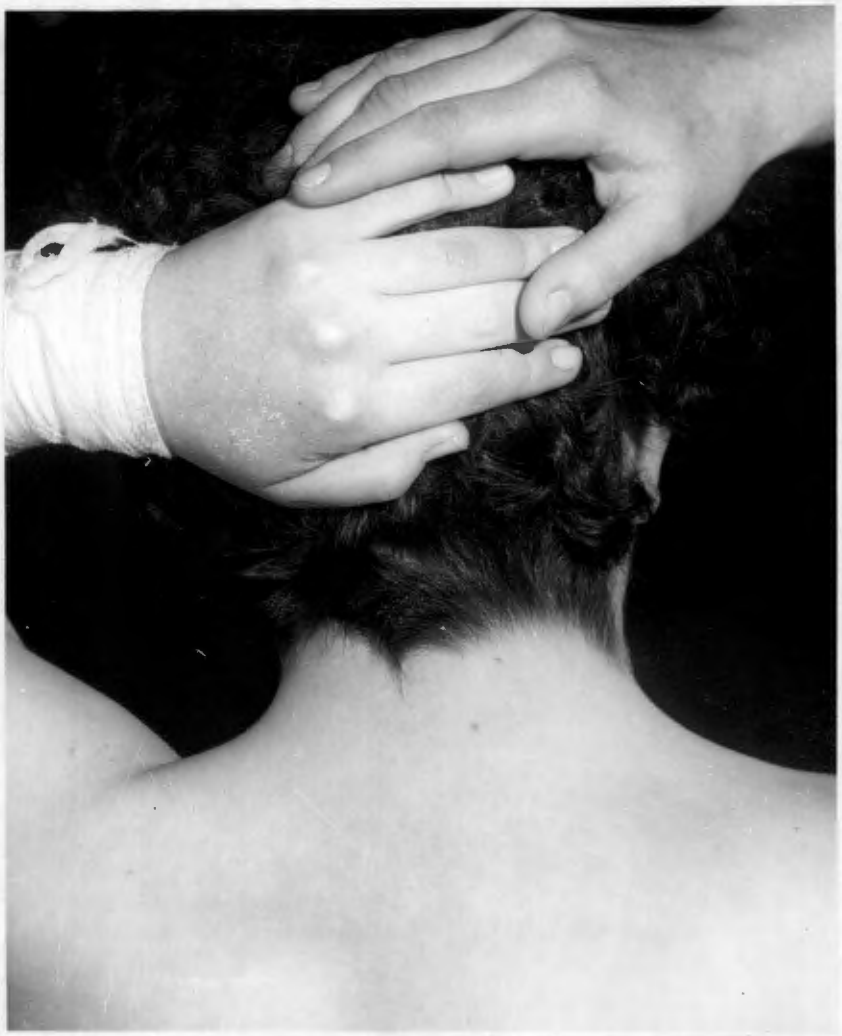


Figure 2.02

Case I : Sch.

This shows the low nuchal hair-line. On the right side webbing of the neck may be noted.

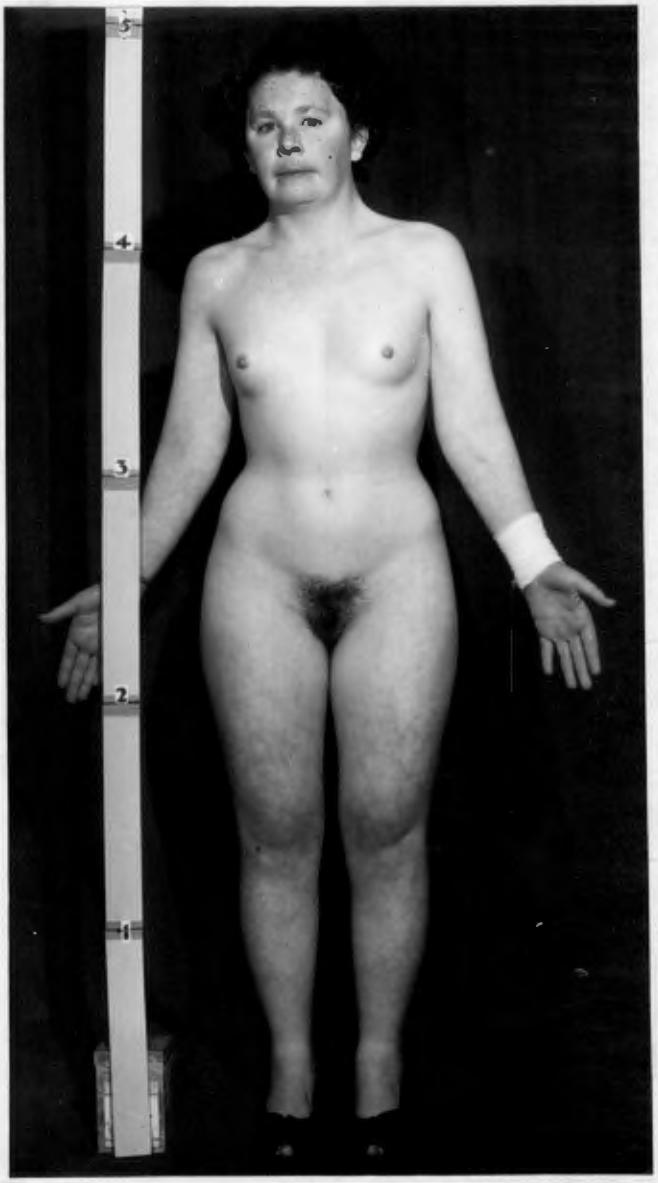


Figure 2.03

Case I : S.L. after oestrogen therapy

Note enlargement of breasts, nipples and areolae, feminisation of the contours. The hair shows signs of attention.

Case XI : J.M. Coloured female aged 17 years. (Figure 2.04)

She complained of primary amenorrhoea and lack of development of secondary sex characters. She was short and thick-set with flat breasts, inverted nipples, absent pubic and axillary hair, and infantile genitalia. There was asymmetry of the eyes, strabismus and nystagmus. X-Rays showed slight generalised osteoporosis, abnormal 12th ribs, and an absent lumbar vertebra. The nuclear pattern was male.

Urine F.S.H. was positive at 192 m.u.

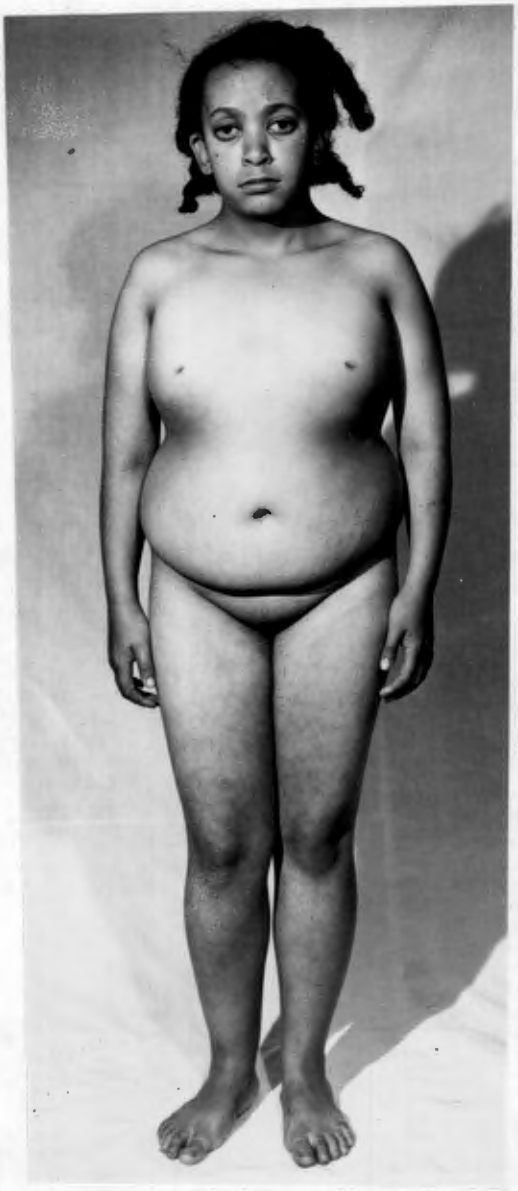


Figure 2.04

Case II : J.M.

Note thick-set build, flat breasts with small well-separated nipples and absence of pubic hair.

Case III : L. R. White female aged 9 years when first seen in 1952

(Figure 2.05)

The patient had always been small for her age. She had numerous congenital anomalies, including webbing of the neck, low hair-line, small 5th finger-nails, a high, arched palate, extra epiphyses of the phalanges and coarctation of the aorta.

At birth she had curious, transient swellings of the limbs, which have occurred at intervals until the present day. A diagnosis of Turner's Syndrome was made when she was first seen and it was anticipated that she would exhibit infantilism. An original F.S.H. excretion was negative at 12 m.u. She had a male nuclear pattern.

In 1956, the patient had no breast development and menstruation had not appeared. The F.S.H. excretion was positive at 48 m.u. confirming the diagnosis of ovarian failure.

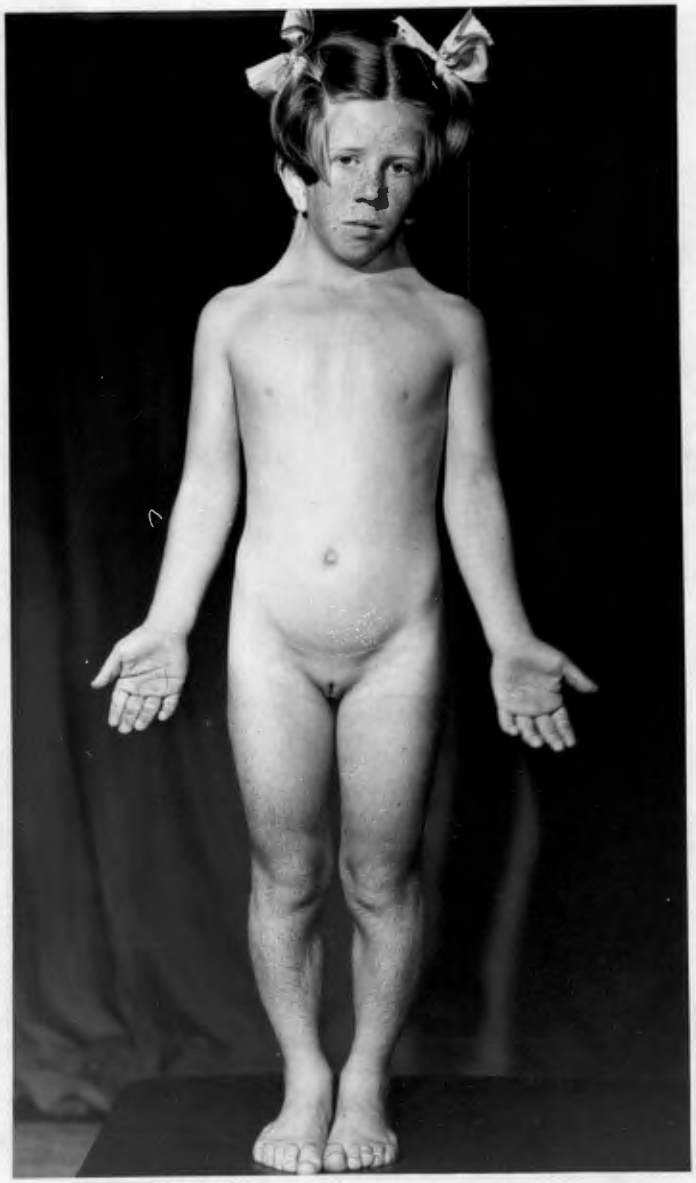


Figure 2.05

Case III : L.R. aged 9 years

This illustrates the stocky build, "shield"-chest and webbing of the neck.

Case IV : E. J. Coloured female aged 16 years. (Figure 2.06)

This patient had pneumonia in early childhood which was followed by severe, chronic suppurative bronchiectasis. She presented with primary amenorrhoea and general lack of development.

Her height was 4' 5½", the breasts were absent, pubic and axillary hair was scant, and the genitalia infantile. Bilateral corneal opacities and numerous pigmented moles were present (Figure 2.07). The nuclear pattern was female.

The chronic pulmonary sepsis provided an alternative cause for her retardation but the finding of a high urinary gonadotrophin excretion (positive at 96 m.u.) confirmed the diagnosis of gonadal dysgenesis.

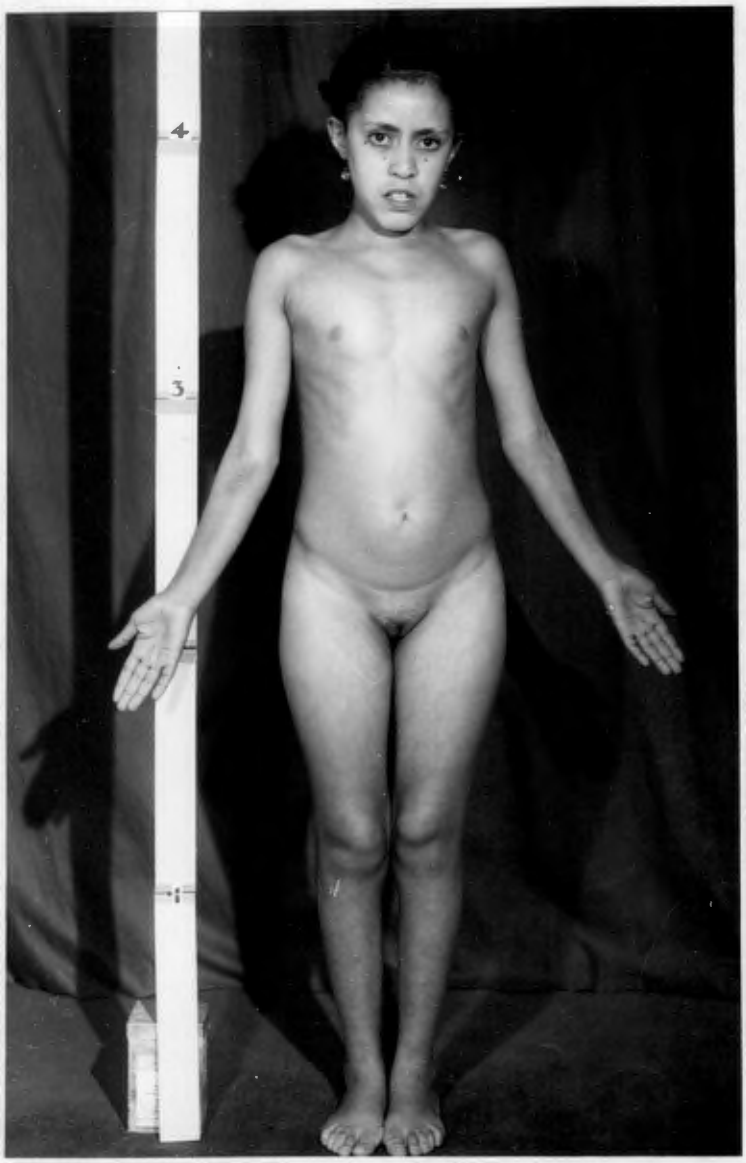


Figure 2.06

Case IV : E.J.

Note absence of breast development and of pubic hair.

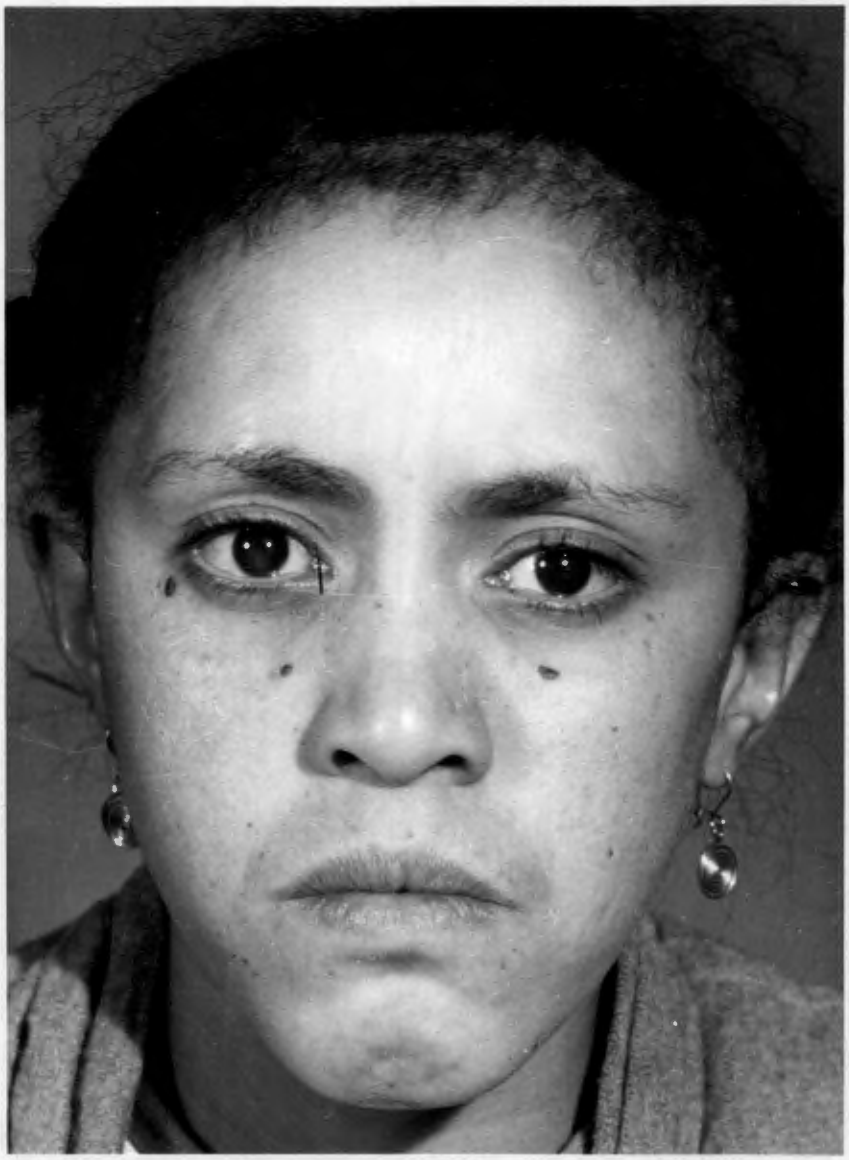


Figure 2.07

Case IV : E.J.

Face showing numerous pigmented moles ;

corneal opacity may be seen in right eye.

Case V : M. du T. White female aged 21 years. (Figures 2.08 and 2.09)

The patient presented with primary amenorrhoea, and was 4' 7½" tall. Her eyes were asymmetrical, the mandible hypoplastic, the palate arched and the neck short and thick.

Mammary development was surprisingly good, but the nipples were small and the areolae pale. Sex hair was decreased and the genitalia were infantile.

Because of an original P.S.H. level positive at 6 m.u. but negative at 12 m.u., hypopituitarism was favoured. However, other tests of pituitary function were normal and, as a result of the skin sexing test, laparotomy was undertaken. This displayed the typical appearance of gonadal dysgenesis; histology of the vestigial gonads showed "adult ovarian stroma partly lined by cells resembling germinal epithelium". No follicles were seen, but groups of cells were observed which resembled ovarian hilus cells or Leydig cells of the testis.

Well-developed breasts are rarely reported in proven cases of gonadal dysgenesis. Breast biopsy was accordingly undertaken. A large core was removed at depth from the central part of the breast. Histologically, this showed the presence of fat only, there being no trace of functioning mammary tissue.

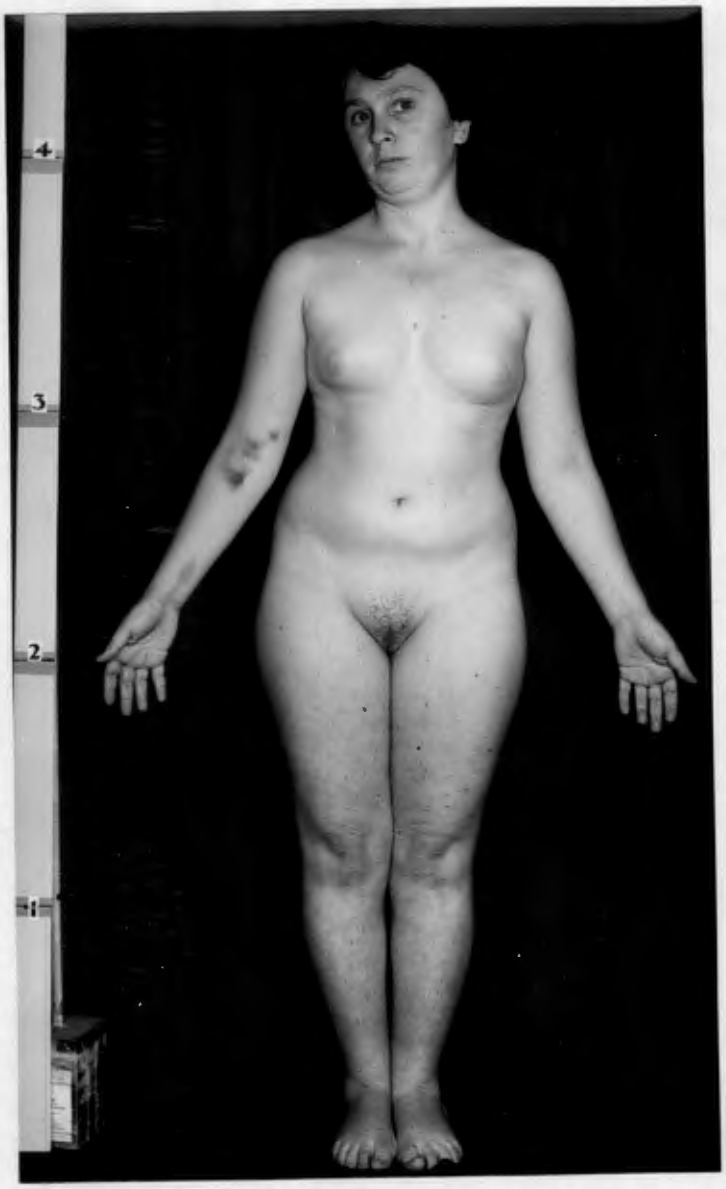


Figure 2.08

Case V : M. Gu F.

The breasts are apparently well-developed; note poor pubic hair growth and numerous pigmented areas on thighs.

Figure 2.09

Case V : M. Gu F.

Note absence of axillary hair. The breast size is well illustrated in this view. On biopsy no functioning mammary tissue was found (see text).

Case VI : E. P. White female aged 22 years. (Figures 2.10 and 2.11)

This patient had been a lifelong friend of Case V. The two girls had lived in the same small South African town, had been in the same class at school and continued their friendship subsequently. It was remarkable that Case VI should present with the same complaints of primary amenorrhoea and lack of height.

She was 4' 6" tall and had moderate breast development with infantile nipples and pale areolae; axillary hair was absent and pubic hair scant. The genitalia were infantile. There were no skeletal anomalies.

P.S.H. excretion was negative at 24 and 48 m.u. on three separate occasions. In view of this, hypopituitarism was diagnosed. The presence of numerous pigmented moles, particularly on the thighs, led to suspicion of gonadal dysgenesis. The male skin sex pattern provides strong supportive evidence of this diagnosis.

After eighteen months of oestrogen therapy there was further enlargement of the breasts. Biopsy at this stage was reported - "although no lobule form is evident, the changes present suggest some degree of cyclical activity".

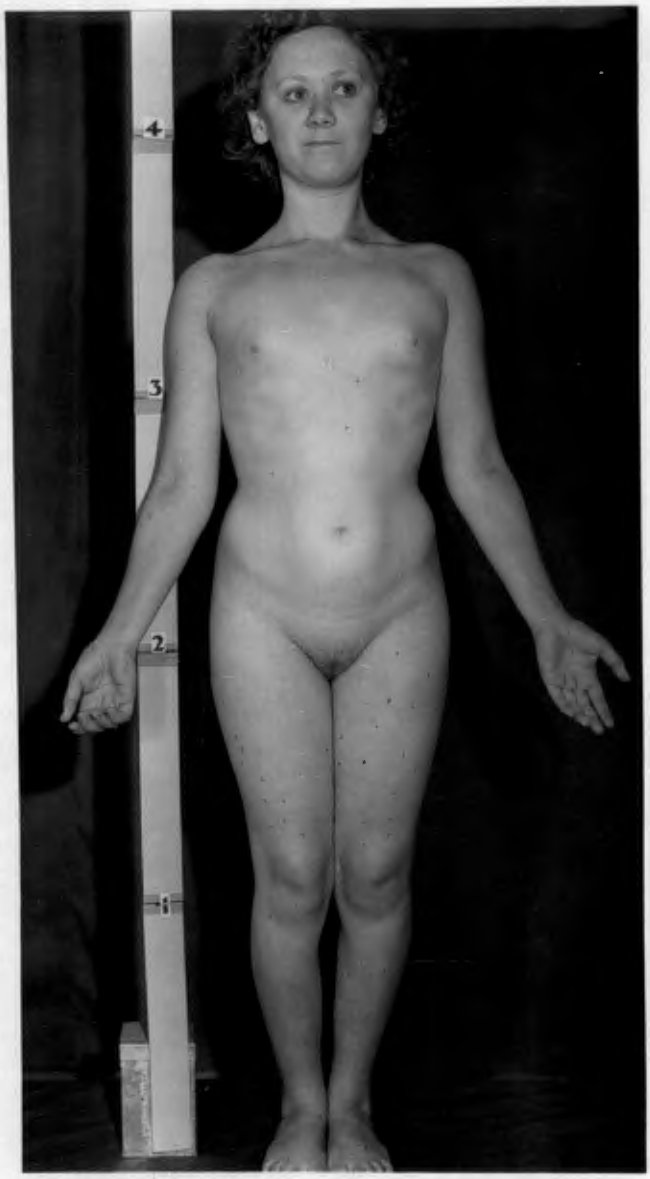


Figure 2.10

Case VI : M. D.

Note poor pubic hair and numerous pigmented moles which suggested the diagnosis.

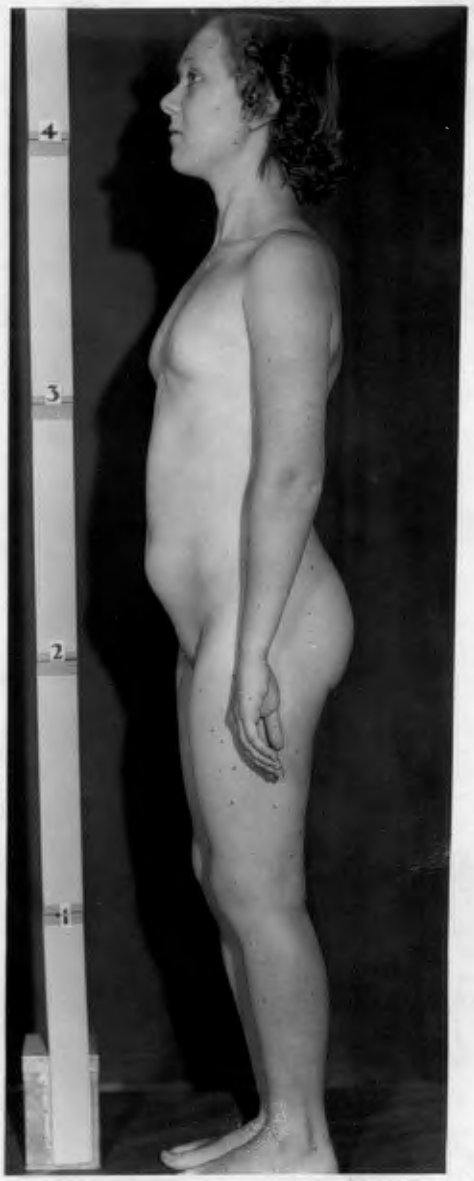


Figure 2.11

Case VI : M. D.

The lateral view shows moderate breast development. This picture was taken before therapy; biopsy was done after 18 months of oestrogen.

Case VII : J. T. European female aged 21 years.

This patient, an intelligent and attractive nurse, consulted a gynaecologist because of secondary amenorrhoea. She claimed that the menarche had occurred at 15 years and menstrual bleeds ensued at one to three month intervals for the following five years. Blood loss was moderate in amount. At the age of 20 years these bleeds ceased. The vaginal bleeds were not accompanied by any abdominal cramps or discomfort.

There was no history of mumps and the patient denied the occurrence of hot flushes.

The patient was 4'10" tall with a normal, pleasant facial appearance. (Figure 2.12). The breasts were hypoplastic (Figure 2.13), the nipples inverted and the areolae pale. The chest was somewhat broad, but there was none of the pathognomonic congenital stigmata of Turner's syndrome.

Urine F.S.H. excretion was positive at 96 m.u. The skin sex pattern was male.

Laparotomy was undertaken and, surprisingly, disclosed the typical appearance of dysgenetic gonads. Histology showed

stroma resembling that found in adult ovaries, but this was scanty in amount. Follicles and undoubted interstitial cells were not seen.

Oestrogen therapy (one mgm Stilboestrol daily) has resulted in considerable improvement. The breasts have grown satisfactorily (Figure 2.14); the nipples and areolae are darker and more prominent. In addition, cyclical vaginal bleeds occur and the patient feels far more energetic and alive.

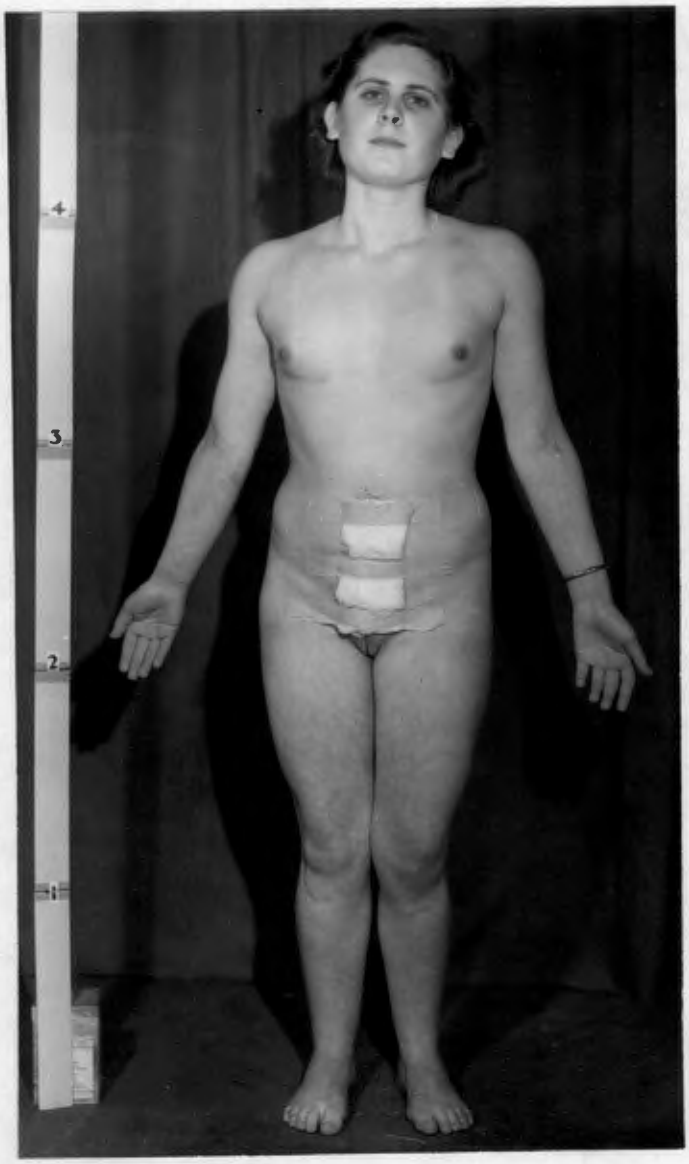


Figure 2.12

Case VII : J. T.

The facial attractiveness and "normal" appearance did not suggest gonadal dysgenesis.

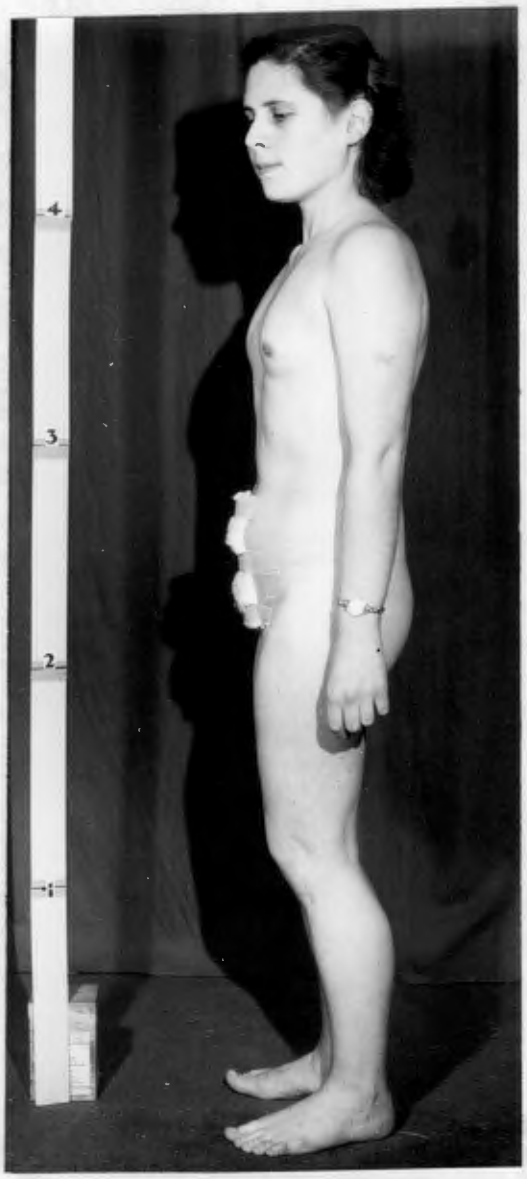


Figure 2.13

Case VII : J. T.

The lateral view shows the hypoplastic breasts.

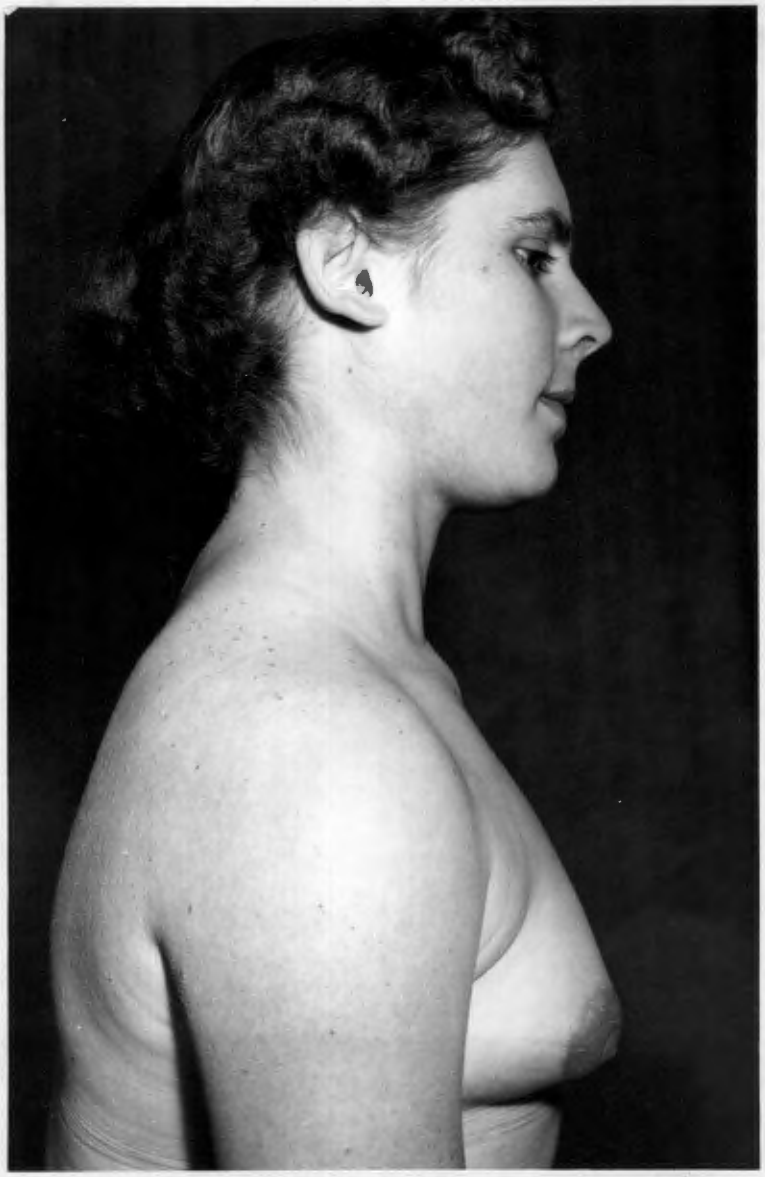


Figure 2.14

Case VII : J. T. after oestrogen therapy

Note enlargement of breasts and large, dark areolae.

Case VIII : M. R. Coloured female aged 30 years. (Figure 2.15)

This patient suffers from manic depressive psychosis. During the course of electroconvulsive therapy she sustained a fractured spine. X-Rays showed a pathological degree of osteoporosis.

She had never menstruated, was 4' 6" tall, had a thickset chest with absent breasts and infantile nipples; the genitalia were infantile.

On three separate occasions the urinary F.S.H. excretion has been found negative at 24 m.u. The skin cell nuclear pattern was male, which once again makes the diagnosis of gonadal dysgenesis highly probable.

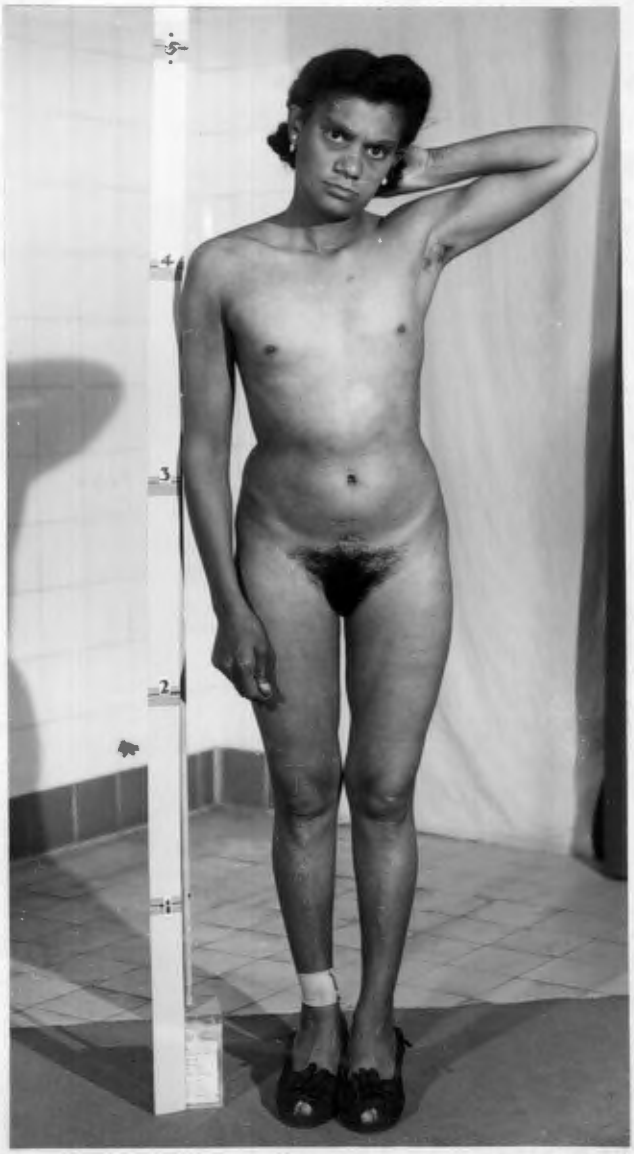


Figure 2.15

Case VIII : M. R.

The breasts are undeveloped, axillary hair sparse, but pubic hair abundant.

Case IX : J. J. White female aged 40 years. (Figure 2.16)

This short (4' 6") obese female, with shape resembling a cottage loaf, presented with chronic backache. She had never menstruated. The breasts were composed of fat only and the nipples were inverted. There was no axillary hair but moderate pubic hair. Genitalia were infantile.

The neck was short, thick and webbed, the hair-line exceedingly low; no other anomalies were noted. X-Rays revealed gross osteoporosis with partial collapse of the first lumbar vertebra.

Urine F.S.H. excretion was positive at 96 m.u. The skin cell nuclei showed a male pattern.

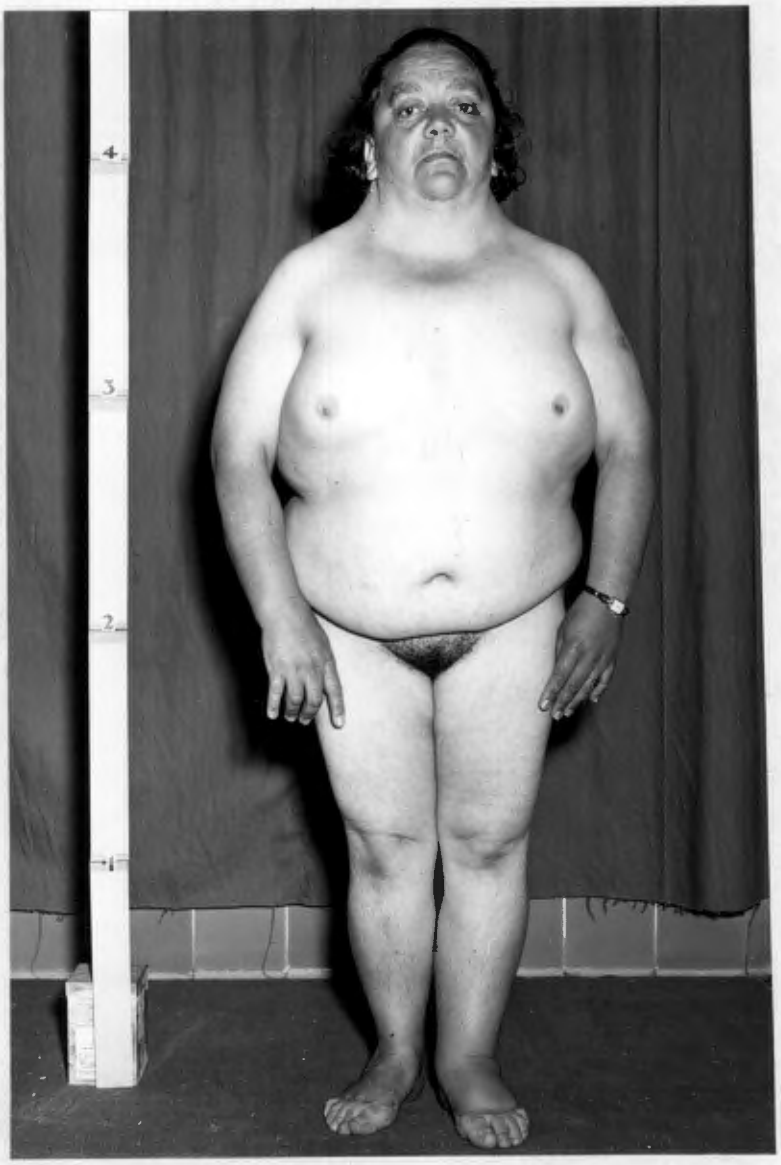


Figure 2.16

Case IX : J. J.

Note the short, thick, webbed neck. The "breasts" felt puffy without palpable mammary tissue; the nipples are inverted.

Case X : E. A. Coloured female aged 14 years. (Figure 2.17)

She had always been small for her age and was brought to hospital on this account. Menstrual bleeding had not occurred. At the age of three years there had been an episode of painless swellings of the knees and wrists; X-Rays at the time were normal.

She was 3' 8" tall. There were no secondary sex characters. The external genitalia showed comparatively well-developed labia majora and clitoris but poor labia minora.

Urine F.S.H. excretion was negative at 6 m.u. on two occasions. Skin biopsy provided apparent proof of gonadal dysgenesis.

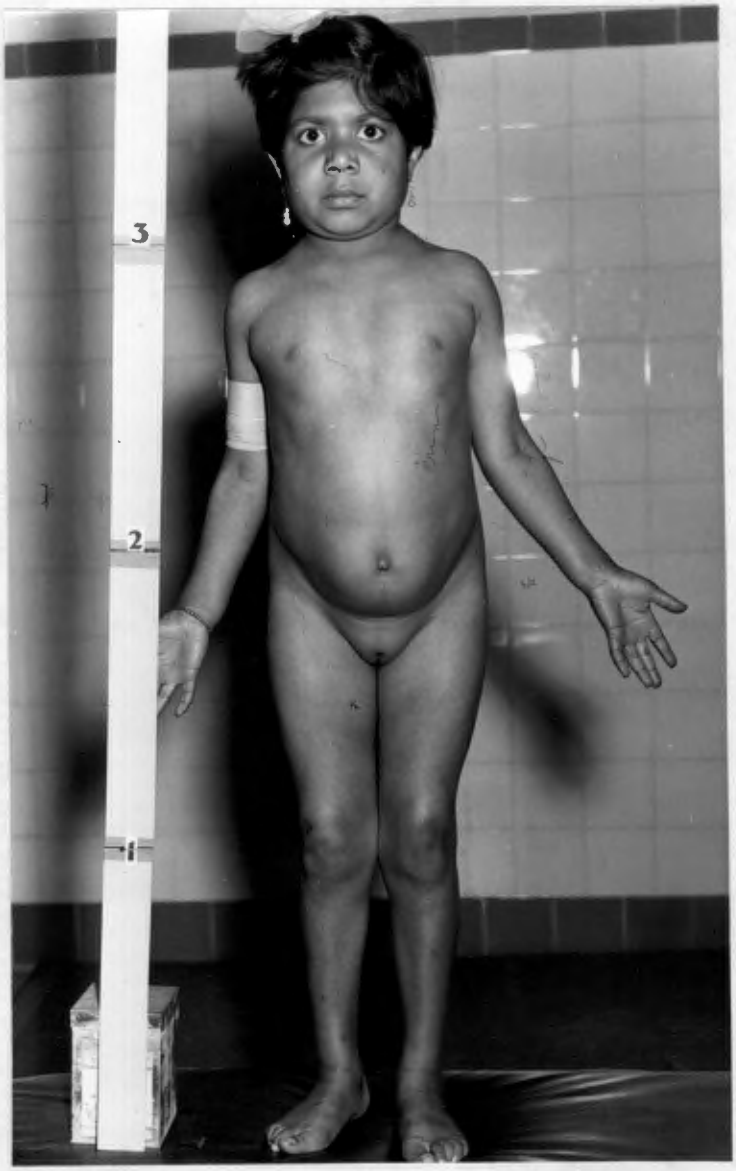


Figure 2.17

Case X : R. A.

Note the small, undeveloped physique.

Case XI : S. W. White female aged 22 years. (Figure 2.18)

Was admitted for plastic repair of a hare-lip. She was 4'10" tall, had never menstruated, had a hypoplastic mandible, very numerous pigmented moles and freckles and a rather low nuchal hair-line.

The breasts were underdeveloped, axillary and pubic hair moderate in amount; the external genitalia were relatively infantile.

P.S.H. excretion was positive at 96 m.u.

The skin biopsy again confirmed the diagnosis.

Figure 2.18

Case XI : S.V.

The breasts are underdeveloped;
pubic hair growth is fair.

Case XII : M. de J. White female aged 22 years. (Figures 2.19 and 2.20)

This rather attractive school-teacher presented with primary amenorrhoea. Her height was 5' 6½" and, apart from flat breasts, she appeared a perfectly normal female - axillary and pubic hair being moderately profuse. The genitalia, however, were infantile.

Urine F.S.H. excretion was strongly positive at 6 m.u. but negative at 96 m.u. Laparotomy was undertaken, and typical primitive gonadal ridges were seen. Histology showed ovarian stroma, no follicles, but aggregates of cells resembling ovarian hilus cells.

This was the only tall patient in the series, and the diagnosis was unexpected because of her normal, attractive appearance and her normal skin sex pattern.

Figure 2.19

Case XII : H. de J.

Showing normal height and thin, cumuchoid proportions.

Figure 2.20

Case XII : H. de J.

The flat breasts are well-shown in this view.

Case XIII : R. T. White female aged 12 years. (Figure 2.21)

Presented with failure to grow; she had been treated for tuberculous peritonitis for three months, although there was no real indication of any active organic disease at the time ! She was a mentally backward child.

Her height was 4' 3½" ; the facies was typical of gonadal dysgenesis with hypoplasia of the mandible and a "bird-like" appearance. There were no secondary sex characters.

She showed the interesting anomaly of a short fourth right metacarpal. (Figure 2.22) . Nuclear sex was female.

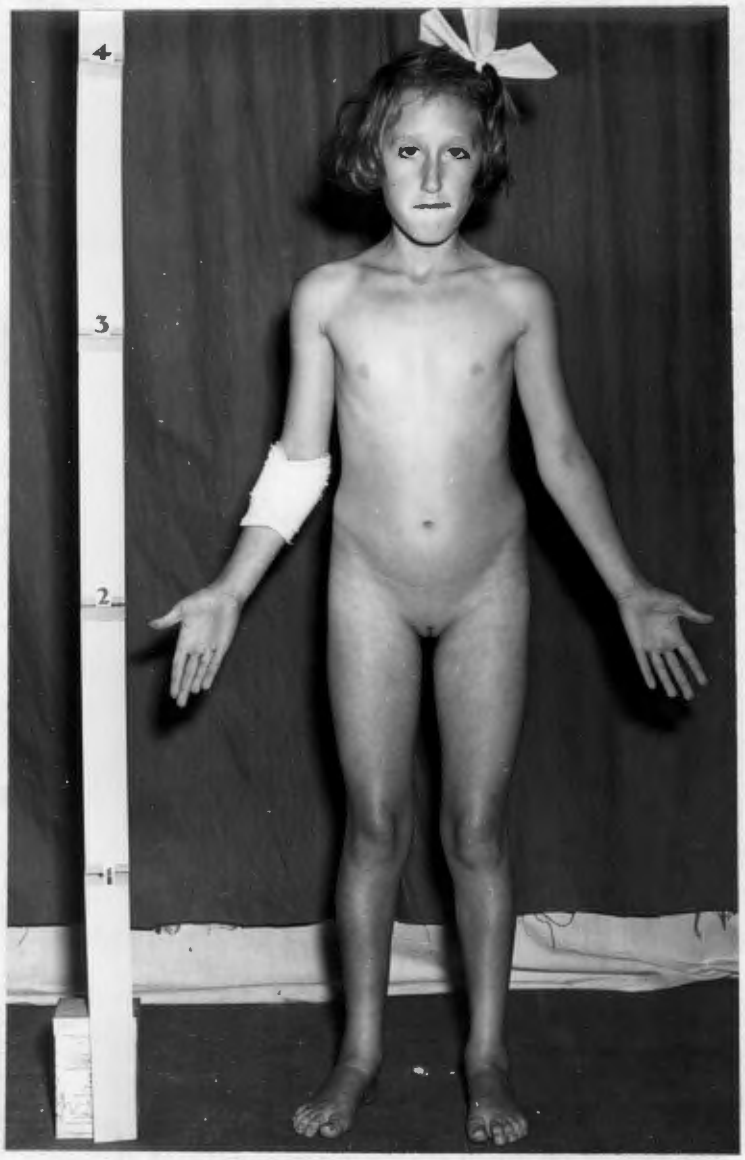


Figure 2.21

Case XIII : R. T.

The facies is asymmetrical and "bird-like",

the body poorly developed.

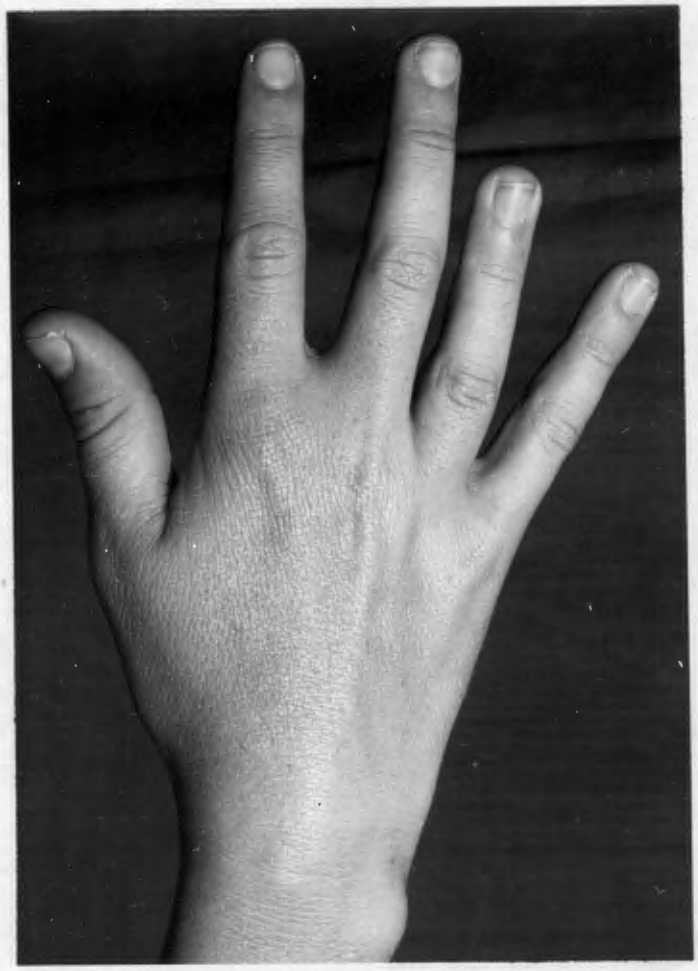


Figure 2.22

Case XIII : R. T.

This shows the small right fourth finger due to a short metacarpal.

Case XIV : J. S. White female aged 22 years. (Figure 2.23)

This nurse had never menstruated (apart from a scanty sanguineous discharge lasting one day), was 4' 9" tall, had webbing of the neck, a low hair-line, hypertension (B.P. 160/110) without apparent coarctation of the aorta, a slightly wide carrying angle, absent breast development, and infantile genitalia. She showed strikingly blue sclerotics. The nuclear pattern was male.

Figure 2.23

Case XIV : J. S.

The short, squat body-build is illustrated with webbing of the neck and hypoplastic breasts.

Case XV : K. H. White female aged 21 years. (Figure 2.24)

This short (4' 9") female had always been slightly retarded both physically and mentally; she had never menstruated.

The breasts were underdeveloped, although some functioning tissue was present; the genitalia were infantile.

There was a short metacarpal of the third left finger (Figure 2.25) and webbing between the 2nd and 3rd toes of each foot. Very numerous pigmented moles and cafe-au-lait patches of pigment were present. Urine F.S.H. excretion was 37 rat units. Nuclear pattern was female.

The diagnosis was proved by laparotomy.

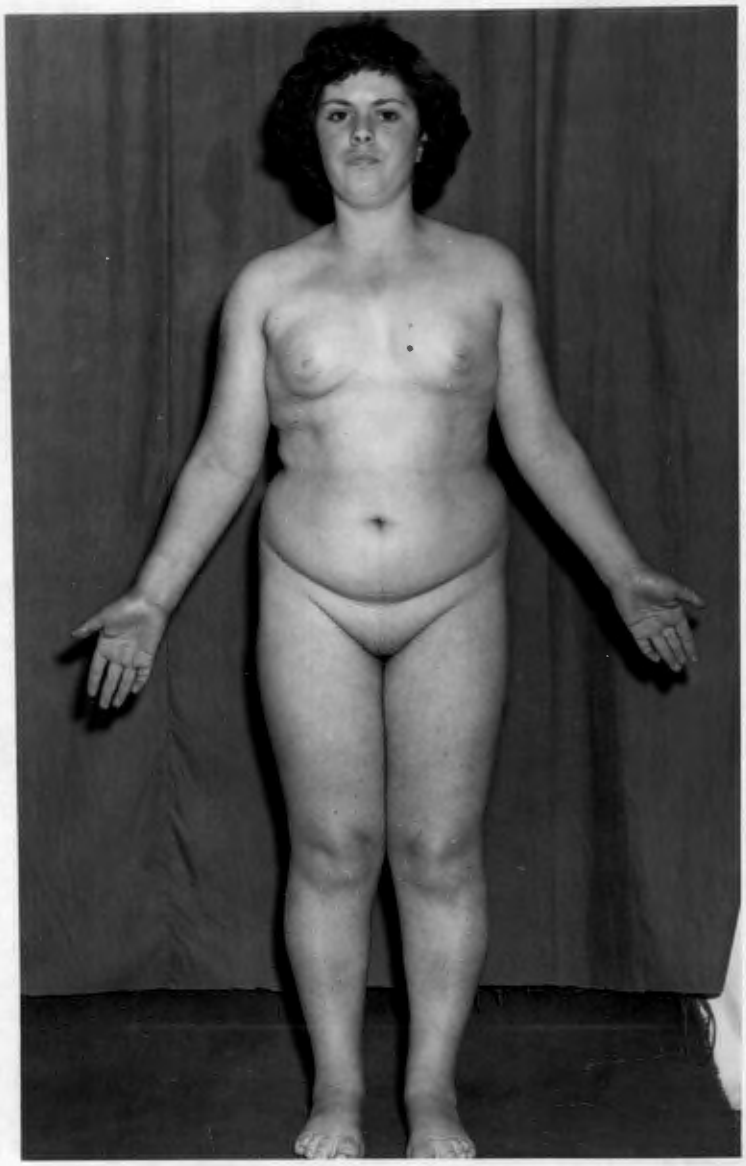


Figure 2.24

Case XV : K. H.

In this dumpy female, some breast tissue was felt.

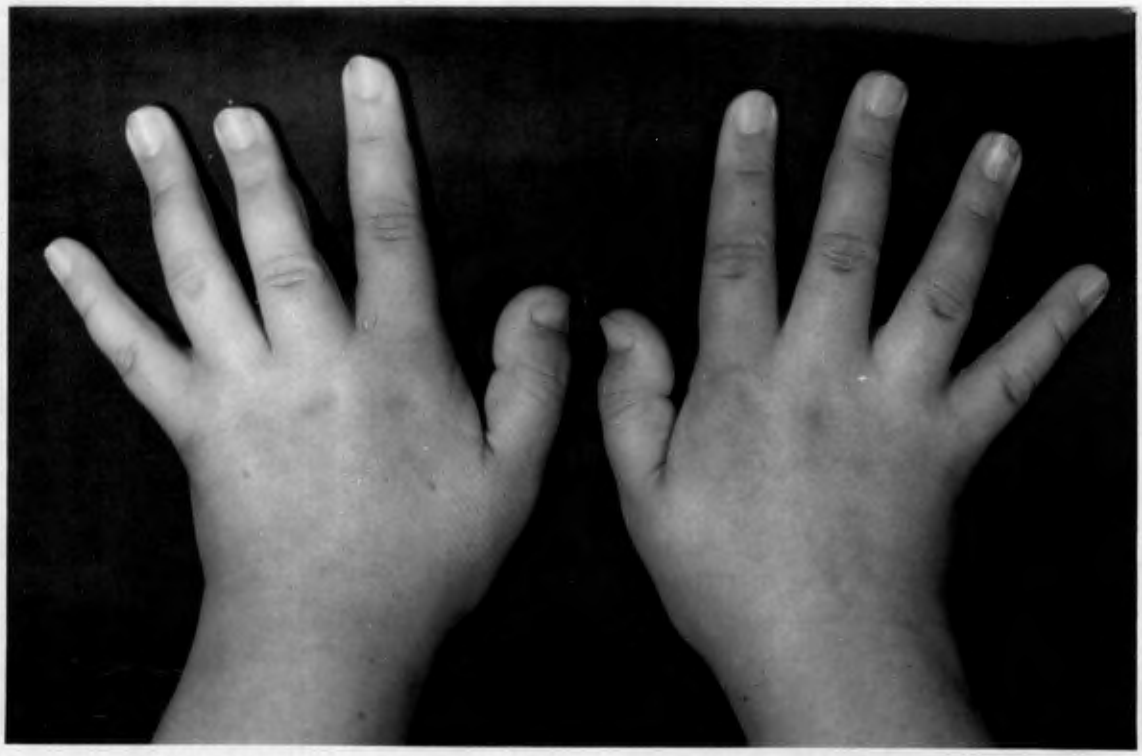


Figure 2.25

Case XV : I. E.

The left third finger is small due to shortness of its metacarpal bone.

Case XVI : R. L. Coloured female aged 17 years. (Figure 2.26)

Presented because of primary amenorrhoea and small stature.

She was 4' 5" tall and looked much younger than her years. Secondary sex characters were not present and there were no congenital anomalies.

X-Rays showed slightly delayed bone-age. Polymorphonuclear leucocytes showed a male pattern.

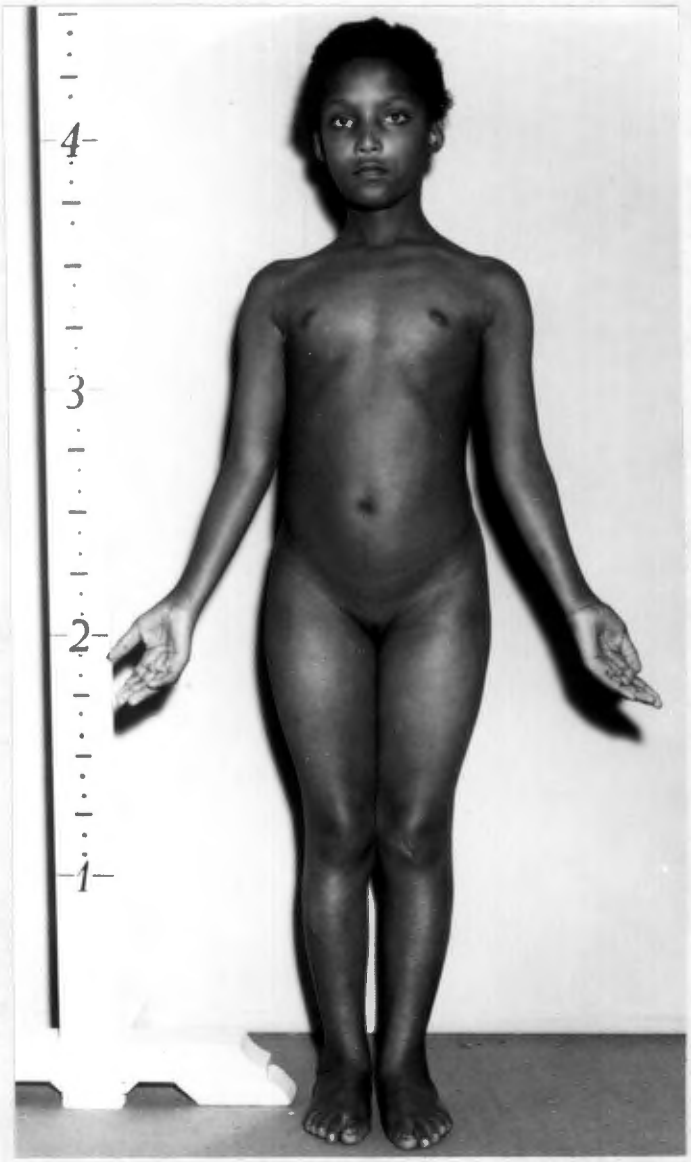


Figure 2.26

Case XVI : E. L.

Note the young appearance of this patient and the absence of secondary sex characters.

Case XVII : L. M. Coloured female aged 20 years. (Figure 2.27)

Was first seen at the age of 17 years complaining of primary amenorrhoea. Laparotomy disclosed typical vestigial gonads.

She was seen again 3 years later, when her height was 4'11". There was very poor mammary development with inverted nipples (Figure 2.28), sex hair was absent, and the external genitalia were infantile; no adnexae were felt and the uterus was minute. Dark moles were present on the face, but there were no other anomalies. The skin sex pattern was male.

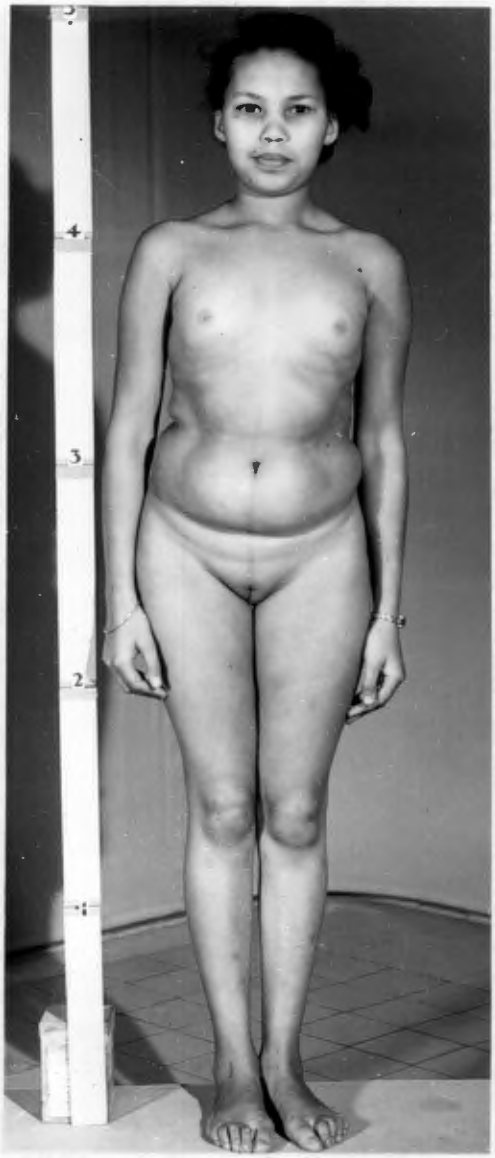


Figure 2.27

Case XVII : L. M.

Note poor mammary development and absence of pubic hair.

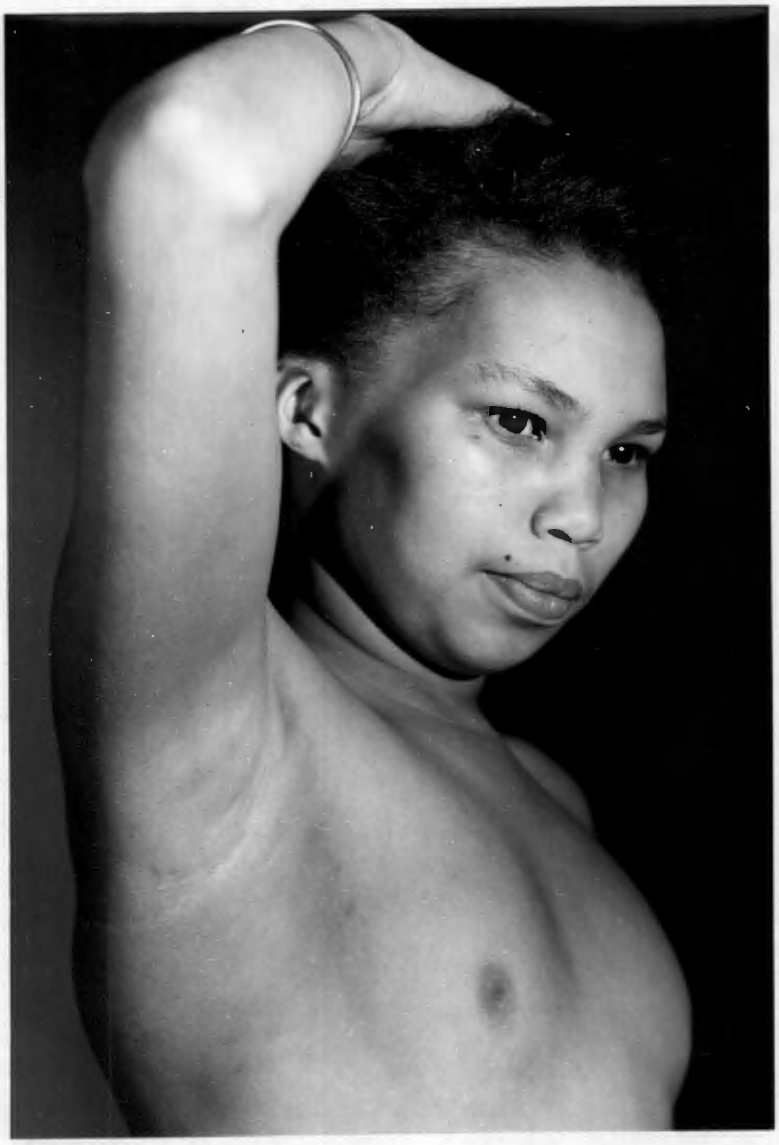


Figure 2.28

Case XVII : L. M.

This shows the absent axillary hair, poor breasts and inverted nipples.

Case XVIII : A. O. White female aged 52 years. (Figure 2.29)

This patient had sustained a fracture of the neck of the right femur following a trivial fall. She had never menstruated; axillary and pubic hair had always been poor and the breasts had failed to grow.

She was 5' 0" tall and had a curious, flat-faced appearance. Apart from lack of secondary sex characters, no abnormalities were found. The nipples were inverted.

X-Rays revealed an exceedingly gross degree of osteoporosis of the vertebrae (Figures 2.30 and 2.31). Blood and skin nuclear patterns were female.

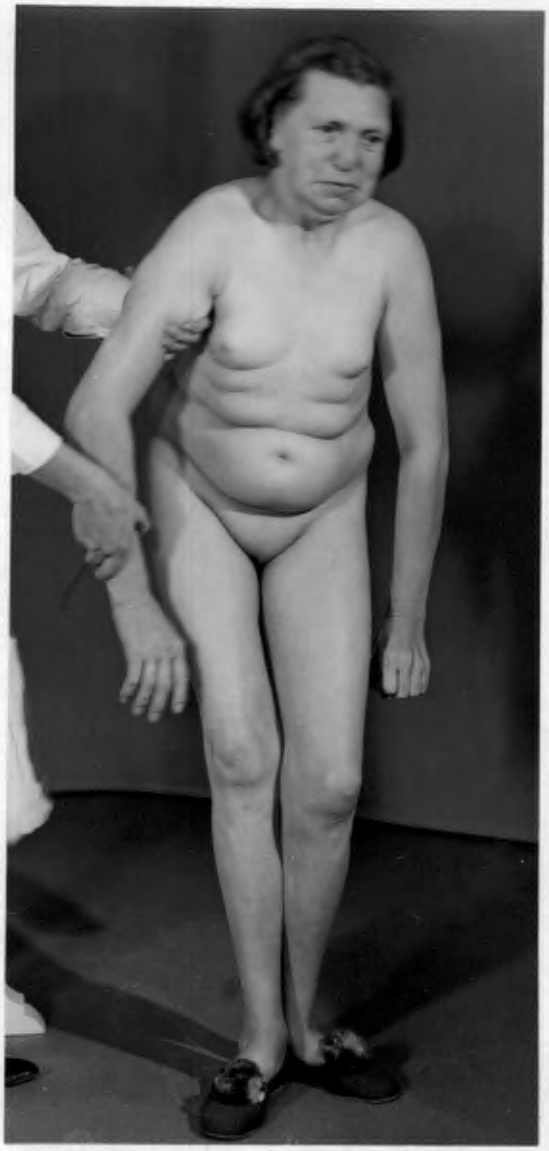
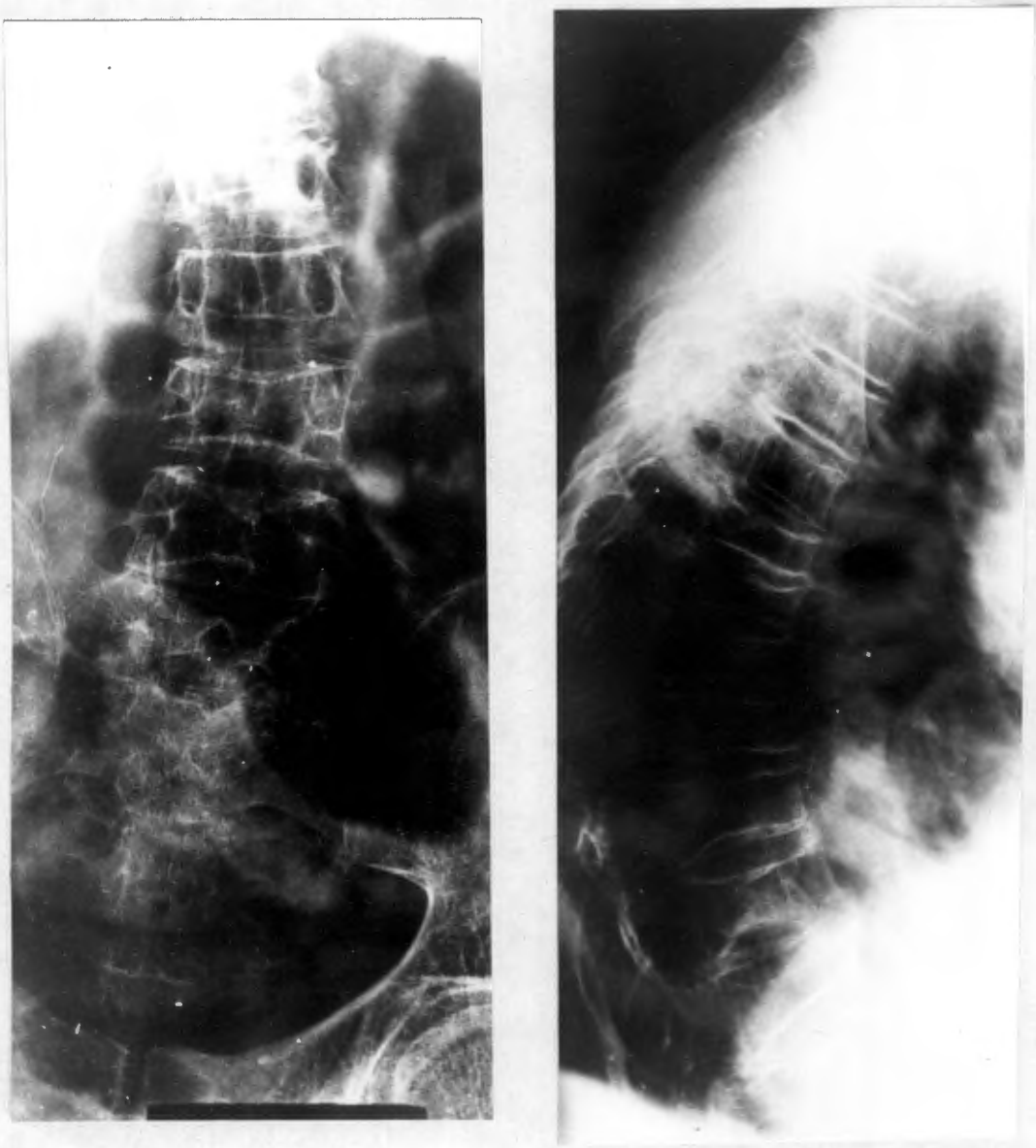


Figure 2.29

Case XVIII : A. O.

This short, frail, bent patient had fatty breasts and no sex hair.



Figures 2.30 and 2.31

Case XVIII : A. O. - X-Rays

Anterior and lateral views of vertebrae showing severe osteoporosis.

Case XIX : B. S. White female, aged 9 years.

This affectionate, mentally-backward child had developed normally until the age of 3-4 years. From that time physical and mental retardation had become apparent.

At the age of 9 years her height was 3'10½" (normal 4' 3") and her weight 52 lbs. (normal 58 lbs.). There was no evidence of systemic disease. Apart from mild microcephaly no physical abnormalities were found.

Urine P.S.H. excretion was not measured, but blood smears showed a male pattern in the polymorph nuclei, supporting the diagnosis of gonadal dysgenesis.

Case XI : R. S. Coloured female aged 19 years. (Figure 2.32)

Presented in 1953 with primary amenorrhoea. She was 4' 1" tall with normal physical proportions; the breasts were small with inverted nipples and normally-dark areolae (she had taken oestrogens for some months prior to examination). Axillary hair was absent and pubic hair scant. There were no recognisable congenital anomalies.

The external genitalia were normal, although the labia were considered to be small. Rectal examination revealed a small cervix; no uterus was felt.

Laparotomy was performed. A minute uterus was found with two fallopian tubes leading to typical elongated ovarian streaks. Gonadal biopsy revealed ovarian tissue with occasional growing follicles. Skin sex pattern was male.

Cyclical oestrogen therapy has resulted in regular withdrawal bleeds and further development of the breasts.

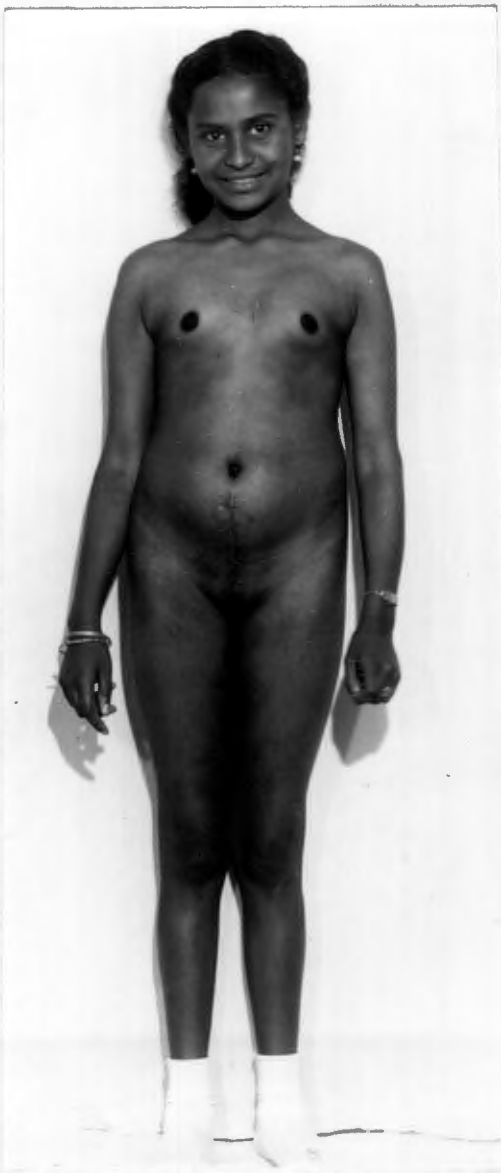


Figure 2.32

Case XX : R. S.

Note scanty pubic hair; dark areolae are the result of oestrogen therapy.

Case XXI : E. R. Coloured female aged 24 years. (Figure 2.33)

She presented with primary amenorrhoea and failure to grow. There had been no breast development at puberty, but pubic and axillary hair had appeared at the age of 15 years. There was no significant past history.

On examination she was 4' 2" tall with an arm-span of 4' 4", lower segment of 2' 0" and upper segment of 2' 2". Her weight was 72 lbs. There was webbing of the neck and a hypoplastic mandible; several pigmented moles were seen. The breasts were undeveloped; the nipples and areolae poorly-formed and well-separated. Axillary and pubic hair were scant. External genitalia showed hypoplastic labia minora, but a well-developed clitoris (Figure 2.34). Vaginal examination revealed a minute uterus; adnexae were not palpated. The leucocyte nuclear pattern was female.

Case XXII : I.B. White female aged 22 years. (Figure 2.35)

This patient attended because of primary amenorrhoea. At the age of 14 years, the breasts begun to grow and sex hair was noted. There was no history of mumps nor of any other significant illness. There were no hot flushes.

She was 5' 1" tall. The body-build was that of a normal female. The breasts were well-developed with normal nipples and areolae; pubic and axillary hair was adequate. There were numerous freckles over the upper chest, but recent sun-bathing might have accounted for this. There were no other obvious congenital anomalies. Skin and leucocyte nuclear patterns were female. Urinary F.S.H. excretion was 89 rat ovarian units (normal for a patient of this age is 8 - 9 ovarian units).

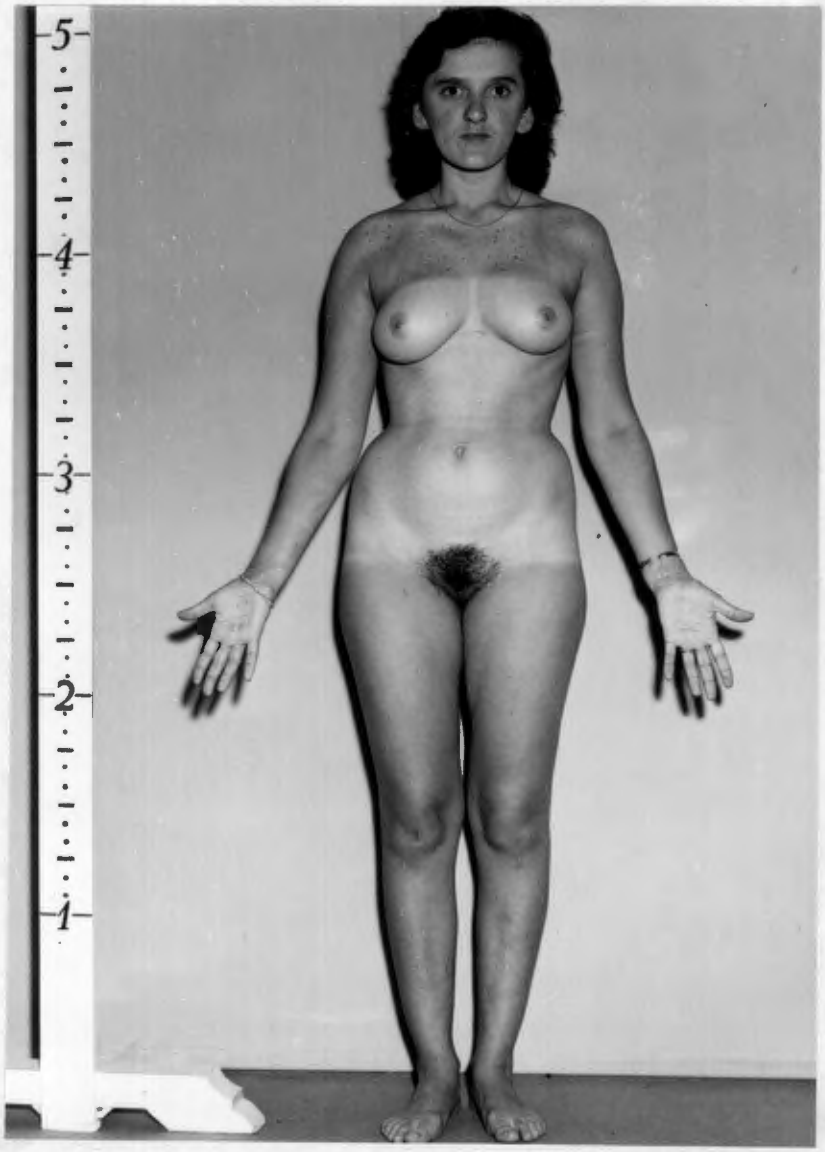


Figure 2.35

Case XXII : I. B.

Note good breast development, moderate amount of pubic hair and numerous freckles over the upper chest - these might be accounted for by recent sun-bathing.

Case XXIII : Marg. D. Coloured female aged 29 years. (Figure 2.36)

This patient did not menstruate until she was 18 years old. She had 3 painless vaginal bleeds, each lasting 4 days with intervening intervals of about a month. Since that time, vaginal bleeds had only occurred in response to oestrogen withdrawal therapy, except for one spontaneous bleed at the age of 22 years. Sex hair appeared at 18 years, and breast development at 20 years.

At the age of 22 years the patient married; libido was normal, but dyspareunia was experienced. There had been no pregnancies nor miscarriages. There were no significant past illnesses. Several members of the family were short, but all female relatives had menstruated normally.

On examination, her height was 4' 8½", the span 4'11" and the lower segment 2' 4". The breasts were very well developed, axillary and pubic hair moderate in amount. There was none of the typical congenital anomalies. Pelvic examination revealed a minute uterus; adnexae were not felt.

The leucocyte pattern was female.

Laparotomy disclosed typical vestigial ridges of gonadal dysgenesis and a tiny uterus. Histology showed ovarian stroma and a few developing germinal follicles.

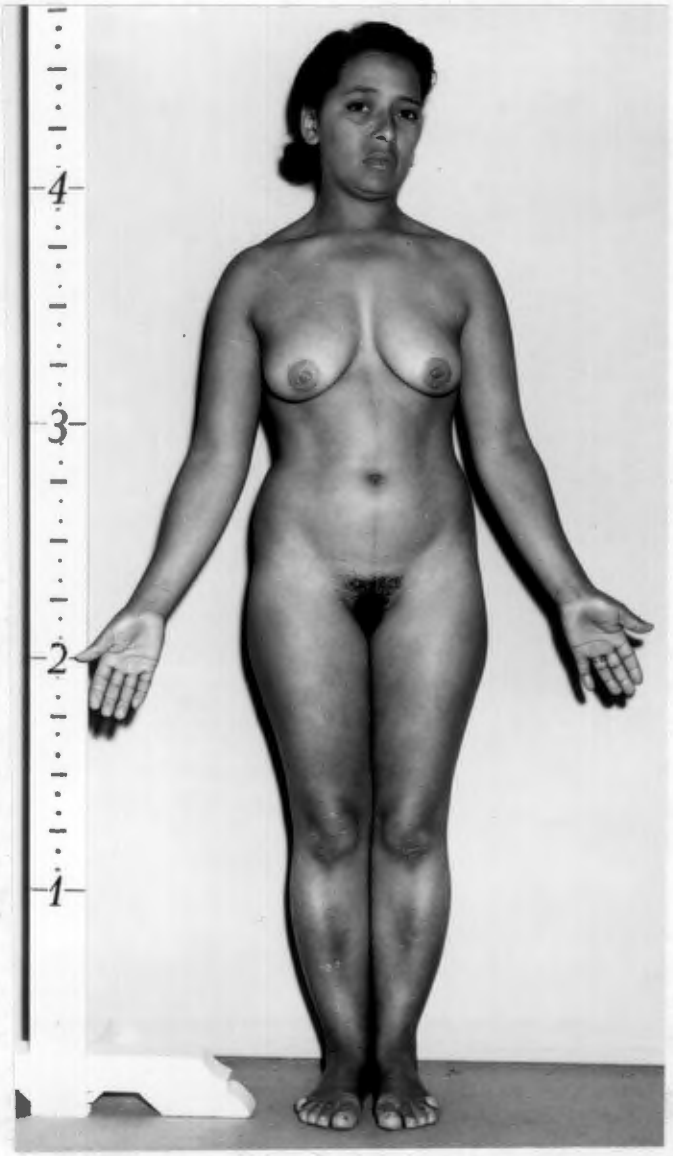


Figure 2.36

Case XXIII : Mark. D.

This short female has a normal appearance with good breasts and moderate pubic hair.

TABLE 1.

PATIENT	AGE AT 1st ATTEND-ANCE	BREASTS	PUBIC HAIR	AXILLARY HAIR	TEST OF ADRENAL FUNCTION	URINARY FSH EXCRETION	SKIN & LEUCO-CYTE SEXING	COMMENTS
Case I S.L.	18	Flat. Pin-point nipples	+	+	17-k.s. 2.4, 2.6 mg/ day. I.T.T. Thorn Test - Normal	Positive at 96 m.u.	Male	Webbing of neck and other anomalies. Good response of Stilboestrol
Case II J.M.	17	Flat. Inverted nipples	0	0	17-k.s. 4.2,5.2 mg/ day. I.T.T. Thorn Test - Normal	Positive at 192 m.u.	Male	Some anomalies
Case III L.R.	9	Nil	Few downy at 13 years	0	17-k.s. 6.2,3.8 mg/ day. I.T.T. Thorn Test-Normal. Plasma Cortisol 4.5 micro-gram/ 100 ml.plasma	Positive at 6 m.u. at 9 yrs. 48 m.u. at 13 yrs.	Male	Classical case: webbing Coarctation of aorta Transient swellings
Case IV E.J.	16	Absent Infantile nipples	Diminished	Diminished	17-k.s. 7.5 mg/day Soffer T., Thorn T., I.T.T. Normal	Positive at 96 m.u.	Female	Corneal opacities Pigmented moles +++
Case V Madu T.	21	Large breasts small nipples	Diminished	0	17-k.s. 6.3,9.7 mg/ day. Soffer T., Thorn T. I.T.T. Normal.	Negative at 6 m.u.	Male	Large breasts; low F.S.H. Laparotomy Breast biopsy = fat. Later androgenous depression.

TABLE 1 (Contd)

PATIENT	AGE AT 1st ATTEND-ANCE	BREASTS	PUBIC HAIR	AXILLARY HAIR	TEST OF ADRENAL FUNCTION	URINARY FSH EXCRETION	SKIN & BUCCO-CYTE STAIN	COMMENTS
Case VI M.D.	22	Moderate breasts	Diminished	0		Negative at 48 m.u. (2 tests)	Male	No increase in F.S.H. Breast biopsy done after oestrogens
Case VII J.T.	21	Hypoplastic breasts	+	+		Positive at 96 m.u.	Male	No anomalies; 5 years menstruation: attractive; laperotomy. Good response to Stilboestrol
Case VIII M.R.	30	Absent breasts	++	+	17 k.s. 5.9 mg/day	Negative at 48 m.u. on 3 tests	Male	Manic depressive psychosis Moderate osteoporosis
Case IX J.J.	49	Fat breasts, inverted nipples	+	0	17-k.s. I.T.T. normal	Positive at 96 m.u.	Male	Severe osteoporosis Webbing of neck Low hair line
Case X R.A.	14	Nil	0	0	17-k.s., Thorn T., Soffer T., I.T.T. all normal.	Negative at 6 m.u. (2 tests)	Male	No anomalies. Shortness of stature. Too young to assess hypogonadism

TABLE 1 (Contd.)

PATIENT	AGE AT 1st ATTEND-ANCE	BREASTS	PUBIC HAIR	AXILLARY HAIR	TEST OF ADRENAL FUNCTION	URINARY FSH EXCRETION	SKIN & LEUCOCYTE SEXING	COMMENTS
Case XI S.W.	22	Under developed	+	+		Positive at 96 m.u.	Male	Hare-lip. Pigmented moles +++
Case XII H. de J.	22	Flat	+	+		Negative at 96 m.u.	Female	Laperotomy. Tall, attractive, "normal".
Case XIII R.T.	12	Nil	0	0	Pl.Cortisol 10.3 microgram/100 ml. plasma		Female	Facies typical. Short metacarpal. Not finally proven.
Case XIV J.S.	22	Flat	0	+			Male	Typical. Webbing; low hair line. High B.P. Blue sclerotics.
Case XV K.N.	21	Flat	0	Diminished		Positive at 37 rat units (Normal for age = 3-9 units)	Female	Short metacarpal Laperotomy.

TABLE 1 (Contd.)

PATIENT	AGE AT 1st ATTEND-ANCE	BREASTS	PUBIC HAIR	AXILLARY HAIR	TEST OF ADRENAL FUNCTION	URINARY 17KS EXCRETION	SEX & LEUCOCYTE SEXING	COMMENTS
Case XVI R.L.	17	Flat	0	0			Male	No anomalies
Case XVII L.M.	17	Poor	Diminished	Diminished	17-K.S. normal		Male	No anomalies Laparotomy
Case XVIII A.G.	52	Flat. Inverted nipples	Very poor	Absent	17-K.S. normal	11-12 rat ovarian units	Female	Curious facial appearance Severe osteoporosis Not proved
Case XIX B.B.	9	Nil	0	0			Male	Under-developed physically Mental retardation No anomalies
Case XX R.S.	19	Small. Inverted nipples	Scant	0	17 K.S. normal		Male	No anomalies Laparotomy: Developing ovarian follicles

TABLE 3 (contd.)

PATIENT	AGE AT 1st ATTEND-ANCE	BREASTS	PUBIC HAIR	AXILLARY HAIR	TEST OF ADRENAL FUNCTION	URINARY FSH EXCRETION	SKIN & LEUCO-CYTE SEXING	COMMENTS
Case XXI E.R.	24	Nil	Diminish-ed	Diminish-ed			Female	Short. Webbing of neck. Large clitoris
Case XXII I.B.	22	Well develop-ed	"	"		89 rat ovarian units. (Normal for her age = 8-9 units)	Female	No anomalies. Short Good breasts Not proved
Case XXIII Marg.D.	29	Large	Moderate	Moderate			Female	Short No anomalies Several spontaneous periods Laperotomy

CHAPTER III

INVESTIGATIONS AND REFLECTIONS

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INVESTIGATIONS AND REFLECTIONS

During the course of this investigation it became apparent that the criteria for diagnosis of this syndrome required extension. Research was undertaken into several aspects which had not previously been emphasized. The results of these investigations with some random thoughts on several facets of gonadal dysgenesis will now be presented.

1. GONADOTROPHIN EXCRETION AND GONADAL DYSGENESIS

For absolute proof of the diagnosis of gonadal dysgenesis laparotomy or peritoneoscopy has previously been required, with the demonstration of the typical gonadal streaks. The finding of a high level of urinary gonadotrophin (F.S.H.) excretion is generally accepted as presumptive evidence of the diagnosis, but this may be misleading. For instance, high levels have been found in patients whose ovaries have been removed or damaged (e.g. by mumps or other forms of oophoritis), or in post-menopausal women. The history generally allows these patients to be distinguished. In 1942 Albright et al. postulated the existence of a condition of "premenarchial menopause". Here the menopause occurs so early that it actually precedes the menarche! The patient thus presents with primary amenorrhoea and shows a high level of gonadotrophin excretion; the correct diagnosis is supported by a history of precocious hot flushes.

In gonadal dysgenesis the urinary F.S.H. excretion does not exceed normal levels until the patient reaches the age of puberty (Skjelbred 1953, Vulliamy 1953 and Wilkins 1950). Case II, L. R., of this series showed a normal F.S.H. excretion at the age of 9 years; at 13 years a strongly positive result was obtained at 48 m.u. Silver (1951) has reported a case of gonadal dysgenesis with raised F.S.H. excretion at the age of 2½ years.

Rarely a typical case of "ovarian agenesis" has been described in an adult in whom the urine gonadotrophin level was not raised (Sternlieb et al. 1954). The patient of Dorff et al. (1947) showed no gonadotrophic activity at the age of 16½ years; she also had a B.M.R. of -25% and a serum cholesterol level of 300 mg. %. Accordingly, the authors postulated partial anterior hypopituitarism associated with the ovarian failure to explain the unexpected low urine F.S.H. excretion. Hertz et al. (1950) describe a female of 35 years whose F.S.H. excretion was low on 9 separate tests; there was no evidence of hypopituitarism and the diagnosis of "ovarian agenesis" was proved by laparotomy. These authors offer no explanation for this anomalous finding. Carpentier et al. (1956), in a recent report on the value of vaginal smears in the determination of genetic sex, refer to 3 of 10 patients with gonadal dysgenesis and male nuclear chromatin pattern, in whom urinary F.S.H. excretion was not raised; in one of these 3 the diagnosis was proved by laparotomy. Further details are not available. In the present series low F.S.H. excretions have frequently been found (Table 1).

Notwithstanding these few exceptions, the finding of an abnormally high urine F.S.H. level in a female with primary amenorrhoea may be taken as strong confirmatory evidence of gonadal dysgenesis. A low level certainly does not gainsay the diagnosis. A theory is to be presented to account for the occurrence of gonadal dysgenesis with low urinary F.S.H. excretion. (PART II, CHAPTER XIII).

2. CORTISONE AND F.S.H. LEVELS

The effect of cortisone and A.C.T.H. on urinary F.S.H. excretion has been investigated by several workers (Smith 1951, Maddock et al. 1953, Sohval and Soffer, 1951). In post-menopausal women, whose levels of excretion are high, it has been found that cortisone administration has little or no depressant effect (Bishop 1954). Recently, Brown (1956) estimated separately urinary F.S.H. and I.C.S.H. in women with high levels of excretion of gonadotrophins; cortisone therapy in post-menopausal women appeared to cause a rise in excretion of F.S.H. relative to I.C.S.H., but the change in total gonadotrophin output was neither striking nor constant . Cortisone 100 mg. daily for 10 days was administered to several patients in the present series whose initial F.S.H. readings were high; no alteration in these readings was detected. This finding in gonadal dysgenesis lends support to the view that cortisone in this dosage exerts no measurable suppressive effect on the pituitary gland with regard to its production of F.S.H.

3. THE CONGENITAL ANOMALIES OF 'TURNER'S SYNDROME'

In the past, considerable stress has been placed on the presence of certain congenital anomalies. The most notable of these include webbing of the neck, cubitus valgus, pes cavus, abnormalities of the cervical vertebrae, ribs, palate, fingers, eyes and ears, and, in particular, coarctation of the aorta. In the present series the relative infrequency of these phenomena has been striking (Table 1.) At the beginning of this investigation, cases were diagnosed only if these anomalies were present; with familiarity it became clear that many cases of gonadal dysgenesis existed who showed no anomalies at all. Thus, coarctation of the aorta was diagnosed in only one instance, webbing of the neck in only 5. Similarly, cubitus valgus was rare - in only one case was it considered to be present to a minor degree. This anomaly, especially, presents difficulties. Figure 3.01 is reproduced from a recent article on gonadal dysgenesis. In the anterior view quite gross cubitus valgus is seen; yet, in the lateral view, marked flexion of the elbows is apparent. Very minor flexion of the elbow joint allows considerable abduction of the forearm, which closely simulates cubitus valgus on photography. Does this anomaly really exist?

It is interesting to note two cases showing short metacarpal bones (Case XIII : R. T. and Case XV : K. H.). In neither case was there a familial incidence of this anomaly, which has been noticed particularly in the syndrome of pseudohypoparathyroidism (Albright et al. 1942 a). A case reported by Rees (1949) showed the same defect.

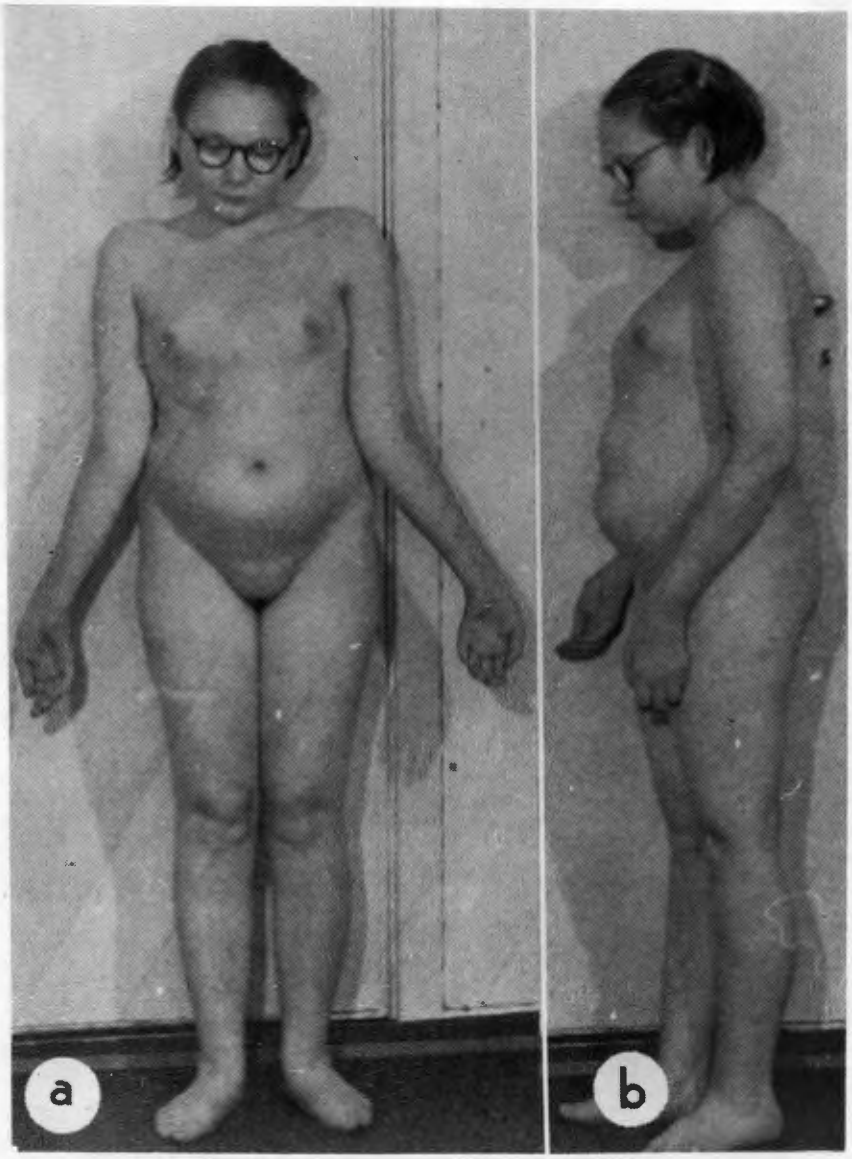

Figure 3.01

Cubitus valgus?

The anterior view shows apparent cubitus valgus; flexion of the elbow joint, as seen in the lateral view, allows abduction of the forearm.

4. MOLES AND SWELLINGS

Gonadal dysgenesis, in common with many other endocrine disorders, shows features so characteristic that the diagnosis is often possible at first glance. Apart from the widely-known manifestations, two are of interest.

First, most of this series of patients have exhibited numerous freckles or darkly pigmented moles. These have been commented on in some previous papers, (Oberman 1955, Wilkins et al. 1944, Gordan et al. 1955, Sternlieb et al. 1954, Dorff et al. 1948, Skjelbred 1953), but have not been mentioned in other reports, even where photographs display this feature prominently. In Case VI, M. D., an original diagnosis of pituitary infantilism had been made in view of the low F.S.H. values. On review of her photographs (Figure 2.10), these moles were strikingly obvious and it was decided to recall her for re-assessment; gonadal dysgenesis was then proven.

Another curious feature, which may permit the diagnosis to be made at a very early age, is the presence of swellings and localised oedema at birth or in the immediate post-natal years (Silver 1951, Barlow et al. 1955, Skjelbred 1953, Haney 1952, Keay et al. 1954, Russell et al. 1955, Vallimmy 1953, Oberman 1955). Three of this series gave a history of such swellings.

Case III, L. R., had consulted several specialists because of transient, unexplained swellings of the limbs; even at the age of 13 years, she visited an Orthopaedist because of persistent oedema of one foot. Case IV, E. J., suffered from otherwise unexplained, intermittent hydrarthroses of the knees. Similarly Case X, R. A., had had an undiagnosed episode of swellings affecting the knees and wrists.

There is no satisfactory explanation for these swellings, but an interesting theory has been evolved in Europe. Bonnevie and Ullrich (Ullrich 1949) have attempted to correlate certain malformational syndromes in the human with defects occurring in the so-called Bagg-Little mice - a strain produced by inbreeding following exposure to X-Rays. It is claimed that a bleb of cerebrospinal fluid migrates during foetal life in these mice, and produces damage due to local, physical pressure effects, e.g. aplasia of the pectoral and other muscles, deformities of the neck and limbs, transient oedemas, etc. Such blebs have been demonstrated in human foetuses, and the syndromes they produce bear some relationship to the defects encountered in gonadal dysgenesis. On the European Continent, therefore, Turner's Syndrome usually is regarded as one member of this large group of malformations (Rossi and Caflisch 1951). Whether such a mechanism exists or not, the theory is an interesting one, and James (1952) suggests the title of Bonnevie-Ullrich-Turner Syndrome for the whole group.

5. BREAST DEVELOPMENT

Four of this series had good breast development when they first presented. One had received oestrogen therapy previously; the other 3 had not taken any endocrine preparation. Several cases have been described with good mammary development (Herts et al. 1950, Lisser et al. 1947 and Wilkins et al. 1944), although hypoplasia is to be expected in the absence of oestrogenic stimulation. As this finding seemed anomalous, it was decided to perform biopsies of the breasts in two patients in this series; in each case a representative core was taken from the central part of the breast at depth. In the patient who had not taken oestrogen (Case V, M. du T. - Figures 2.08 and 2.09) her apparently normal breasts consisted of fat only with no evidence of functioning mammary tissue. The breasts of the other patient (Case VI, M. D. - Figure 2.11) showed some lobulation and "evidence of cyclical activity"; this biopsy was taken after a period of oestrogen therapy, and the changes may reflect the influence of this hormone.

It is interesting that no functioning mammary tissue was found in a large biopsy specimen taken from the apparently well-developed breasts of Case V, M. du T. It is conceivable that, in other reported cases the breasts have contained functioning tissue, but biopsy data are not available. In the ensuing discussion on menstruation in gonadal dysgenesis (PART I, CHAPTER IV) reference will be made to evidence of oestrogen secretion in this syndrome. Whether this oestrogen is derived from the adrenal glands or the

primitive gonads is a matter for speculation at present.

6. ANTHROPOMORPHIC MEASUREMENTS

Pelvic X-Rays were taken of several patients in this series, and full anthropomorphic measurements were made in some. The results show that there was no variation from the pattern found in normal females. Some android features were found, but since these are not uncommonly present in women, one cannot attach much significance to this finding. Cases have been reported with more distinctly android pelves, (Gordan et al. 1955), where these have been taken to represent minor manifestations of the genetic maleness of the patient - comparable to the rarely-reported clitoral enlargements or prostatic remnants (Gordan et al. 1955; del Castillo et al. 1947; Pich 1957).

7. AXILLARY HAIR AND ADRENAL FUNCTION

Many, but not all, patients with gonadal dysgenesis show diminution of pubic and axillary hair. In fact, 7 of this series had good sexual hair growth. It is currently held that axillary hair is very largely dependent on adequate adrenocortical function. (Albright et al. 1942). In consequence it has been suggested that adrenocortical deficiency exists in cases of gonadal dysgenesis. Search for impaired adrenal function has been made by means of Thorn and Soffer Tests, Insulin Tolerance Tests, and estimation of 17-ketosteroid excretion and plasma Cortisol. In patients so tested, results were normal (Table 1). This suggests that there is no impairment of function of the adrenal cortex in gonadal dysgenesis. Furthermore, in those cases with deficient pubic and axillary hair, failure of the adrenal glands could not be held responsible. A similar investigation in a case of oestrogen-producing testes with no axillary hair (see later) failed to show impairment of adrenocortical function.

8. OSTEOPOROSIS IN GONADAL DYSGENESIS

Many authors have commented on slight osteoporosis in gonadal dysgenesis (Albright et al. 1942, Wilkins and Fleischmann 1944, Lisser et al. 1947, del Castillo et al. 1947, Skjelbred 1953, Jackson and Sougin - Mibashan, 1953). Marked osteoporosis seems to have been commented on only once, in a patient who also showed hypocalcaemia and tetany (Geffen, 1956).

Generally the osteoporosis is attributed to oestrogen-lack, analogous to the common form of post-menopausal osteoporosis in women. In the present series, 3 patients showed moderate to severe osteoporosis. Case VIII, M. R., sustained a fractured vertebra during electroconvulsive therapy; her X-Rays revealed moderate diffuse osteoporosis. Two older patients, Case IX, J. J. and Case XVIII, A. O., had severe degrees of osteoporosis, the former with wedging of several vertebrae, the latter with gross vertebral deformities and a fractured neck of femur following relatively trivial trauma (Figures 2.30 and 2.31).

There is another possible explanation of the osteoporosis in gonadal dysgenesis. Osteogenesis imperfecta tarda has been described as one of the associated congenital anomalies (Lisser et al. 1947, Oberman, 1955). One patient in the present series showed strikingly blue sclerotics - one of the multiple defects which make up the syndrome of

- osteogenesis -

osteogenesis imperfecta. She did not show "thin" bones. Many authorities regard osteogenesis imperfecta as a type of congenital osteoporosis. Dent (1955) says "I sometimes wonder if there is any real difference between" osteogenesis imperfecta tarda and idiopathic osteoporosis. If the osteoporosis of gonadal dysgenesis is due to oestrogen-lack, why is it not found more commonly? Is it possibly not endocrinal in origin, but rather an associated anomaly which might be erratic in its occurrence?

It would seem that the hereditary nature of the osteoporosis in gonadal dysgenesis is unlikely. In osteogenesis imperfecta the inadequately formed bones are obvious radiologically at an early age; in gonadal dysgenesis, the osteoporosis is slight in young patients, severe degrees having been described only in older patients. This suggests that it is a progressive lesion, probably best explained by prolonged sex hormone lack.

9. NUCLEAR SEXING IN THIS SERIES

As may be seen in Table 1, 15 of 23 patients showed male nuclear patterns. When this is found in patients with female body-form and normal female external genitalia, the diagnosis of gonadal dysgenesis appears almost obligatory. (Exceptions to this rule are discussed below - PART I, CHAPTER VI).

In the majority of cases, "sexing" was done on skin biopsy specimens, but simpler and equally efficient determinations may be made on other tissue cells, e.g. leucocytes, oral or vaginal smears. Of these, the leucocyte method provides a rapid and apparently reliable test. The technique is well reviewed by Lennox (1956) and Davidson and Smith (1956).

As a result of this "sexing" method a useful confirmatory diagnostic procedure is available. Cases VI, VIII and X may be presumed to suffer from gonadal dysgenesis in view of the skin nuclear examination - despite their low F.S.H. excretions. Case VII who presented with secondary amenorrhoea would not normally have been considered as a case of gonadal dysgenesis. Because of the unexpected nuclear pattern, laparotomy was undertaken and gonadal dysgenesis was confirmed.

10. "OVARIAN STROMA" IN GONADAL DYSGENESIS

The histological reports on the gonads of 3 patients in this series refer to the presence of "adult ovarian stroma". While some authorities deny a distinction between ovarian and testicular stroma (Grumbach et al. 1955), most appear to accept that the two types may be differentiated. Gordan et al. (1955) found the female type of stroma in 2 cases with androgenic manifestations; Greenblatt et al. (1955) and Russell et al. (1955) report similar histological appearances in 2 patients, one of whom showed a male skin pattern. At first glance it appears curious that gonads, which are, in fact, testicular vestiges, should show an ovarian type of stroma. But it is possible that, in the absence of testicular function, the gonadal stroma shares the propensity of the rest of the genital tract towards feminisation. In other words, the testis might exert a local effect on its own stroma which renders it distinctive.

11. "FOLLICLES" IN GONADAL DYSGENESIS

The vestigial streaks of gonadal dysgenesis do not show a uniform histological appearance. The most primitive have been composed of stromal tissue without primordial follicles. In other cases there has been evidence of more mature development with tunica albuginea, primordial follicles and follicular cysts (Kerkhof and Stolte, 1956; Russell et al. 1955). Presumably in such instances some maturation of the ovaries had already taken place before development was interrupted by the responsible agent (genetic or acquired intra-uterine). These subjects should show a female nuclear pattern, since the partial ovarian development suggests that the gonads were fundamentally ovaries. In Case XI, R. S., growing follicles were seen on histological examination. This patient showed a male pattern on skin biopsy. If these gonads were embryonic testes, the presence of ovarian elements is surprising. This curious finding will be discussed more fully in PART II, CHAPTER XII.

CHAPTER IV

MENSTRUATION IN GONADAL DYSGENESIS

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MENSTRUATION IN GONADAL DYSGENESIS

A review of the literature shows that it is rare for gonadal dysgenesis to be diagnosed, except where there has been primary amenorrhoea. Isolated patients have been reported with very scanty menstrual bleeds. Albright et al. (1942) refer to a 21 year old girl who had a slightly bloody vaginal discharge on a few occasions; one patient reported by Varney et al. (1942) had menstruated 3 or 4 times between the ages of 14½ and 16 years (she also had some breast development); and Lisser et al. (1947) mention two patients each of whom had had one scant bleed. Briggs and Kupperman (1956), reviewing sex differences in leucocyte morphology, refer to a "woman with amenorrhoea and the neck-webbing typical of Turner's syndrome, who could not be said to have true gonadal dysgenesis since spontaneous menstruation had occurred in the past". The validity of their conclusion about this patient might be questioned in view of the history of Case VII, J. T. (discussed below).

In this series, 3 patients claimed to have menstruated. In one instance this consisted of a "single show" lasting one day. Case XXIII, Marg. D. had several bleeds lasting 4 days each at the age of 18 years, after which menstruation ceased. Case VII, J. T., stated that she had menstruated for 5 years. Her menarche had appeared at the age of 15 years and bleeding ensued at one to three monthly intervals until she was

20 years old. Blood-loss, which generally extended over 3 days, was moderate in amount and was not associated with abdominal cramps or discomfort of any sort. In view of the history of secondary amenorrhoea and a high F.S.H. excretion, some form of secondary ovarian failure was diagnosed. There was no history of mumps and the patient denied the occurrence of hot flushes. Her short stature led to suspicions and a skin biopsy was done to determine the cell nuclear pattern. Unexpectedly this proved to be male. Vaginal curettage could not be done in view of the atrophic state of the mucosa.

Laparotomy disclosed a minute uterus and the typical vestigial streaks of gonadal dysgenesis lying on the posterior aspects of the broad ligaments. Histology showed stroma resembling that found in adult ovaries, but this was scant in amount; follicles and interstitial cells were not seen.

Oestrogen therapy (one mgm daily) was instituted and within six months impressive increase was noted in breast size (Figures 2.13 and 2.14), the areolae had enlarged and darkened, cyclical withdrawal bleeds had been established and general feminisation of the contours had occurred.

Comment: The unexpected history of menstruation (eliguenorrhoea) in this patient with gonadal dysgenesis is most difficult to explain. J. T. impressed one as a most co-operative, intelligent and reliable witness. She denied having taken any form of hormonal preparation during the years of menstruation. Yet, in the absence of oestrogen, menstruation should not occur. Evidence of small amounts of

oestrogen secretion , even with male sex chromatin pattern, has been observed in some cases of gonadal dysgenesis, e.g. some mammary development, some oestrogen effect on vaginal smear. (This seems as puzzling as the presence of androgen effect in boys who have no testicular tissue !) Yet, in J. T., a very small therapeutic dose of oestrogen caused considerable mammary growth. This argues against previous circulating oestrogen of any magnitude. Normally, breast tissue is more sensitive to oestrogen than is the endometrium (as indicated by breast development preceding menstruation at puberty); here is an instance of menstruation without breast development in a patient whose mammary tissue proved highly responsive to oestrogen.

J. T.'s skin cell pattern was male in type; presumably the gonads were embryonic testes. If oestrogen had been present, it must have been derived from this vestigial male gonad or, perhaps, from the adrenal glands. No extra-ovarian tissue (supernumerary or accessory ovaries) was discovered at laparotomy.

The case described by Briggs and Kupperman (1956) appears similar to J. T. She, too, presented with secondary amenorrhoea, but had a female nuclear pattern; however, webbing of the neck was present. It seems feasible that she was suffering from gonadal dysgenesis.

If the history of these two patients is accepted,

one must conclude that circulating oestrogen was present (of gonadal or adrenal origin) and that this produced endometrial bleeding. In J. T., the effect was not evident on breast or uterine development. (Data of Briggs and Kuppermann's patient are not available.)

In this paper, the widening concept of gonadal dysgenesis is stressed. Undoubtedly, the condition is assuming a position of great importance as a cause of primary amenorrhoea; it would appear that one must consider it, too, in some patients with secondary amenorrhoea.

CHAPTER V

NORMAL-LOOKING FEMALES

WITH IMMATURE OVARIES

CHAPTER V

NORMAL-LOOKING FEMALES

WITH IMMATURE OVARIES

1. GONADAL DYSGENESIS IN NORMAL-LOOKING FEMALES

In 1955, Swyer described two patients with an unusual clinical picture under the heading of "Male Pseudohermaphroditism. A Hitherto Undescribed Form". Briefly, these patients showed normal height with eunuchoidal proportions and female appearance and genitalia, except that one had an enlarged clitoris. They did not develop secondary sexual characters nor did they menstruate. Their nuclear patterns were male. They had no congenital anomalies of the Bonnevie-Ullrich-Turner type. Attempts to place these patients into one of the recognized categories of intersex appear to have failed. In the 1955-56 Year Book of Endocrinology a precis of Swyer's paper is followed by an editorial comment which confirms this dilemma. (Gordan 1956).

One patient in the present series (Case XII, H. de J.) showed a similar clinical picture to the two cases cited above, but her "genetic sex" was female. H. de J. showed no recognizable congenital anomalies; she appeared, in fact, to be a normal, thin

female with poor breast development (Figures 2.19 and 2.20). Her F.S.H. excretion was not raised. Yet laparotomy disclosed typical dysgenetic gonads.

Similar tall patients have been described by other observers. Sun and Rakoff (1956) include, in a series of 15 patients with gonadal dysgenesis, one who was 5' 4" tall and had normal skeletal proportions. She, however, had a high urinary F.S.H. excretion and the diagnosis was confirmed at laparotomy.

Greenblatt et al. (1956) refer to another tall patient without the anomalies of Turner's syndrome, but with poor breasts, primary amenorrhoea and otherwise normal female appearance, except for enlargement of the clitoris. The urine F.S.H. excretion was normal and skin sex was female. Gonadal dysgenesis was proved at laparotomy.

Case XII, H. de J., displayed an almost identical picture; there was, however, no clitoral enlargement.

A Reconsideration: The two patients described by Swyer were apparent females with primary amenorrhoea; they had poor mammary development, eunuchoidal proportions, normal axillary and pubic hair. The external genitalia were normal, except for clitoral enlargement in one. Each displayed a rudimentary uterus, a normal, non-oestrinised vagina, normal cervix and apparently

normal oestrogen levels. F.S.H. excretion was normal in one, low in the other. Blood-smears showed male patterns. Laparotomies were not performed.

Swyer considers gonadal dysgenesis in the differential diagnosis. He dismisses the condition on the grounds of numerous distinctions between his patients and those with the hitherto-accepted classical syndrome. In the light of the cases reported above, including H. de J., it is apparent that his cases differ in no specific manner from the less common variants of gonadal dysgenesis. Table 2 summarises the salient features of "classical" gonadal dysgenesis, atypical gonadal dysgenesis, Swyer's "new" syndrome and classical male pseudohermaphroditism. From a perusal of this table, it becomes clear that Swyer's cases are, in fact, variants of the syndrome of gonadal dysgenesis. The difficulty in classification seems to have arisen because his cases showed a number of atypical features, all of which have been described separately in other patients.

A consideration of these unusually "normal" patients with gonadal dysgenesis is to follow; an explanation on genetic lines will be put forward to account for these and other atypical cases, and a theory will be presented to explain their unusual height.

TABLE 2.

	Stature	Congenital anomalies	Breasts	Sex Hair	Vagina	Cervix	Chromosomal Sex	Gonado-trophins	Oestrogen	Gonads
"Classical" Gonadal dysgenesis	Short	Usual	Under-developed	Usually scanty	Infantile	Infan-tile	Male or female	High	Low	Primitive streaks
Atypical gonadal dysgenesis e.g. H. de J.	May be tall or normal height	Often absent	Usually under-developed	May be normal	Small or normal	Infan-tile or normal	Male or female	High normal or low	Normal or low	Primitive streaks or may show some develop-ment.
Sayer's "new" syndrome	Tall or normal	Absent	Under-develop-ed	Within normal limits	Normal unoestro-genised.	Normal	Male	Normal	Appar-ently normal.	?
Classical Male pseudo-hermaphro-ditism.	Normal or tall	Absent	Variable	Absent or scanty.	Short; may be oestrog-enised.	Minute or absent.	Male	Normal	Low	Developed testes

2. TALL FEMALES WITH OVARIAN HYPOPLASIA

Two patients were seen who appeared clinically to resemble H. de J. However, in these, somewhat different gonadal states were encountered.

Case A. B. : Aged 22 years. (Figures 5.01 and 5.02)

The menarche occurred at 15 years and was followed by irregular periods for the next six years. These lasted one to three days, were generally scant in amount and came on at one to three monthly intervals. There had been several amenorrhoeic episodes of four to six months duration. The menstrual bleeds were completely painless. In early childhood the patient had suffered from mumps, but no details of this illness were available; she could not recollect abdominal pain.

The patient was 5'10" tall with eunuchoid proportions (arm span 6' 1"; symphysis pubis to ground 3' 1"; top of head to symphysis pubis 2' 9"). Axillary and pubic hair were moderate in amount. Most striking was complete lack of development of breast tissue. Two very small nipples with pale areolae were present, but no underlying breast tissue could be palpated.

Blood-smear examination showed female nuclear pattern; urinary F.S.H. excretion was negative at 6 m.u.

Laparotomy disclosed dysgenetic gonads lying in the site normally occupied by the primitive ridges of gonadal dysgenesis. But, these gonads differed from the usual "streaks", in that they showed a slight bulge towards the lateral ends, a shape somewhat reminiscent of an Indian club. Biopsy was taken from these bulging ends and histology showed that both ovaries contained primordial follicles with occasional follicular cysts. In addition, the left ovary contained at least two developing follicles.

Case J. Mc. : Aged 23 years. (Figure 5.03)

This patient presented with primary amenorrhoea and infertility. From the age of 17 years she had received intermittent courses of treatment, consisting of oestrogen with or without progesterone. These courses had produced withdrawal vaginal bleeds, but no spontaneous menstruation had occurred.

There had been no breast development but pubic and axillary hair were satisfactory. The patient had married at the age of 20 years, and had enjoyed satisfactory sexual relationships with her husband, although some difficulty was experienced due to the narrowness of the vagina.

On examination she was tall (5' 5½"); the proportions were eumchoidal (span 5' 7½"; symphysis pubis to ground 2'11"; top

of head to symphysis pubis 2' 6½"). There was no mammary tissue palpable; the nipples were small and the areolae pink. Vaginal examination revealed a very small uterus. Skin and leucocyte nuclear patterns were female. Urinary F.S.H. excretion was not determined.

At laparotomy gonads were seen which appeared identical to those of A. B. Histology was reported as showing some primordial follicles and a few follicular cysts.

Comment: Both of these patients showed tall, eunuchoid stature; one had oligomenorrhoea, the other primary amenorrhoea. Both had very poor mammary and uterine development; nuclear pattern was female. Laparotomy showed partial ovarian development; the gonads were of an abnormally elongated shape, smaller, and situated rather higher in the broad ligaments than are normal ovaries. Case A. B. showed a low excretion of F.S.H. In neither case were the classical anomalies of Turner's syndrome present.

It is postulated that these patients were not suffering from the syndrome known as gonadal dysgenesis. Instead, it is suggested that they were suffering from a defect in pituitary gonadotrophin production - which allowed partial ovarian maturation and partial menstruation in one, but which was insufficient to produce breast or uterine development or to prevent the eunuchoidal skeletal proportions. Similar patients have been described by Proom et al. (1955) and Kerkhof and

Stolte (1956). In the former's case, substantiation of the diagnosis was obtained by a response to gonadotrophin therapy. Cases of this sort must clearly be distinguished, as different therapy may be indicated (see later). For this reason alone laparotomy is justified in suspected cases.

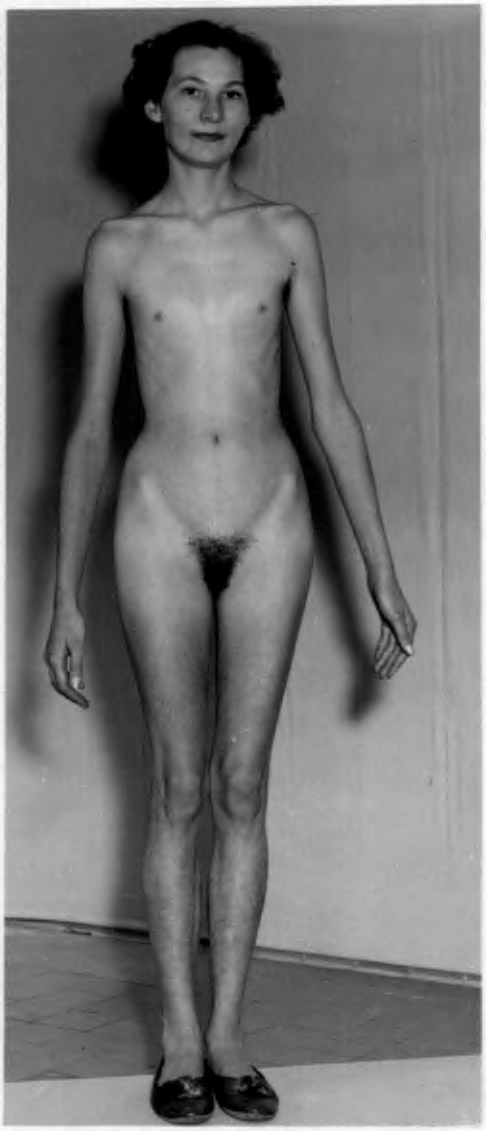

Figure 5.01

Case A. B. - Anterior view

Notice the tall, thin, eunuchoid proportions, moderate amount of pubic hair and absence of breast development.

Figure 5.02

Case A. B. - Lateral view

This emphasizes the thin stature and lack of breast development; axillary hair is adequate.

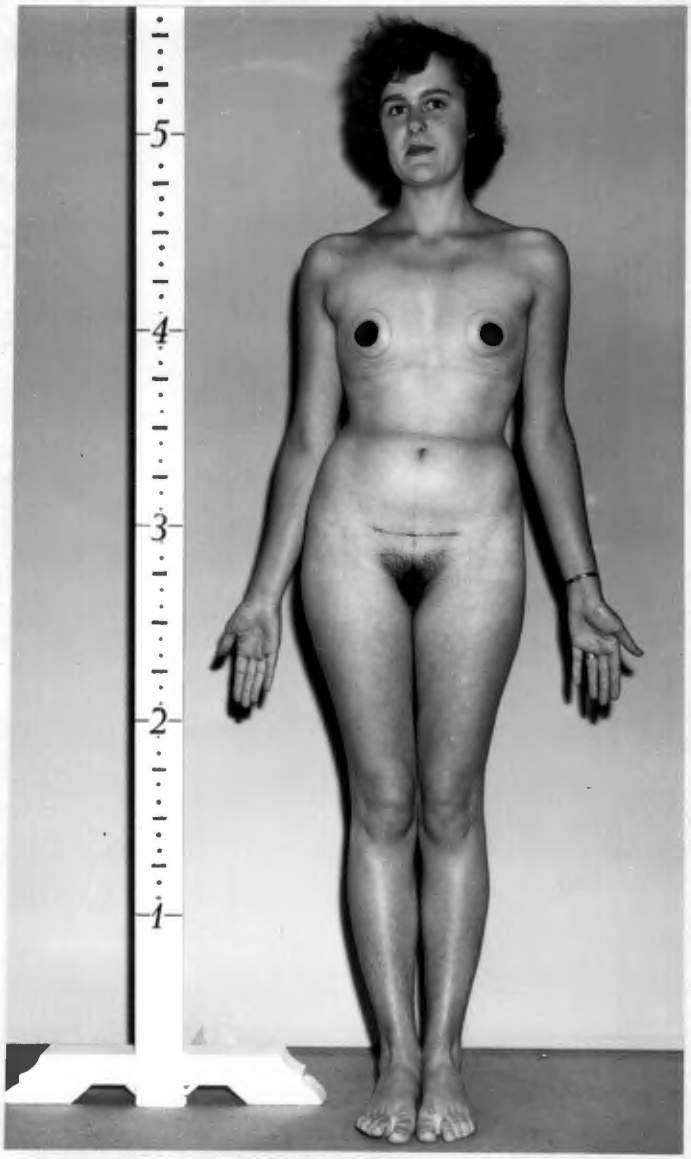

Figure 5.03

Case J. Ew.

This view shows the tall, somewhat eunuchoid stature, moderate pubic hair and poor breast development. The large dark areolae appeared after the use of oestrogen.

CHAPTER VI

THE DIAGNOSIS OF

GONADAL DYSGENESIS

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THE DIAGNOSIS OF

GONADAL DYSGENESIS

The typical manifestations of gonadal dysgenesis were outlined earlier in this paper. From a consideration of this series and the cases reported in the literature, it has become obvious that many of the classical criteria need not obtain. Patients need not be short, nor unattractive; axillary and pubic hair may be luxuriant and adrenal function unimpaired. The congenital stigmata of "Turner's Syndrome" may be absent and good breast development may be found. The urinary gonadotrophin excretion need not be raised, and, in fact, a theory will be presented to account for subnormal excretion levels. A case has been described with pseudo-hermaphroditic genitals (Grumbach et al. 1955; see later) and an earlier chapter refers to a patient in whom menstruation is claimed over a 5 year period.

The diagnosis depends on a high index of suspicion. Gonadal dysgenesis appears to be the commonest cause of :-

1. Primary amenorrhoea, whatever the appearance of the patient (cf. Case XII : H. de J.).

- 2. Marked -

2. Marked shortness of stature, in the absence of gross disease or skeletal dysplasia. The diagnosis must, therefore, be considered where growth is delayed, even before puberty and in the absence of congenital anomalies (cf. Case X : R. A.).

Gonadal dysgenesis is often suggested by the appearance of the subject. In a patient with sexual infantilism, the facies, the short stature, the presence of numerous pigmented moles, freckles or minor anatomical defects should recall the diagnosis - even if the more striking congenital anomalies are absent. The nuclear sex, if male, probably provides the most reliable diagnostic criterion short of laparotomy.

Few other conditions present the combination of male nuclear sex and female build and genital appearance :

1. There are very few reports available of genetic sexing in true hermaphrodites. It is conceivable that a male nuclear pattern might be found in a patient with "normal" or "near-normal" female external appearance. Examination of the external genitalia will generally distinguish the true hermaphrodite: the phallus is usually larger than a normal clitoris; and in most cases there is a single orifice at the base of the phallus; two separate openings are rarely found. In cases

where distinction is impossible on clinical grounds, laparotomy may be necessary.

2. Male pseudohermaphroditism with a large phallus and bilaterally undescended testes might simulate gonadal dysgenesis with enlargement of the clitoris. Since gonadal dysgenesis is regarded as a minor form of male pseudohermaphroditism (see PART II, CHAPTER X), the distinction between these conditions is often academic.

3. The syndrome of oestrogen-producing testes (PART II, CHAPTER XII) presents a distinctive clinical picture, characterised by normal breast development, lack of pubic and axillary hair and absence of uterus or cervix. These features make the diagnosis ineluctable.

Apart from these few exceptions the diagnosis of gonadal dysgenesis is virtually certain in individuals with female appearance whose nuclear patterns are male.

Substantion of the diagnosis may prove difficult in those cases with female nuclear patterns. The place of urinary F.S.H. excretion levels in the diagnostic armamentarium has already been discussed. Low levels are not of value in excluding gonadal dysgenesis. A high level of excretion indicates primary gonadal failure; this might be congenital, i.e. gonadal dysgenesis, or acquired, as a result of mumps or some other form of oophoritis.

If a patient with primary amenorrhoea has a high gonadotrophin excretion, it may be presumed that the ovarian failure took place before puberty. Such a patient should develop the tall, eunuchoid proportions that generally accompany primary prepubertal hypogonadal states. The absence of this type of body-build in an adult patient with prepubertal, hypergonadotrophic gonadal failure strongly suggests gonadal dysgenesis. For this reason, three patients are included in the present series despite lack of proof of the diagnosis. Case XIII, R. T., is too young to be labelled hypogonadal; she is retarded physically and her facial appearance puts gonadal dysgenesis in mind; her nuclear pattern is female and F.S.H. determination is unlikely to be of value at present. Case XVIII, A. O., with primary amenorrhoea and absence of secondary sex characters (with inversion of the nipples) also shows a female nuclear pattern; her non-eunuchoid appearance and odd facies suggest the diagnosis. Most difficulty is provided by Case XXII, I. B. This rather short, well-proportioned patient exhibits none of the congenital stigmata of the syndrome, has good breast development and a female nuclear sex. Her F.S.H. excretion, measured in rat ovarian units, is extremely high; this must be interpreted as evidence of primary gonadal failure. The cause of this failure is not clear - acquired ovarian damage, e.g. by mumps, cannot be excluded. In her case, particularly, it may be argued that the absence of eunuchoidism favours gonadal dysgenesis.

These 3 patients illustrate some of the difficulties experienced in establishing the diagnosis, where the nuclear pattern

is female. Familiarity with the vagaries of the syndrome, coupled with a knowledge of its prevalence, makes it likely that gonadal dysgenesis is the correct diagnosis in each of these patients. Laparotomy, vaginal culdoscopy or peritoneoscopy would appear necessary to confirm or refute this conclusion.

CHAPTER VII

THE TREATMENT OF

GONADAL DYSGENESIS

CHAPTER VII

THE TREATMENT OF GONADAL DYSGENESIS

(1) Psychological Management

Treatment cannot donate function to the primitive gonads. But one can do much to aid the patient.

An excellent psychological study by Hampson et al. (1955) shows that patients with gonadal dysgenesis are female in orientation, irrespective of their chromosomal patterns. Support for this view is derived from my own experience with the present series. Detailed analyses were not undertaken, but a knowledge of the patients, gained from repeated visits and discussions, indicated a normal female outlook in all cases. Two of the patients were married and appeared to derive normal satisfaction from sexual intercourse. Grumbach et al. (1956) state that "gender, including erotic orientation, is not automatically determined by the sex chromosomes, nor by the sex hormones". The major factor, no doubt, has been the effect of environment. In other words, patients with gonadal dysgenesis are assigned to the female sex and reared as females. They have no reason to

-regard-

regard themselves as anything but female. The psychological orientation, therefore, is that of a normal female and no hint of their underlying genetic masculinity is apparent.

Care must be taken to ensure that patients understand the basic physiological defect and that they have no fears of being regarded as freaks. Psychological management should include frank discussions aimed at eliminating these morbid speculations. Certainly the finding of a male chromosomal pattern should be withheld from the patients and relatives. This information can only give rise to confusion and distress. Therapy must be directed towards further feminisation of these neuter individuals.

(2) Oestrogens

Even small doses ($\frac{1}{2}$ mgm Stilboestrol daily) assist by stimulating mammary growth, feminizing the body contours, producing cyclical menstrual bleeds and furthering the development of the uterus and vagina. Figures 2.01, 2.03, 2.13 and 2.14 show the striking response in mammary size which followed oestrogen administration in Cases I and VII, S. L. and J. T. Gratifying results have been seen in all the patients who have been treated in this way. It has been interesting to observe the effects of oestrogen on areolar pigmentation. In almost all cases, darkening of these areas rapidly occurred. In Case III, L. R., however, 1 mgm of Stilboestrol produced no appreciable pigmentation after a

year of therapy. In 2 patients the areolae darkened, but, despite maintenance of therapy, they later became noticeably paler. This effect seems at variance with the accepted views on oestrogen and areolar pigmentation.

Very striking, too, has been the insistence by many patients that oestrogens produced more energy, greater drive and enthusiasm. This contention was supported, in some instances, by the views of independent observers. The father of one patient insisted that his daughter had displayed far more energy on the badminton court, following the institution of therapy ! Libido does not appear to have been increased in those patients in whom it has been possible to assess it; it must be stated, however, that the majority of the adult patients appeared to be normally-balanced from this point of view before therapy was instituted.

It is possible, on theoretical grounds, that oestrogen therapy will produce a growth-spurt, if given before epiphyseal closure, although it does not appear to have been effective in many reported cases. In the young patient it may be undesirable to administer oestrogens, in view of the psychological effect of mammary growth and menstrual bleeds.

Possibly, too, oestrogens might delay ageing processes, notably osteoporosis, to which these patients are particularly prone. The relationship of oestrogens to atherosclerosis and myocardial infarction in these "sex-hormone-less" females can only be speculative at present.

(3) Androgens

These, in small doses, may likewise encourage growth. Unfortunately, as reported by van Crefeld and de Vaal (1949), increased hair on the face and body might result. It is of the utmost importance that adequate growth-charts be kept of all young patients who receive hormonal therapy. In this way it may be possible to assess the efficacy of treatment with regard to height.

At present, androgens appear to have little or no place in the therapy of gonadal dysgenesis.

(4) Gonadotrophins

Though not strictly germane to the treatment of gonadal dysgenesis, the place of gonadotrophins must be discussed. Little response can be expected from the inert-looking vestiges which are generally found. But the partially-developed, hypoplastic ovaries seen in Cases A. B. and J. Tw. might well respond. In these cases, oestrogens might even be harmful by further suppressing an already slothful pituitary gland; gonadotrophins, on the other hand, might produce further maturation of the gonads with a small possibility, at least, of subsequent fertility. Gonadal dysgenesis and ovarian hypoplasia appear to be distinguishable only on laparotomy.

CHAPTER VIII

CONCLUSIONS (PART I)

CHAPTER VIII

CONCLUSIONS (PART I)

Turner's syndrome can no longer be regarded as the prototype of gonadal dysgenesis. Indeed, only a small proportion of cases conform to Turner's original description, and the diagnosis of gonadal dysgenesis must be entertained in all cases of primary amenorrhoea. Experience in a general endocrine clinic supports the belief that gonadal dysgenesis is the commonest cause of primary amenorrhoea - whatever the appearance of the patient.

The facial appearance of the patient is frequently helpful. While certain features, e.g. mandibular hypoplasia, asymmetry or ocular abnormalities are suggestive, there is often an indefinable oddness of the physiognomy which puts the diagnosis in mind. A history of bizarre swellings or the presence of numerous pigmented moles or naevi is supportive evidence; certainly the diagnosis should not be discarded because the patient is tall or because of good breast development. Even spontaneous menstruation would not appear to exclude gonadal dysgenesis.

Oestrogen therapy should be tried in all cases to assist development of the breasts and vagina. It may be undesirable in patients with "ovarian hypoplasia", which is considered the result of pituitary gonadotrophic failure.

The considerable clinical variability of gonadal dysgenesis has been established since methods of nuclear sexing have been available. As a result of these techniques, gonadal dysgenesis is being diagnosed more readily. It seems that the time is now ripe for detailed analysis of this augmented number of cases. Do these cases with genetic male nuclear structures differ in any way from those with female? Are any of the numerous congenital anomalies linked to one or other genetic sex? These and many other questions might be answered by careful scrutiny of a large number of cases.

CHAPTER XX

SUMMARY (PART I)

CHAPTER IX

SUMMARY (PART I)

Part I consists of a critical review of the syndrome of gonadal dysgenesis.

(1) The earliest reports of this condition are mentioned and the features of the "classical" syndrome are described. The nuclear "sexing" technique and its application to gonadal dysgenesis is reviewed.

(2) Case-reports of 23 patients with gonadal dysgenesis are presented. Certain investigation and reflections arising out of this study are reported :

i. Gonadotrophin excretion is discussed in relation to the syndrome.

ii. The effect of cortisone on the raised F.S.H. excretions was found to be negligible.

iii. Attention is drawn to the comparatively infrequent occurrence of the classical congenital anomalies in gonadal dysgenesis. Scepticism is expressed about the existence of cubitus valgus.

iv. Cutaneous moles and freckles are commonly found in the syndrome; reference is made to the occurrence of transient swellings and localised oedema, and to the curious theory which is proposed to explain them.

v. Breast development in gonadal dysgenesis is discussed in the light of biopsies performed on two patients.

vi. Anthropomorphic measurements were made in some subjects and were shown not to deviate from the normal female patterns.

vii. Tests of adreno-cortical function showed no impairment - even where sex hair growth was deficient. This tends to confute the view that the adrenal cortex governs axillary hair growth.

viii. Three patients are described who showed moderate to severe osteoporosis. The explanation of this finding is discussed.

ix. The results of the nuclear "sexing" test in this series are presented with a demonstration of its value in diagnosis. Some curious histological findings are analysed in relation to the nuclear patterns obtained.

(3) A patient is described who claimed to have menstruated for 5 years. Possible mechanisms of this phenomenon are debated.

(4) Gonadal dysgenesis is reported in a "normal-looking" female of above-average height. She is compared to two patients described by Swyer under the heading of "Male Pseudohermaphroditism : A Hitherto Undescribed Form". Reasons are given for regarding Swyer's cases as variants of the syndrome of gonadal dysgenesis.

(5) Two patients are reported who showed tall, eunuchoid proportions with low F.S.H. excretion and hypoplastic ovaries which were not typical of gonadal dysgenesis. It is postulated that these patients suffer from pituitary gonadotrophin failure rather than primary ovarian underdevelopment.

(6) The diagnosis of gonadal dysgenesis is discussed with particular reference to nuclear "sexing". It is pointed out that this syndrome is probably the most common cause of primary amenorrhoea - whatever the appearance of the patient.

(7) The treatment of gonadal dysgenesis is outlined. This should include careful psychological management and the use of oestrogens. Gonadotrophins should be used for cases of hypo-gonadotrophic ovarian hypoplasia.

- (8) It -

(8) It is suggested that detailed analyses of large numbers of cases of gonadal dysgenesis might prove fruitful.

PART II

GONADAL DYSGENESIS

AND

HERMAPHRODITISM

CHAPTER X

THE RELATIONSHIP

OF

GONADAL DYSGENESIS

TO

HERMAPHRODITISM

CHAPTER X

THE RELATIONSHIP

OF GONADAL DYSGENESIS TO

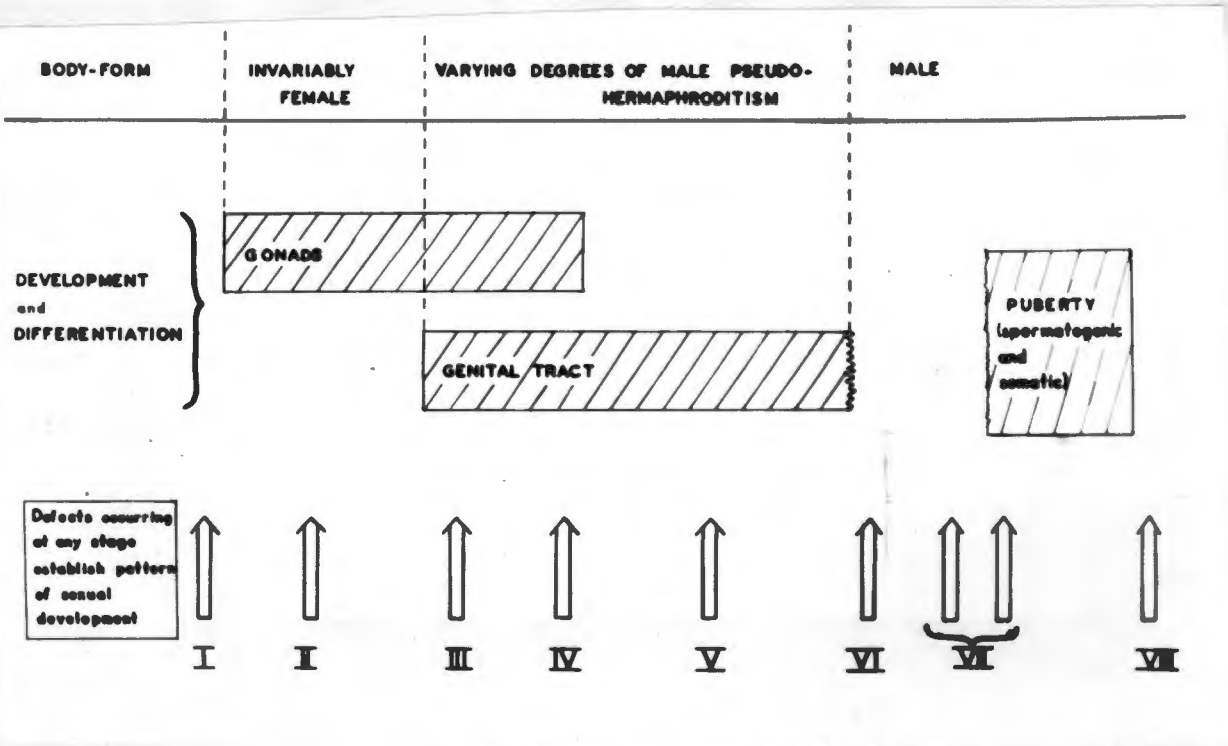
HERMAPHRODITISM

The experiments of Jost and others have led to an elucidation of the status of gonadal dysgenesis in relation to other hermaphroditic conditions. It was shown quite clearly that loss of testicular function at a vital stage of embryonic development was followed by feminization. The earlier this "castration" of genetic male embryos occurred, the more physically complete was the feminization and the less obvious were the tokens of the genetic maleness of the foetus. The later the "castration", the more male features were present. These might be subtle manifestations such as mild enlargement of the clitoris or the persistence of prostatic remnants; or the clinical picture might show only the slightest deviations from normal male development. Grumbach et al. (1955) applied the results of these experiments to human beings, suggesting that male pseudohermaphroditism was the result of intrauterine testicular damage in genetically-determined male embryos. Gonadal dysgenesis appeared to be the extreme form of this aberration, in which testicular function was lost before any male differentiation had occurred, so that all subsequent development

was along female lines. This provided a neat and satisfactory explanation of the presence of male nuclear patterns in the apparent female bodies of patients with gonadal dysgenesis. It explained, too, the presence in gonadal dysgenesis of male remnants such as prostatic elements - here, presumably, some male differentiation had taken place before the testes failed. Grumbach et al. reported a patient with some congenital anomalies of Turner's syndrome, a male skin sex pattern and pseudo-hermaphroditic external genitalia; this case seemed to provide the final link in the chain which joined gonadal dysgenesis to male pseudohermaphroditism.

Thus the entire spectrum could be represented diagrammatically as in Figure 10.01.

In this diagram, male eunuchoidism is included, since it represents a form of prepubertal gonadal failure. Klinefelter syndrome will be discussed fully in a later chapter; some forms, at least, appear to be due to gonadal failure at or about pubertal age; these forms show male nuclear patterns ("False Klinefelter Syndrome" of Nelson, 1956) and would appear to have a place in this spectrum of events.



This diagram illustrates the possible results of gonadal failure - intra-uterine or post-natal - at various stages of male development. This gonadal failure could be due to congenital or acquired factors.

The ultimate body-form depends on the stage of embryonal development at which the testicular defect occurs. Any residual differentiation of the genital tract can only occur in a female direction.

At any stage, it is suggested, the primary defect may reside in the gonads or the pituitary gland, since full function of both is necessary for normal maturation. (See later.)

I. "Castration" at this stage? ... Agonadal individuals (? male forms possible).

II. ..... Gonadal Dysgenesis (genetic males with female body form).

III. ..... Gonadal Dysgenesis with some androgenic manifestations.

IV. ..... Male Pseudo-hermaphroditism (recognisable testes, but female characters in external genitalia).

V. ..... Male Pseudo-hermaphroditism with minimal female features.

VI. ..... Male Eunuchoidism.

VII. ..... Some varieties of Klinefelter Syndrome ("False Klinefelter Syndrome" of Nelson, 1956).

VIII. ..... Normal stature, with complaint of sterility and variable loss of libido.

CHAPTER XI

CURRENT CONCEPTS

OF

HERMAPHRODITISM

CHAPTER XI

CURRENT CONCEPTS OF HERMAPHRODITISM

(1) THE KLEMS CLASSIFICATION

Nuclear sexing has thus been extremely valuable in indicating the nature of gonadal dysgenesis and in elucidating the pathogenesis of male pseudohermaphroditism. It is proposed to consider other forms of hermaphroditism in the light of this sexing technique.

It is estimated (Young 1937) that some form of ambiguous sexual development occurs approximately once in every thousand births. Perhaps the simplest classification is that which is based on gonadal histology :-

i. True Hermaphroditism:

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 ovo-testis (i.e. a gonad containing both ovarian and testicular elements).

- ii. Female -

ii. Female Pseudohermaphroditism:

Both gonads are ovaries, but there is development of some male accessory organs (Wolffian duct derivatives).

iii. Male Pseudohermaphroditism:

Both gonads are testes, but female genital ducts and/or external genitalia are found.

This classification was proposed in the year 1876 by Klebs, and appears satisfactory to the present day. Unfortunately it gives no indication of etiology nor of the underlying basic defect; nor does it help in the important decision of sex assignment.

(2) VILKINS' MODIFICATION OF THIS CLASSIFICATION

Wilkins et al. (1955) express their dissatisfaction with the Klebs classification of hermaphroditism. They prefer to divide cases into :

i. Sex Reversal due to active, continued secretion of abnormal hormones by one of the endocrine glands.
The common type of female pseudo-hermaphrodite with adrenocortical overproduction of androgenic hormones fits into this category. This hyper-adrenocorticism is recognisable after birth by precocious somato-sexual development in a male direction and by the very high levels of 17-ketosteroid excretion which persist throughout life. Not only has adrenocortical dysfunction been proved in these patients, but the precise hormonal defect has been demonstrated by several workers (Wilkins, 1950 and 1952, Eberlein and Bongiovanni, 1955, Bongiovanni and Eberlein, 1955, Jailer, 1953, Jailer et al. 1955).

ii. Intersexuality, where there is abnormal development in early foetal life - the

-result-

result of either genetic or intra-uterine influences.

This group is further subdivided into those:

(a) with mixed gonads i.e. true hermaphrodites.

(b) with testes i.e. male pseudohermaphrodites. Three types may be differentiated (Bishop, 1954). First is the masculine type with no apparent abnormality of the external genitalia - non-descent of a testis leading to exploration and unmasking of a uterus and fallopian tube. The second type is "indifferent", and is characterised by hypospadias, a bifid scrotum or the presence of a vagina. The third, or feminine, type includes a rare and distinctive condition attributed to oestrogen-producing testes. (PART II, CHAPTER XII.)

(c) with ovaries. This type contains a very rare form of female pseudohermaphrodite, in whom adrenocortical hyperfunction cannot be demonstrated. It is postulated that this anomaly is due to a temporary phase of intra-uterine adrenal over-activity, affecting a genetic female and causing intersexual development. Since this hormonal imbalance is temporary, it is no longer detectable after birth.

- This -

This classification adds little to that of Klebs, except that it separates a group which is due to measurable hormonal dysfunction.

3. ETIOLOGICAL CONCEPTS

Current concepts of etiology might be summarised as follows :

(i) True Hermaphroditism

This is attributed to a genetic aberration (Wilkins et al. 1955, Greene et al. 1953, Bromwich 1955), although possible hormonal and environmental influences cannot yet be excluded. The pattern of sex chromosomes in these individuals is not known with certainty. They may be male or female on nuclear sexing, with a bias in favour of females (Lennox 1956). Greene et al. have postulated that their true hermaphrodite subject had three sex chromosomes - an XXY pattern. Barr (1954) has suggested an alternative pattern consisting of a single X chromosome, or possibly no sex chromatin at all. If Greene's postulate were true, this XXY chromatin mass should be easily visible and would simulate the normal female nuclear pattern; if Barr's suggested patterns obtained, no sex chromatin would be visible in the cells and the male pattern would be simulated.

- (ii) Female -

(ii) Female Pseudohermaphroditism

The common form is attributed to excessive production of adrenocortical androgenic hormones, which persists after birth. The nuclear pattern is female - as would be expected, since nuclear patterns do not appear to be affected by hormonal influences (Lennox 1956)

The less common form without demonstrable adrenal overaction has been reported with a male skin sex, despite the presence of ovaries (Barr 1954, Jolly 1956). This finding tends to refute the theory of temporary intra-uterine adrenal overactivity, which has been advanced by Wilkins et al. (1955). Indeed, it suggests the probability of a genetic aberration (see later).

(iii) Male Pseudohermaphroditism

The common forms of this abnormality have already been discussed in relation to gonadal dysgenesis and experimental animal work (PART II, CHAPTER X).

The rare type of oestrogen-producing testes cannot easily be fitted into the same spectrum and will be considered separately (PART II, CHAPTER XII).

(4) ILLUSTRATIVE CASE-REPORTS

(i) True Hermaphroditism. (Figures 11.01 and 11.02)

A. G. African aged 20 years.

The patient was raised as a boy and employed as a gardener. At puberty, breasts developed and the expected male changes failed to appear. He did not shave nor display any interest in the female sex. Menses did not occur.

On examination he was tall with a slender female habitus. The breasts were well-developed and contained palpable mammary tissue. The external genitalia consisted of a fairly well-formed phallus and a bifid scrotum, in the right half of which was a gonad which felt like a normal testis (Figure 11.03). At laparotomy a uterus, two fallopian tubes and a single ovary (on the left side) were identified (Figure 11.04). Ovarian tissue was confirmed histologically, whereas biopsy of the right scrotal gonad showed only testicular elements.

Comment: True hermaphroditism was proved by the demonstration of both ovarian and testicular structures in the same individual.

- (ii) Female -

Figure 11.01

Case A. C. - Anterior view

This displays the patient's habitus and good breast development.

Figure 11.02

Case A. C. - Lateral view

The overall femininity of the physique is illustrated in this view.

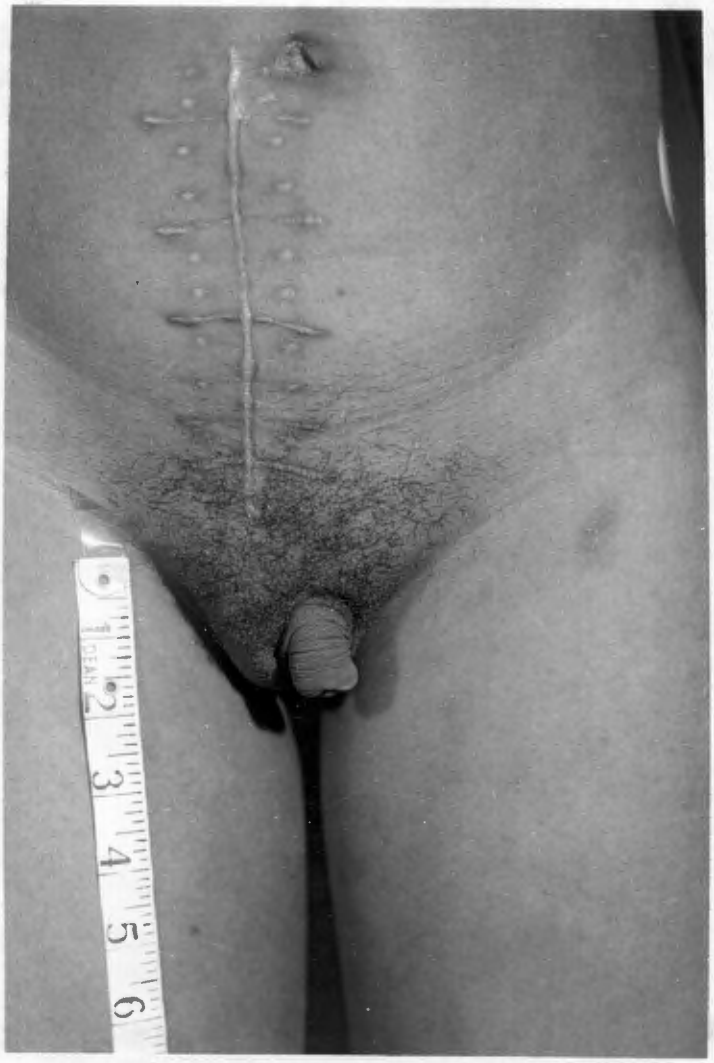


Figure 11.03

Case A. C. - External genitalia

This shows a fairly well-formed phallus and a solitary gonad on the right side.

Figure 11.04

Case A. C. - Pathological specimen

This operation specimen shows a uterus, two fallopian tubes and a left-sided gonad which was shown to be an ovary.

(ii) Female Pseudohermaphroditism. (Figure 11.05)

L. R. European aged 23 years.

This patient was raised as a female. When she was 16 years old, her voice deepened, sex hair appeared and followed a male distribution, and the limb musculature strengthened in a male fashion. Menstruation failed to appear and the breasts did not enlarge.

On examination (Figure 11.05) the scalp hair was cropped short and there was moderate temporal hair recession. Facial and body hair was profuse with a typical male pubic escutcheon. The external genitalia consisted of a minute urogenital sinus with a phallus about 1½" in length. (Figure 11.06). External gonads were not felt. The limbs were hairy and muscular, the breasts undeveloped. Skin nuclear pattern was female. Cystoscopical examination with dye insertion was performed and the radiological appearance is depicted in Figure 11.07.

Urinary 17 - ketosteroid excretion was 134 mg/daily. Laparotomy disclosed a small uterus, well-developed fallopian tubes and two ovaries. No testicular elements were found on histological examination of the latter.

- Comment -

Comment: A typical case of female pseudohermaphroditism due to adrenocortical hyperplasia (proved by the very high excretion of 17 - ketosteroids).

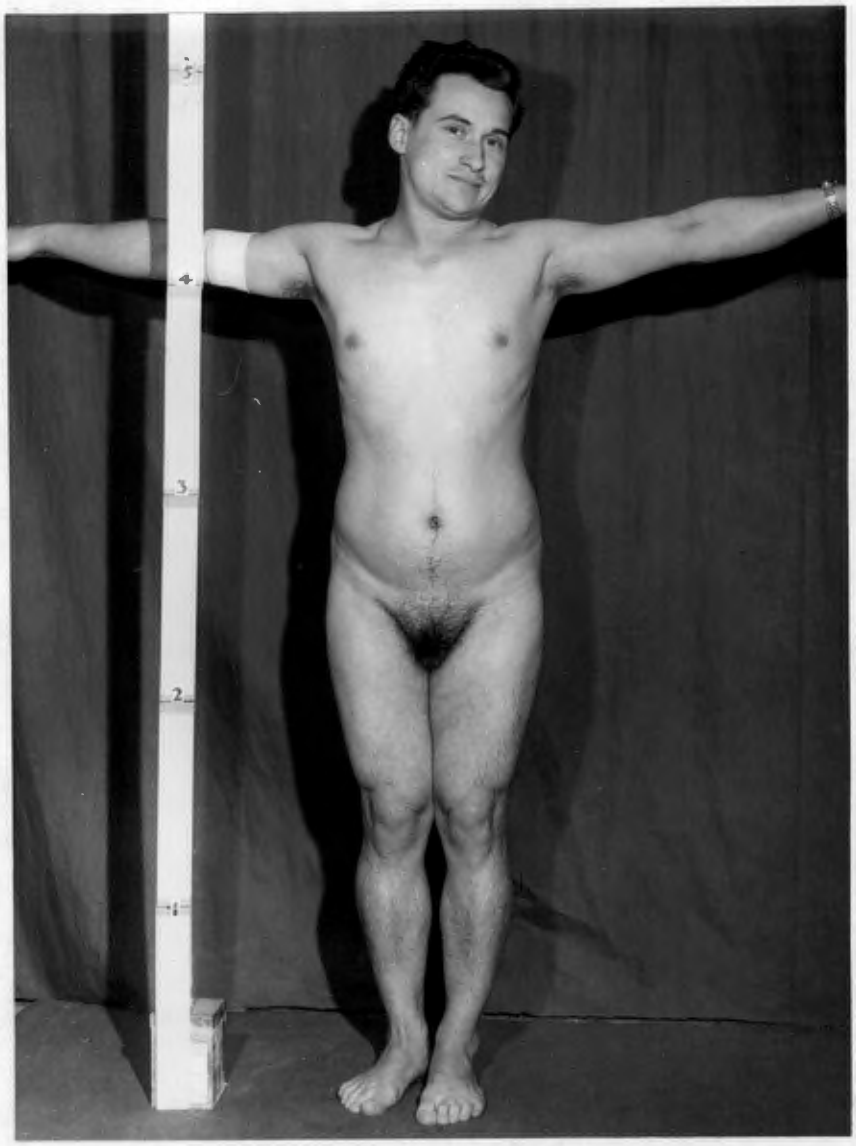


Figure 11.05

Case L. Ross.

Note the short-cropped scalp hair, temporal recession, muscular body and limbs.

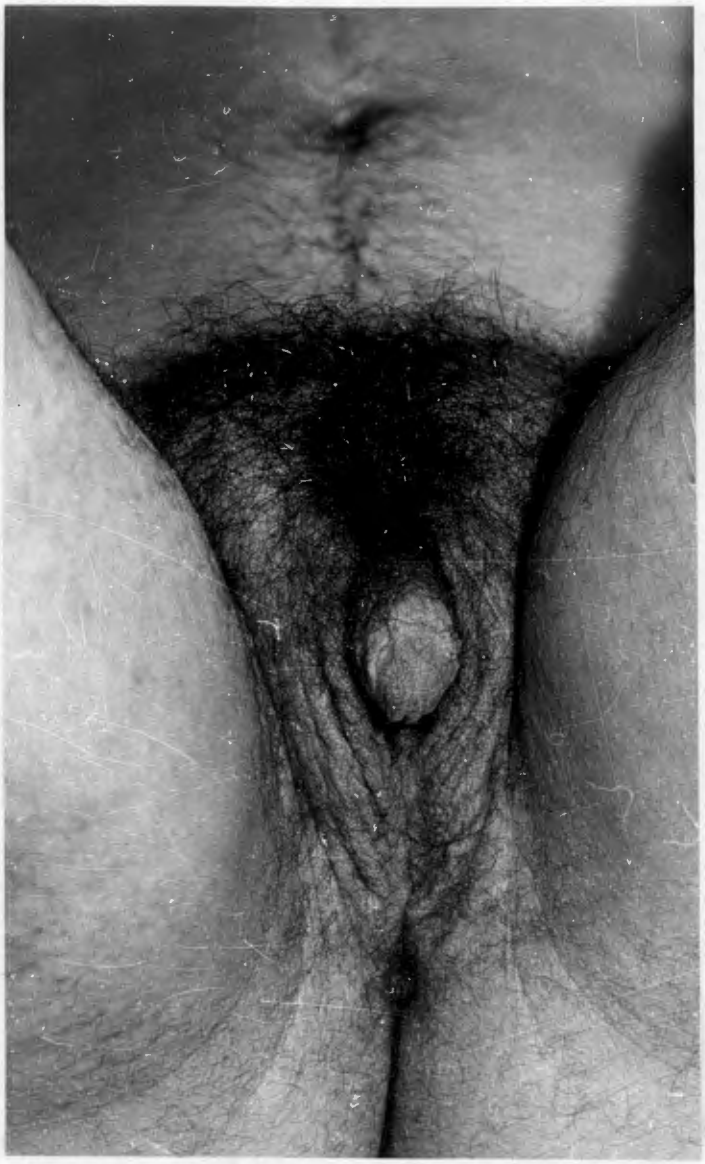


Figure 11.06

Case L. Ross. - External genitalia

This shows a well-formed phallus; the single urogenital sinus was situated immediately below its base.

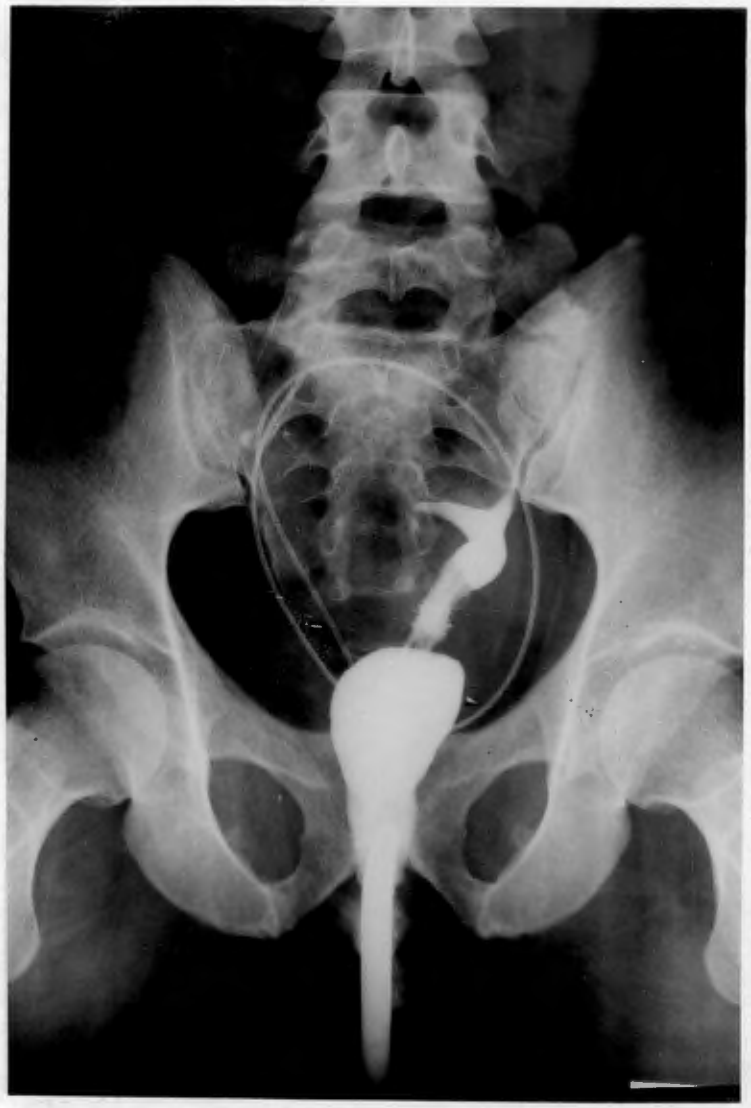


Figure 11.07

Case 1. Mrs. - X-Ray appearance

The injected dye displays the bladder, uterus and two fallopian tubes.

(iii) Male Pseudohermaphroditism - Common Form

M. E. European aged 27 years. (Figure 11.08).

Despite ambiguity about this patient's external genitalia, she was reared as a girl. When she was 14 years old, a practitioner, convinced of her femaleness, amputated a fairly large phallus, at the same time removing 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 male lines. Neither breasts nor menses appeared. Instead the voice deepened, facial hair grew and soon advanced to a degree which required daily shaving. The body contours assumed a muscular male configuration. Oestrogen therapy was instituted with ensuing slight breast development, but no diminution in the masculinity.

The patient continued to live and work as a female, until she decided to seek assistance when she was 27 years old. On examination she was attractive but hirsute; axillary and pubic hair was profuse - the latter of male distribution. The limbs were muscular and hairy, the breasts poorly developed with dark areolae (probably related to prolonged oestrogen therapy). External genitalia comprised hypertrophied labioscrotal folds enclosing a rudimentary vagina, and, anteriorly, the scar of

the amputated phallus (Figure 11.09). In the right fold a bean-sized gonad was felt with an apparent epididymis attached. A small, blind vaginal pouch was present, but there was no evidence of other Müllerian derivatives. 17 - ketosteroid excretion was normal. Skin nuclear pattern was male.

Vaginoplasty was performed and the remaining gonad was excised. This proved to be a degenerate testis (the degeneration probably reflects the action of oestrogen administered over a long period).

Comment: The presence of a phallus and two completely descended gonads (one histologically a testis) strongly suggests the common type of male pseudohermaphroditism with hypospadias and a blind vaginal pouch as the manifestations of partial genital feminization.

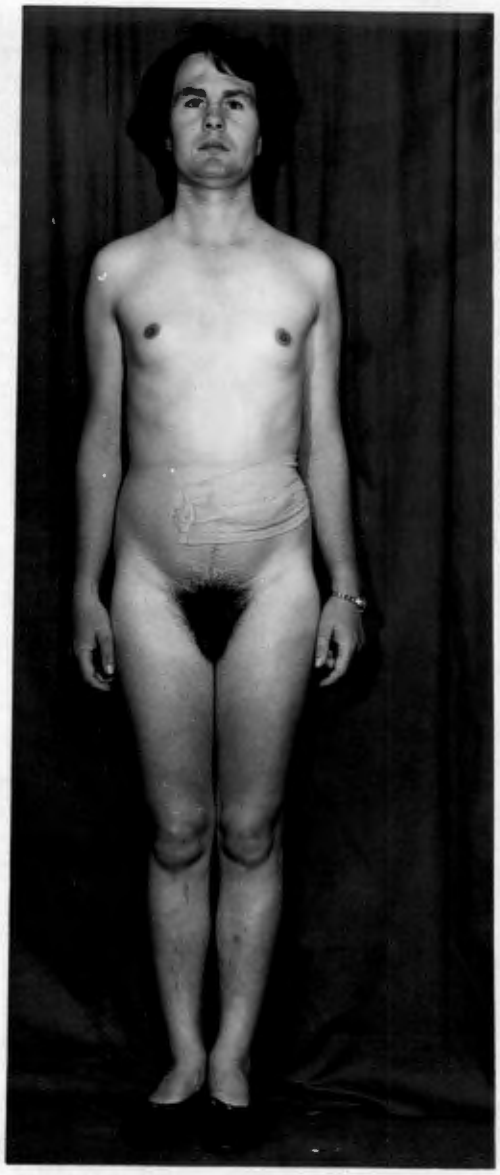


Figure 11.08

Case M. K.

Note the dark shadow of the shaved chin, the rather masculine physique, the poor breasts and dark areolae (due to oestrogen therapy) and profuse pubic hair growth.

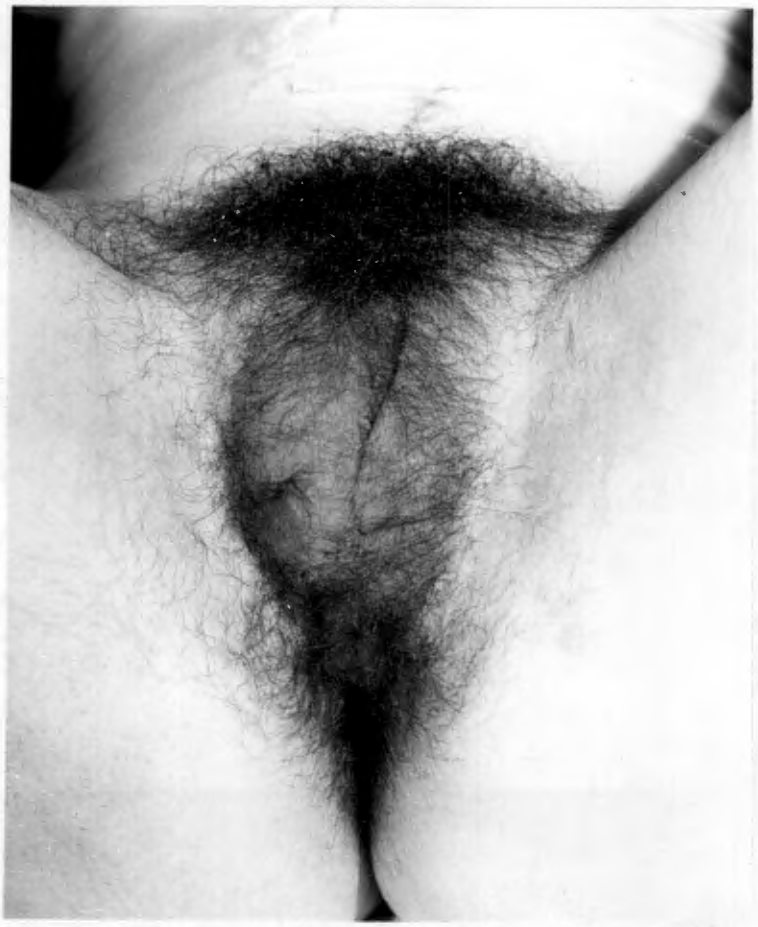


Figure 11.09

Case M. E. - External genitalia

The bulge on the right side contained a gonad with epididymis attached.

(iv) Male Pseudohermaphroditism - Uncommon Form

S. P. Coloured aged 24 years. (Figure 11.10).

The patient presented with pain in the inguinal region following trauma. She had never menstruated. The appearance was that of a normal female with good breast development. Axillary hair was absent; a few downy hairs were seen on the labia majora, but, apart from these, there was no pubic hair. Neither a uterus nor adnexae were felt; speculum examination revealed a blind vagina with no visible cervix uteri. P.S.H. excretion was positive at 96 mouse units; the skin and leucocyte nuclear pattern was male. Two swellings were found in bilateral reducible inguinal hernias; biopsy proved them to be testes.

Comment: This is a typical example of the rare form of male pseudohermaphroditism due to oestrogen-producing testes. This anomaly will be discussed in the next chapter.

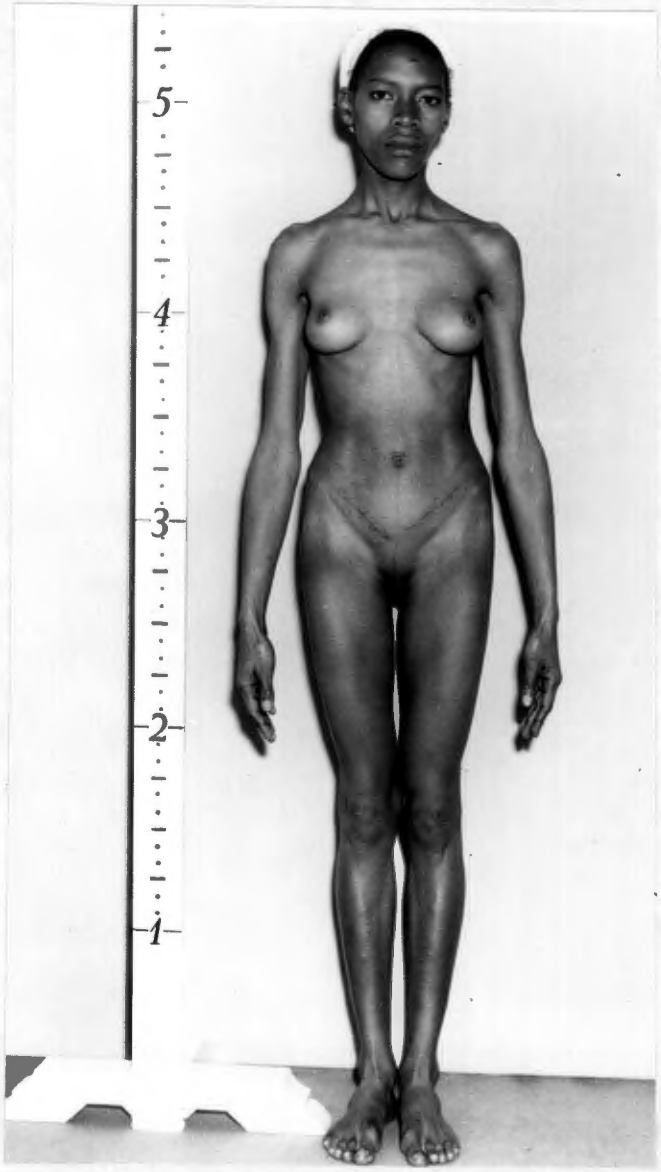


Figure 11.10

Case S. F.

This view shows the thin, eunuchoid build, the good breast development, the absence of pubic hair and the scars in the inguinal regions, from which testes were removed.

CHAPTER XII

HERMAPHRODITISM RECONSIDERED

CHAPTER XXI

HERMAPHRODITISM RECONSIDERED

(1) DISCREPANCIES IN PRESENT-DAY THEORIES

Unfortunately, the etiological concepts outlined in the preceding chapter are not wholly acceptable. Close examination reveals certain discrepancies :

(a) The curious finding of a male nuclear pattern in a patient with female pseudohermaphroditism not due to adrenocortical hyperfunction.

(b) The occurrence of male pubertal changes in some cases of male pseudohermaphroditism. If this condition results from testicular failure which allows subsequent partial feminization, why does this feminizing process not continue through the pubertal period? Male pubertal changes, which appear to depend upon normal gonadal endocrine function, are unexpected.

(c) The lack of raised urinary gonadotrophin output in male pseudohermaphroditism. If this condition represents a sort of late form of gonadal dysgenesis, one should find the high gonadotrophin excretions which accompany any primary

gonadal failure. Studies made on these patients have seldom shown this, except in the syndrome of oestrogen-producing testes, which appears to justify separate etiological consideration.

(d) The body-form in completely agonadal subjects. Some individuals are reported in whom thorough search fails to reveal even the primitive streaks of gonadal dysgenesis (Gross and Meeker, 1955). Such agonadal cases may show male or female external appearance. On the above theories, one would not expect male differentiation to occur without the masculinizing influence of testes.

(e) The presence of a female nuclear pattern in a case of gonadal dysgenesis with androgenic manifestations (clitoral hypertrophy) (Gordan et al. 1956). A large clitoris was also found in Case XXI, E. R., who showed a female nuclear pattern. Minor tokens of masculinity in gonadal dysgenesis are explained by the relationship of this syndrome to male pseudo-hermaphroditism - that is, gonadal dysgenesis with androgenic manifestations is regarded as an incomplete form of the latter abnormality. The nuclear pattern should then be male.

(f) The recent demonstration of female nuclear patterns in "men" with primary prepubertal hypogonadism (e.g. Klinefelter syndrome) (Bradbury et al. 1956; Riis et al. 1956; Jackson et al. 1956; Plunkett and Barr, 1956). Reference to another patient with male eunuchoidism, apparently of primary gonadal etiology, and with a female leucocyte pattern is made by Briggs and Kupperman (1956). They appear to have regarded this finding as a reflection of the fallibility of the sexing method. The subsequent reports seem to vindicate the method. The case-report of a patient with primary hypogonadism and female nuclear sex follows:

(2) TESTES IN A GENETIC FEMALE

Case-report: A. V. European aged 35 years.

The first intimation of abnormality was at puberty, when the penis and testes remained small, the voice failed to break and sex hair-growth did not occur. Erections and emissions were occasionally experienced, but interest in women was lacking; homosexual tendencies later developed. Intermittent testosterone therapy stimulated some penile growth and mild facial hirsutes.

On examination (Figure 12.01) he was obese, of feminine build, with a span greater than his height. (Height 5' 4"; span 5' 5½"). The penis was small, the testes fully descended, but soft and tiny. Epididymes were present. There was sparse facial hair-growth, adequate axillary hair and a female pubic escutcheon. The voice was high-pitched.

Urinary F.S.H. excretion was strongly positive at 48 m.u. Testicular biopsy showed an abundance of Leydig cells, germinal cell aplasia with persistence of Sertoli cells - a pattern conforming to the expanded concept of Klinefelter syndrome, as described by Heller and Nelson (1945). Skin and leucocyte nuclear patterns were female.

Nelson (1956) has studied 134 individuals with the diagnosis of Klinefelter syndrome. He claims that it is possible to separate two distinct forms: 1). The first group he calls "True Klinefelter syndrome"; these show a characteristic

testicular histology (small completely hyalinised tubules, occasional Sertoli cells and variable numbers of Leydig cells); they have a female chromatin pattern. 2). Another group shows similar testicular histology, but certain differences are apparent - the tubules are larger and more uniformly spaced; active spermatogenesis is possible; and the Leydig cells do not tend to aggregate as much. This group, Nelson calls "False Klinefelter syndrome". The nuclear pattern is male.

Nelson contends that this second group is the result of post-pubertal sclerosis from unrecognised causes. "True Klinefelter syndrome", in view of the female nuclear sex, is best regarded as an early intra-uterine anomaly affecting a genetic female. The diagnosis is made only at puberty, when the abnormal small testes, the gynaecomastia and the eunuchoid habitus become apparent. Support for the genetic nature of this anomaly is gained from its occurrence in several pairs of brothers and in 9 members of a single family. Nelson's suggested title of "Female Pseudohermaphrodite with gonadal dysgenesis" is not a good one, since the term "female pseudo-hermaphrodite" is generally accepted as indicating an individual with ovaries and intersexual development. Here the gonads are histologically testes.

Case A. V. appears to conform to Nelson's concept of "True Klinefelter syndrome". A theory, based on experimental animal work, has been propounded to account for male nuclear patterns in apparently female bodies (as seen in some cases of gonadal dysgenesis). But there is no satisfactory

explanation of female patterns in apparently male bodies. The development of testes in a genetic female requires interpretation.

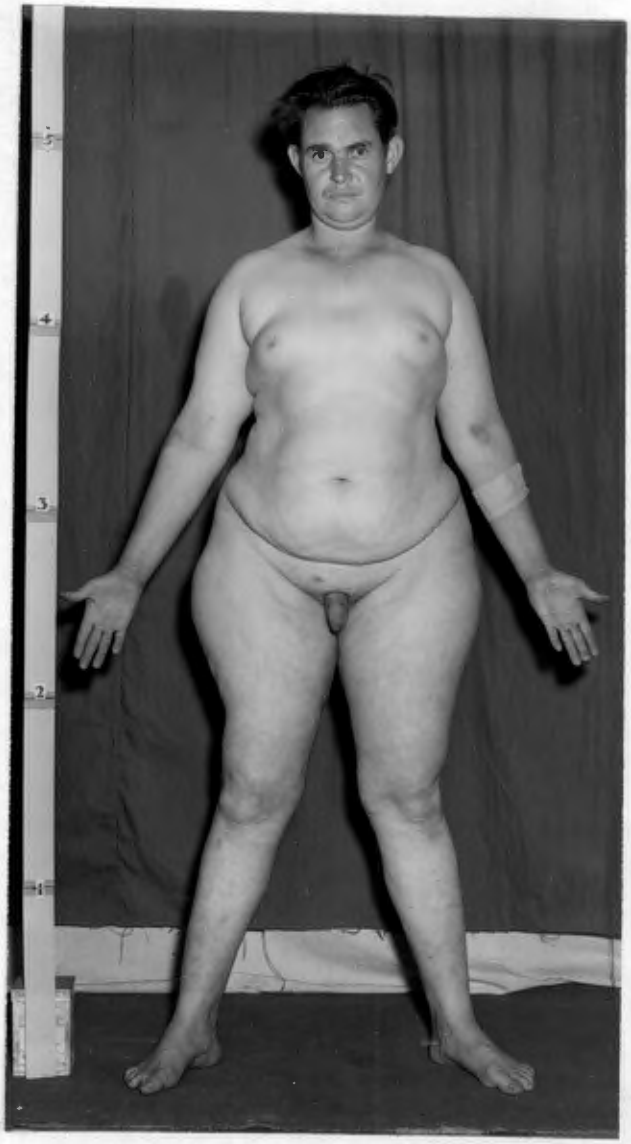


Figure 12.01

Case A. V.

Note the feminine build with wide hips and fatty breasts and pelvic girdle. The penis increased in size after testosterone therapy.

(3) A REVISED THEORY OF SEXUAL DIFFERENTIATION

The abovementioned discrepancies seem at variance with either the validity of the "sexing" method and its interpretation as an index of genetic sex, or with the theories of sexual differentiation. As yet, normal males and females have not been shown to differ from their expected nuclear patterns. That such a divergence is seen only in people with abnormal sexual development suggests that the fault lies in our theories rather than in the "sexing" methods. A revised theory is now offered to account for those intersexual states which appear to be primarily anatomical rather than hormonal in etiology (i.e. states other than female pseudohermaphroditism with proven adrenocortical hyperfunction).

It has been postulated that a chemical inductor or evocator exerts a very early influence on the primitive genital ridge, stimulating gonadal development into either testis or ovary. (Witschi 1951). It appears possible to incorporate such an "evocator" into a theory which would overcome some of the difficulties discussed above. It is necessary to assume the existence of two evocators, one responsible for the development of ovaries, the other for testes. One or other of these evocators normally predominates to produce a definitive gonad, the function of which is then responsible for the differentiation of the body into male or female form. It is believed that the sex of an infant is

predetermined genetically before any evidence of genital distinction appears. (This belief is supported by study of cat embryos, which show the nuclear sex difference before the gonads have differentiated (Graham 1954; Lennox 1956)).

Normally, in a genetic male, the evocator induces formation of testes. These elaborate a further hormone which is responsible for normal masculinisation. What would happen to a genetic male who was influenced unduly by the wrong, female evocator? Such an individual would develop ovaries, and, in accordance with the theories of Jost and others, would assume the neuter, female form. If this were so, one might expect an occasional "normal" female to show a male type of nuclear pattern. Such an occurrence has not been reported. However, this theory might account for one hitherto unsatisfactorily explained group - the female pseudohermaphrodites without demonstrable adrenocortical overactivity. Despite the presence of ovaries, such individuals have been found with male chromatin pattern (Barr 1954; Jolly 1956). Perhaps these are examples of misdirected "evocation".

Genetic females normally are influenced by the female evocator; ovaries develop with a normal female genital apparatus. Once again let us consider the influence of a male evocator on a female embryo. The gonads would become testes; these might elaborate male hormone of the type necessary for male differentiation - such an individual would show male external genitalia

with female type nuclear pattern. Although this has not been demonstrated in normal males, it has been shown in some eunuchoid males who have no intersexual anatomical features whatsoever (Bradbury et al. 1956; Riis et al. 1956; Jackson et al. 1956) - the "true Klinefelter syndrome" of Nelson (1956).

Finally, if the genital tract remains uninfluenced, i.e. if the evocator system fails completely, then the gonads fail to differentiate, but persist in the primitive state as seen in gonadal dysgenesis. If this occurs in a genetic female, one finds gonadal dysgenesis in a female with female nuclear sex. If it occurs in a genetic male, one finds gonadal dysgenesis in an apparent female with male nuclear sex. Further, if the gonad in a genetic male fails and its influence ceases at a slightly later stage of embryonic development, one finds partial differentiation of the genital tract, in other words, male pseudohermaphroditism.

The above considerations are represented in Table 3. Included in this table are the results of other intra-uterine hormonal imbalances, i.e. excessive androgen or oestrogen production.

These theories, admittedly, are of a speculative character and leave several problems unanswered. Some of these problems will now be considered.

TABLE 1.

	GENETIC MALE	GENETIC FEMALE
Male Evocator in ascendancy	Male gonads; male external genitalia; male "chromatin" (normal males)	Male gonads (? abnormal); male external genitalia; female "chromatin." (e.g. Klinefelter syndrome)
Female Evocator in ascendancy	Female gonads; female external genitalia; male "chromatin" (female pseudohermaphrodites with male "chromatin" and no evidence of hyperadrenocorticism; "normal" female with male "chromatin" possible ?)	Female gonads; female external genitalia; female "chromatin". (Normal females)
Failure of Evocator system	Agenetic gonads*; female external genitalia; male "chromatin".	Agenetic gonads*; female external genitalia; female "chromatin".
Failure of developing gonad	Dysgenetic gonads; male pseudo-hermaphrodites, etc; male "chromatin".	Dysgenetic gonads; female external genitalia; female "chromatin".

Excess / .....

TABLE 3. (Continued)

	GENETIC MALE	GENETIC FEMALE
Excess intra-uterine androgen	Infant Hercules	Common form of female pseudohermaphrodite with female "chromatin" and evidence of hyperadrenocorticism.
Excess intra-uterine oestrogen	Oestrogen-producing testes; female external genitalia with male gonads and male "chromatin".	

* FOOTNOTE: "Agenetic" gonads refers to gonads which have not developed beyond the primitive ridge - in contrast to "dysgenetic gonads", where some development has occurred.

(4) SOME IMPERFECTLY-EXPLAINED FACTS

- 1 - The occurrence of agonadal individuals with either male or female body-form is not explicable in terms of Jost's theories. A congenitally agonadal embryo should be capable only of female differentiation; the recognition of male subjects with agonadism suggests that the fault is not genetic, since masculinising testicular influences must have been present initially. The most feasible explanation is that these gonads were "destroyed" by some acquired, late intra-uterine or post-natal influence (perhaps infective) with subsequent absorption of these damaged organs. (Total absorption of a gonad is not inconceivable - under certain circumstances, even bone can "disappear".) Complete male differentiation would have taken place before the gonadal destruction.

- 2 - Reference was made earlier to a patient with gonadal dysgenesis with male skin sex, whose gonads displayed histological evidence of developing ovarian follicular cysts (Case XX, R. S.). These vestigial gonads, in a chromosomal male, should be embryonic testes. Why did ovarian maturation occur?

The situation might be compared to that encountered in "True Klinefelter syndrome". In the latter, incorrect evocation in a genetic female has been postulated; testes develop instead of the expected ovaries; but

testicular maturation is incomplete, i.e. the testes are abnormal. Conversely, in Case XX, R. S., one could suggest abnormal evocation in a genetic male; ovaries develop instead of testes; and, once again, these ovaries are abnormally immature. Thus, the end-result appears to be a mirror-image of the state of affairs in "True Klinefelter syndrome". This may be illustrated in brief :

	"True Klinefelter Syndrome"	Case XX, R. S.
Genetic Sex	Female	Male
Aberrant influence by:	Male evocator	Female evocator
Gonadal development	Testes, but full maturation is halted	Ovaries, but full maturation is halted
Body-form	Male (adequate testicular function for male differentiation)	Female (since testicular influence lacking)
Subsequent Course:	Failure of spermatogenesis	Failure of menstruation

- 3 - One further group requires elucidation. Greenblatt et al. (1956) report a patient with gonadal dysgenesis (proved by laparotomy), a large clitoris and a female skin sex. Case XXI, E. R., shows the same set of

circumstances. In her case, gonadal dysgenesis may be inferred from the primary amenorrhoea, shortness of stature and webbing of the neck, but laparotomy confirmation is lacking.

On the theories of Grunbach et al. (1956) gonadal dysgenesis-with-androgenic-manifestations (e.g. clitoral enlargement) is really a variety of male pseudohermaphroditism, where the clitoral enlargement is thought to be a subtle token of the original genetic maleness of the subject. As in this form of intersex, these patients should display the male chromatin pattern. Yet in both of the cases cited above a female nuclear pattern was found.

The clitoral enlargement in these cases suggests the influence of androgen. Adrenal androgen production is unlikely - in neither case was there evidence of sexual precocity; nor was there hirsutes of a male type; in Greenblatt's case the urinary excretion of 17 - ketosteroids was only 4.4 and 2.6 mg. per day. It seems likely that the androgen is derived from the gonads. If these gonads are vestigial ovaries - as would be expected from the female chromatin pattern - then they constitute a variety of "androgen-producing ovaries" (the antithesis of "oestrogen-producing testes" referred to earlier). If, however, these gonads are vestigial testes, one must invoke the influence of abnormal evocation to account for the presence of "testes" (albeit vestigial) in a genetic female. This condition might thus be an "early stage" of "True Klinefelter syndrome": A genetic female, under the influence of a male evocator, develops testes. These fail

at an early intra-uterine age, so that body feminization ensues; the failure, however, is not complete, as evidence of some androgen production is provided by the clitoral enlargement. In "True Klinefelter syndrome", a genetic female is influenced by a male evocator. The resulting testes are less completely damaged (perhaps later); male body development (which may be eunuchoid) is permitted, but testicular abnormality is evident both clinically and histologically.

(5) OESTROGEN-PRODUCING TESTES

The condition of oestrogen-producing testes was first recognised and publicised by Goldberg and Maxwell (1948). Since then several reports of this interesting syndrome have appeared (Schneider et al. 1952; Morris 1953).

In this condition, nuclear (genetic) males possess testes which apparently produce oestrogen but insufficient androgen. The body-form and external genitalia are female in type; breasts develop, but menses do not occur. There is no uterus nor cervix, the vaginal pouch ending blindly, often in a small dimple. P.S.H. excretion is moderately high. The gonads characteristically are in the abdomen, sometimes in reducible inguinal hernias; histology shows them to be devoid of ovarian elements, but they contain small tubules with no germinal cells, and Sertoli and Leydig cells in abundance (the appearance of immature, cryptorchid testes). That these testes are the site of oestrogen production is shown by the results of castration - hot flushes may occur, the breasts atrophy, the vaginal smears lose all evidence of oestrogenization and a further rise in P.S.H. excretion occurs. A reversal or disappearance of these castration effects can be brought about by oestrogen administration.

The cause of this strange testicular behaviour is

not known at present. A hereditary factor, perhaps dominant, is suggested by the strong familial incidence of the abnormality - Schneider et al. describe 6 cases in one family. Other hormonal disorders, e.g. congenital adrenal hyperplasia, female pseudohermaphroditism or macrogenitosomia praecox are frequently found in siblings of patients with oestrogen-producing testes. Whatever the cause of the basic defect, the resulting bodily feminisation has not been questioned - it has always been attributed to the oestrogenic excess. It appears that this might not be the important factor. In accordance with Jost's work, it seems more likely that the feminisation is due to lack of male hormone rather than to an excess of female - analogous to the state of affairs in gonadal dysgenesis. One striking difference between gonadal dysgenesis and the syndrome of oestrogen-producing testes (which renders this analogy incomplete) is the development of breasts in the latter syndrome but not usually in the former. This difference is probably explained by the presence of sufficient circulating oestrogen in oestrogen-producing testes, whereas in gonadal dysgenesis the gonads do not generally produce enough oestrogen to bring about breast development.

It is of interest that patients with oestrogen-producing testes show total lack of axillary and pubic hair. As mentioned earlier, Albright et al. (1942) consider the adrenal cortex to be responsible

for axillary hair growth. In Case S. P., 17 - ketosteroids were found to be normal (9.8 mg/day) and plasma cortisol rose from 2 mg % to 12 mg % under the influence of intravenous A.C.T.H. This appears to indicate normal adrenocortical responsiveness and activity. As with cases of gonadal dysgenesis, adrenal underaction could not be implicated in the failure of axillary hair-growth in this case. Wilkins (1950) and Schneider et al. (1942) examined biopsy specimens of skin taken from the mons veneris in cases of this syndrome. They showed that normal hair follicles were present microscopically. Testosterone, applied locally in the form of inunctions or administered systemically, produced no response in hair growth. Wilkins concluded that the lack of hair was due to an end-organ failure (on the part of the hair-follicles) and he suggested that this non-responsiveness was a genetic anomaly.

It is interesting that neither gonadal dysgenesis nor the syndrome of oestrogen-producing testes manifests adrenocortical dysfunction. The latter syndrome almost invariably shows absent body-hair, a finding which is interpreted as a congenital anomaly. Some cases of gonadal dysgenesis show a similar hair-lack, while others have profuse sex hair. Is the hairlessness in gonadal dysgenesis another congenital defect - like the others, erratic in its occurrence?

CHAPTER XIII

THE PITUITARY GLAND

AND

GONADAL DYSGENESIS

CHAPTER XXI

THE PITUITARY GLAND AND GONADAL DYSGENESIS

Jost's "castration" experiments and their application to the study of hermaphroditism have been discussed. Less well-known are the same worker's findings after decapitation. This is the only practical existing method of performing hypophysectomy on growing embryos. Jost (1953) reported the results he obtained by decapitating embryos at various stages of intra-uterine development. If this operation were performed early, feminization of genetically-destined male foetuses ensued; decapitation at later stages was followed by pseudohermaphroditic differentiation; still later, normal male forms were produced. In other words, the results of decapitation paralleled those obtained after gonadal extirpation.

These experiments suggest that pituitary, as well as testicular, hormones are necessary for normal male differentiation. Yet, no clinical counterpart in the human seems to have been described. It is possible that Jost's experiments might account for those cases of gonadal dysgenesis who fail to show a raised or even show a low urinary gonadotrophin excretion (PART I, CHAPTER XII). Cases of this nature have been described by Hertz et al. 1950; Dorff et al. 1947; Wilkins and Fleischmann, 1944; Greenblatt and Carmona, 1955; Carpentier et al. 1955 . In other words, these patients may

show intra-uterine hypogonadism manifesting as gonadal dysgenesis, but secondary to hypopituitarism - just as, in post-natal life, hypogonadism may be primary (with high F.S.H. excretion) or secondary (with low F.S.H. excretion). In the present series, 4 cases of proved gonadal dysgenesis had low excretions of F.S.H. on repeated tests. While doubts may be cast on the reliability of the present F.S.H. determinations, the reproducibility of the results and the experience of so many other workers suggests that cases of gonadal dysgenesis do, in fact, occur without high F.S.H. excretions.

Grumbach et al. (1955) reported a male pseudo-hermaphrodite with some of the anomalies of Turner's syndrome, i.e. short stature, a shield-chest and short broad neck. This case was considered to be a chromosomal male with a form of failure of male sex differentiation, thought to be transitional between that seen in gonadal dysgenesis and the classic forms of male pseudo-hermaphroditism. The following case showed mild pseudo-hermaphroditism due, it is believed, to intra-uterine pituitary failure. The patient is reported in order to strengthen the link between pituitary function and gonadal development.

Case J. L. aged about 70 years. (Figure 13.01)

He was admitted to hospital with a diversity of clinical ailments, most of which were not obviously related to his interesting endocrine condition.

He was 4' 6" tall, weak and wrinkled, with the general physique of a female. The voice was high-pitched and the breasts prominent. The thyroid cartilage was poorly developed; there was no temporal hair recession and pubic and axillary hair was absent. The external genitalia consisted of a diminutive phallus well-separated from an ill-formed, wrinkled, dark scrotum (Figure 13.02). No gonads could be felt; there was no hypospadias.

He was anaemic (4 gm. haemoglobin %) and the smear showed a mixed picture of hypochromia and macrocytosis; the bone-marrow was hyperplastic, not megaloblastic. Serum cholesterol levels were 224 mg. % and 205 mg. %.

Salient features on X-Ray investigation were flat vertebral bodies, slight generalised osteoporosis and a feminine appearance of the bones. Certain bone changes suggested cretinism - lack of fusion of the bones of the calvarium and of the iliac crest epiphyses, and patchy increased density of the tips of the lumbar transverse processes.

Adult cretinism was suspected initially. It was felt advisable to exclude hypopituitarism, of which secondary hypothyroidism might have been the major indication. (Administration of thyroid hormone to cases of "pituitary myxoedema" is considered to be potentially hazardous). In the course of this investigation, an insulin tolerance test was performed. The patient became hypoglycaemic and, despite rapid restoration of blood-sugar levels by means of intravenous glucose, he lapsed into coma. Rectal temperatures were exceedingly low and the patient failed to respond to further resuscitative measures.

The endocrine system at autopsy disclosed several abnormalities. The pituitary gland was very small (3 mms. in diameter) and was not wrinkled. The thyroid gland weighed 12 gm. and was atrophic macroscopically and microscopically; the suprarenals were apparently normal (11 gm. in weight). Minute, incompletely-descended testes were present which showed atrophic seminiferous tubules with no evidence of spermatogenesis and atypical interstitial cells. The epiphyses of the long bones were not obliterated and the costal cartilages were not calcified.

The cell nuclei of several organs were examined for chromatin pattern, which was established as male.

Comment: This patient appears to have had congenital hypopituitarism. This could explain the dwarfism, small testes and thyroid gland, with hypogonadism and hypothyroidism, the hypoglycaemic and hypothermic

osmas, the radiological skeletal abnormalities and, perhaps, the anaemia. In addition, mild pseudohermaphroditism is suggested by the separation of the penis from this ill-formed scrotum and by the lack of testicular descent.

It is suggested that the hypopituitarism was present during intra-uterine life. This led to secondary partial gonadal failure which became manifest as a mild form of male pseudo-hermaphroditism.

The normal size of the adrenal glands is compatible with some activity. If so, the pituitary failure seems to have affected chiefly the production of gonadotrophin and thyrotrophin. This combination occurs not infrequently in acquired hypopituitarism and, in the case described by Dorff et al. (1947) with gonadal dysgenesis and a low F.S.H. excretion, the same two trophic hormones appear to have failed.

The rôle of the pituitary hormones in sexual differentiation has still to be elucidated. The case described, it is suggested, offers a clue to the clarification of this difficult issue.

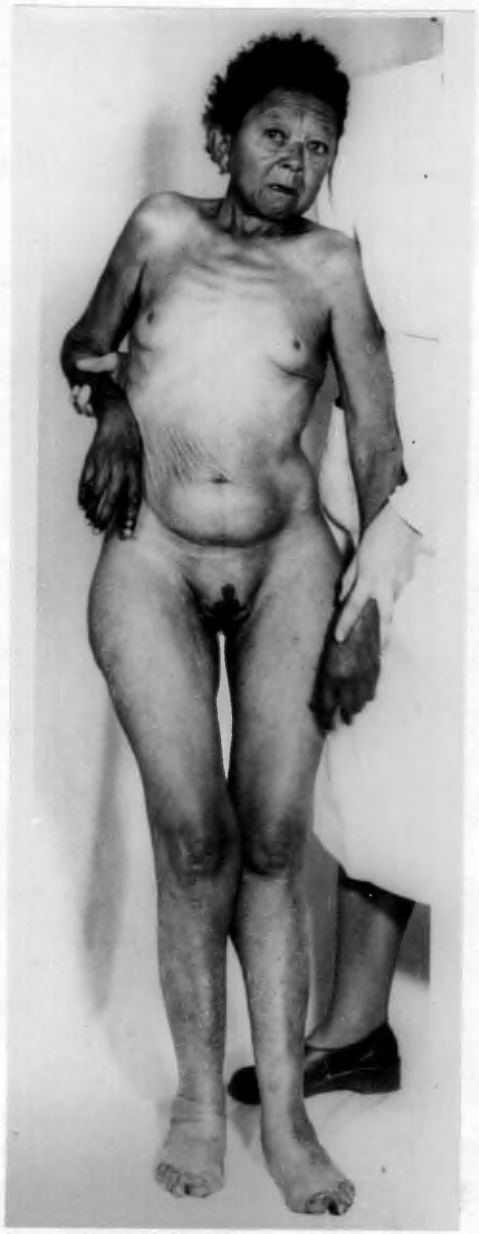


Figure 13.01

Case J. L.

The patient displays a generally feminine physique, breasts and absent pubic hair.

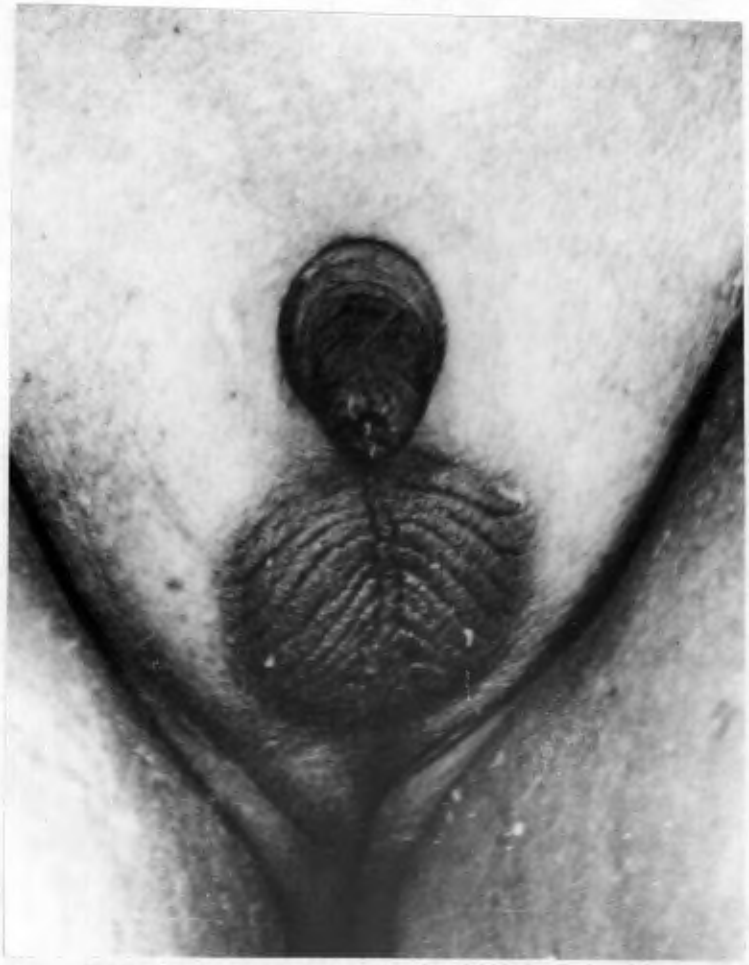


Figure 13.02

Case J. L. - External genitalia

Note the diminutive phallus well-separated from the small, empty, wrinkled scrotum.

C H A P T E R XV

TURNER'S SYNDROME IN THE MALE

CHAPTER XIV

TURNER'S SYNDROME IN THE MALE

In gonadal dysgenesis the body-form is almost invariably female, despite the fact that the majority of cases show a male nuclear pattern. Grumbach et al. (1955) have reported some of the anomalies of Turner's syndrome in association with male pseudohermaphroditism. There are very few reports of Turner's syndrome (i.e. hypogonadism, shortness of stature and congenital abnormalities) in patients with a pure male body build (Flavell, 1943; McCullagh, 1948; Prunty et al. 1953; Greenblatt and Kleburgs, 1948; Dorff et al. 1948; James 1952; Sohval 1951; Sougin-Mibashan and Jackson, 1954; Solis and Schwartz, 1951; Rossi and Caflisch, 1951; Referso-Membrives et al. 1949; Halonen et al. 1956). Two such cases are reported; a third patient, still too young to be regarded as hypogonadal, is described:

Case S. A. Coloured male aged 30 years. (Figures 14.01 and 14.02)

This adult male was 4'10½" tall; there was marked webbing of the neck, but no other obvious skeletal anomaly; muscular development was excellent. The phallus was large. The patient had not experienced normal sexual feelings and had never had an erection or emission. Urinary F.S.H. excretion was positive at 96 m.u. Testicular biopsy was not done.

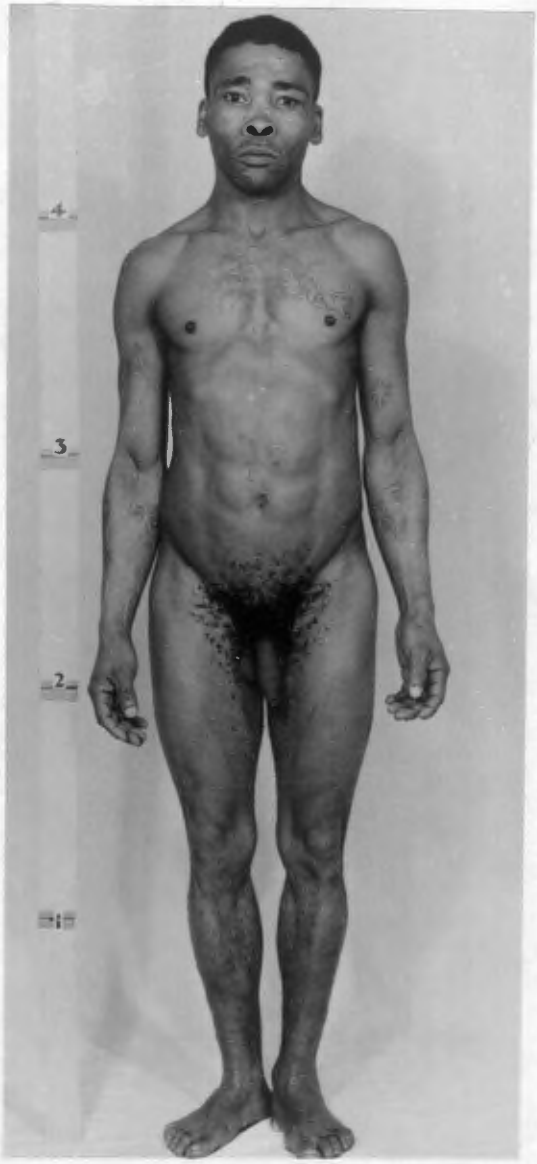


Figure 14.01

Case S. A.

Note the short, muscular physique

and the large phallus.

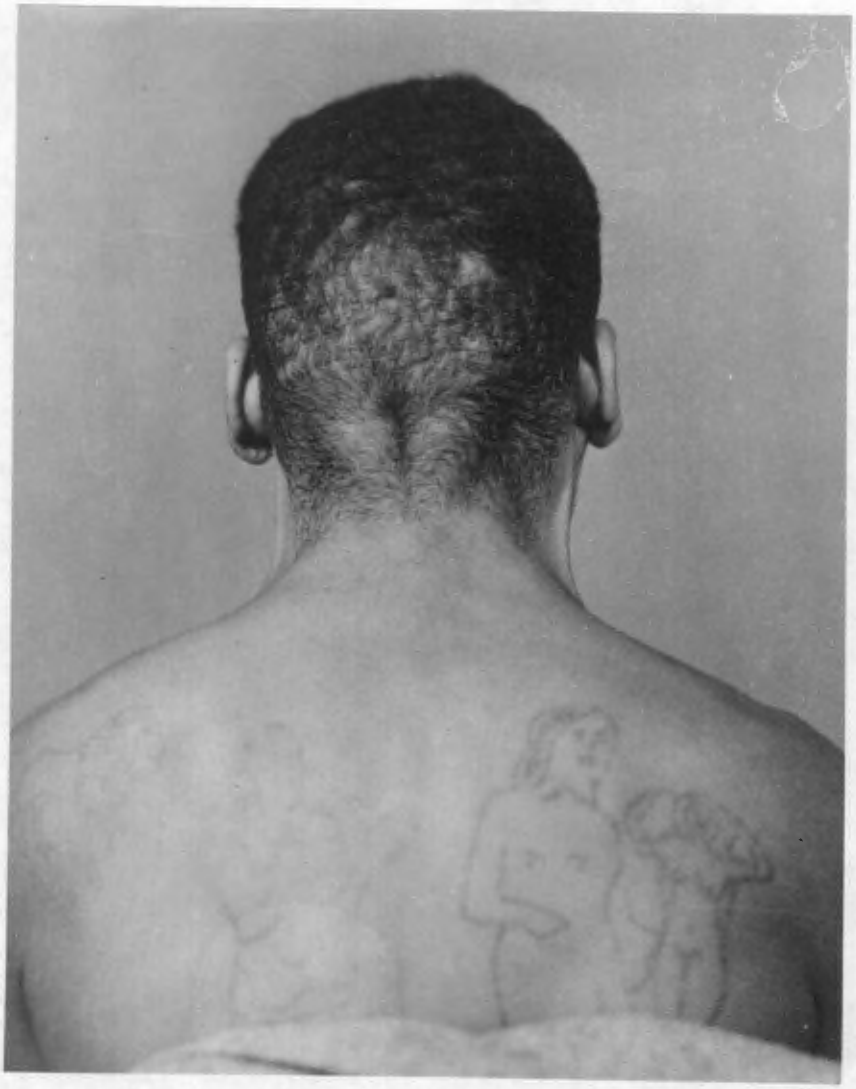


Figure 14.02

Webb S. A.

The webbing of the neck is

well-illustrated here.

Case G. S. aged 14 years. (Figures 14.03 and 14.04)

He had been undersized from birth and had shown no signs of pubertal development. Examination confirmed his physical retardation. The eyes were asymmetrical with marked epicanthic folds, the palate was high and arched, the nipples minute. There was webbing of the neck and hypoplasia of several interscapular muscles. The penis and gonads were infantile.

F.S.H. excretion was negative at 12 m.u. on two occasions. Bilateral testicular biopsies showed histologically infantile development as seen in the first six years of life. The skin nuclear pattern was male.

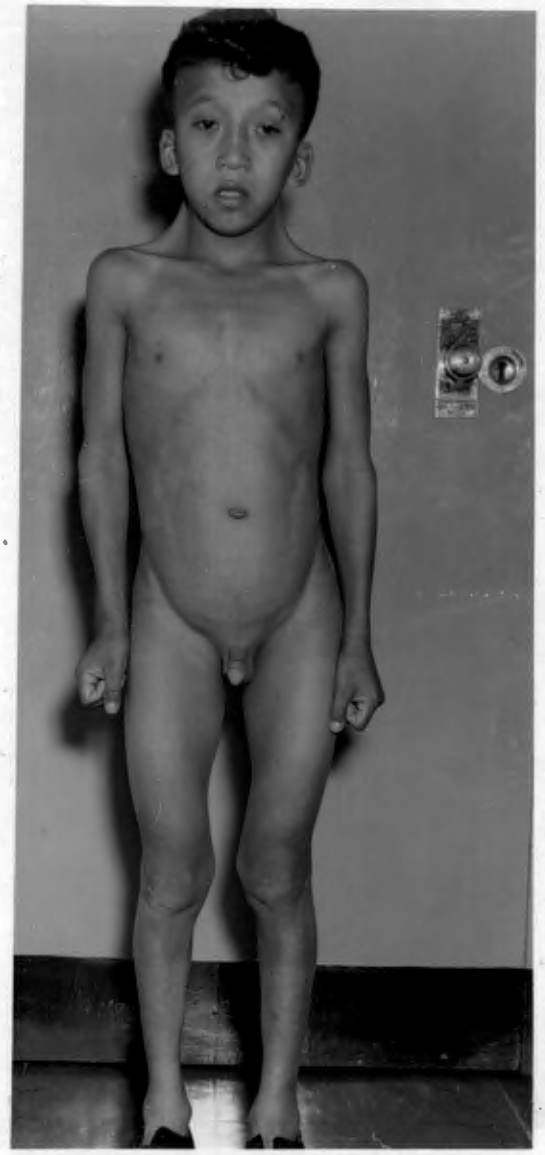


Figure 14.03

Case G. S.

This displays the poor general development, epicanthic folds and webbing of the neck.

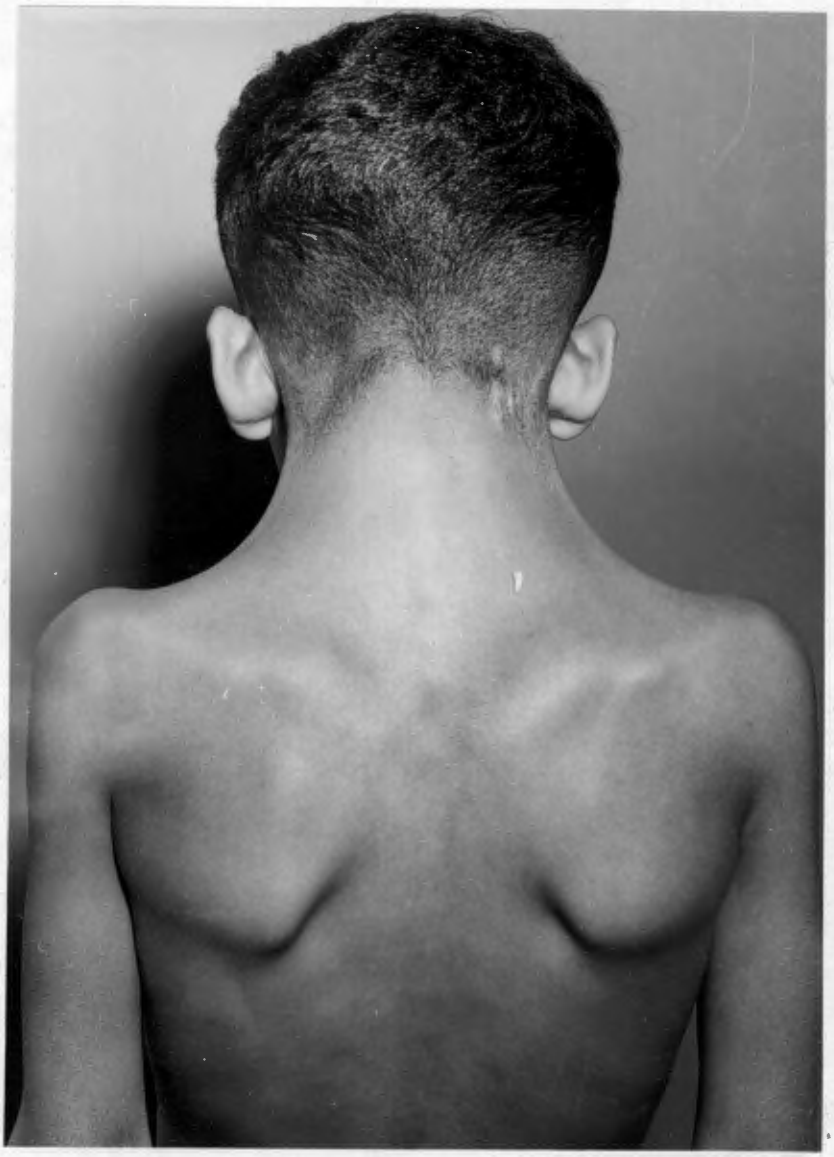


Figure 14.04

Case G. S.

Webbing of the neck
is well-illustrated.

Case A. S. aged 6 years. (Figure 14.05)

He had always been short and small for his age; (present height 3' 4"; weight 34 lbs.). On examination he had webbing of the neck with a low nuchal hairline (Figure 14.06). There was facial asymmetry with striking epicanthic folds. The right 5th finger was fixed in flexion. The right scapula was considerably smaller than the left and the right serratus anterior muscle was absent. Despite this, when he pushed against resistance, the left scapula "winged", but not the right, which suggested that this bone was fixed to the chest-wall on the right. There was mild glandular hypospadias but the penis was comparatively large. X-Rays showed fusion of some cervical vertebrae. He showed, in other words, the anomalies which are commonly referred to as Klippel-Feil's and Sprengel's deformities.

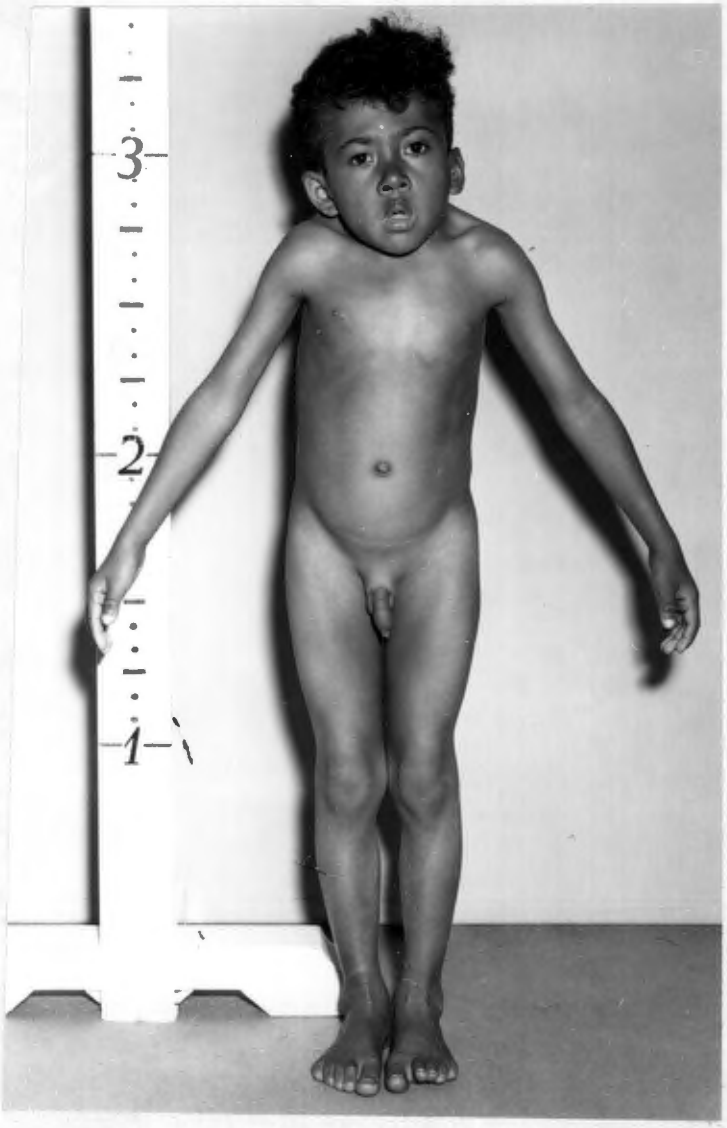


Figure 14.05

Case A. S.

Note small size, short neck and comparatively large penis.

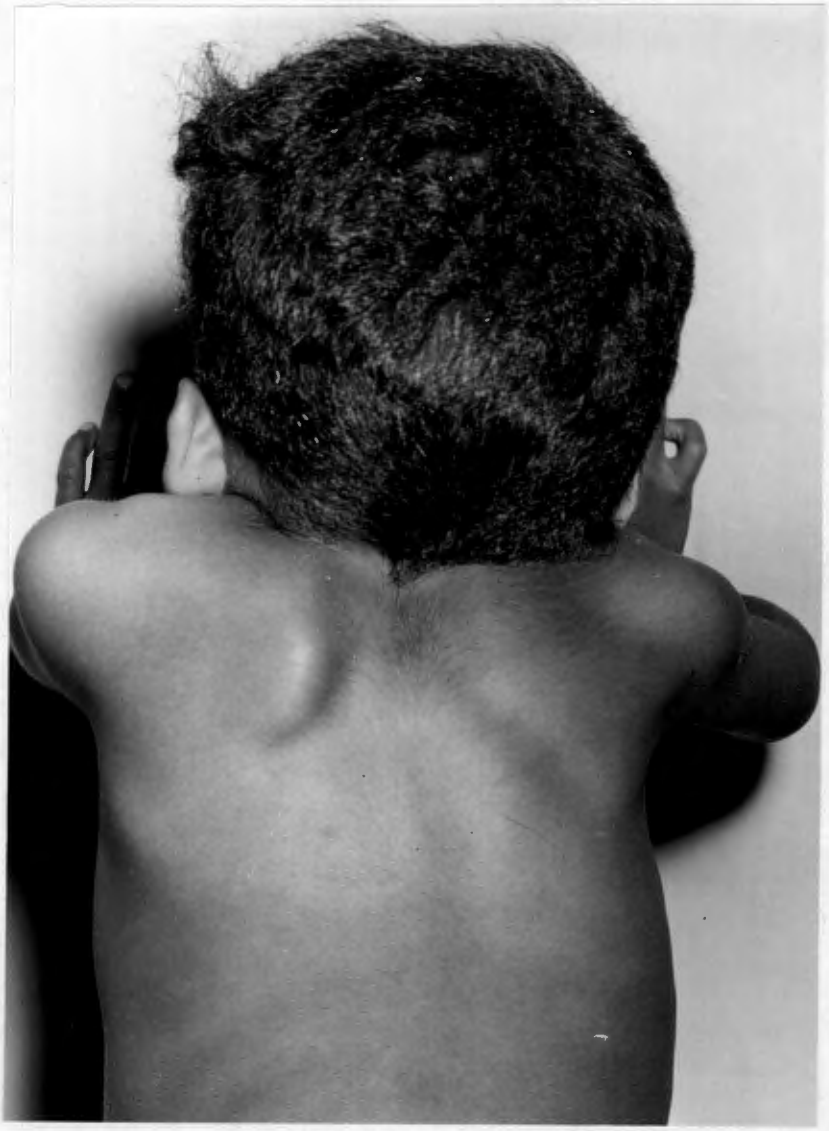


Figure 14.06

Case A. S.

This shows webbing of the neck and a low hair-line.

Comment: Case S.A. is a typical example of Turner's syndrome in the male, showing congenital anomalies, shortness of stature and hypogonadism with high urinary F.S.H. excretion.

Case G.S. shows the classical anomalies, shortness of stature and probable delayed puberty. It is difficult to assess the latter feature at the age of 14 years, but the testicular histology supported gonadal hypoplasia. If infantilism is present, the F.S.H. excretion might rise to higher levels in later years.

Case A.S., aged only 6 years, is short and displays multiple anomalies. Nothing can be said at present about his gonadal development. Hypogonadism is not an invariable concomitant of this abnormal physical state (as was pointed out by Rossi and Caflisch, 1951).

These three cases and others reported in the literature have all shown analogy to "Turner's syndrome in the anatomical female" in their shortness of stature and congenital anomalies. The full syndrome includes some type of gonadal disturbance, as demonstrated by

testicular biopsy or a raised F.S.H. excretion level.

The complete clinical picture has been very variable. In almost all cases, the testes have been hypoplastic. The penis has been small, normal-sized or large. Sohval's patient had gynaecomastia (Sohval, 1951); stature has always been short; webbing of the neck has been present in all reported cases. The excretion of F.S.H. has been recorded as low in most cases, but was raised in the cases of Greenblatt and Nieburgs (1948) and Halonen et al. (1956). Testicular biopsy generally shows tubular hypoplasia; Sertoli cells have been reported (Halonen et al., 1956); Leydig cells may be absent (McCullagh, 1948), infrequent (Halonen et al., 1956), or plentiful (Greenblatt and Nieburgs, 1948; Sohval, 1951). In other words, there is hypoplasia of testicular components, not dysgenesis as seen in anatomical females with Turner's syndrome.

Despite this lack of uniformity, it seems justifiable to group the reported cases of "Turner's syndrome-with-male-body-form" separately.

It is not easy to fit Turner's syndrome in the male into an etiological theory. Why have these patients not shown the customary physical feminisation? It is suggested that the genetic aberration which causes the syndrome of gonadal dysgenesis (see later) affects these individuals somewhat late in embryonic life; by this time, irreversible changes have taken place in a male direction, the final result being "gonadal-dysgenesis-with-male-body-form".

CHAPTER XV

GENERIC CONSIDERATIONS

CHAPTER XV

GENETIC CONSIDERATIONS

Although it is conceivable that the general Bonnevie-Ullrich-Turner syndrome might be due to an intra-uterine disturbance acquired during early foetal life, there is much to suggest that a genetic origin is more likely. Combinations of genetic aberrations are seen in states such as mongolism, the Lawrence-Moon-Biedl syndrome and osteogenesis imperfecta. The hereditary tendency of gonadal dysgenesis might be obscured by the essential infertility of the sufferers.

The hereditary nature of the disorder is supported by Rossi and Caflisch (1951), who quote several instances of familial appearance of the syndrome. In some of the families mentioned by them, cases of infantilism (i.e. gonadal dysgenesis) occur with non-infantile siblings who have, for instance, webbing of the neck but who are capable of reproduction. The authors adduce evidence of direct parent-child transmission of anomalies and claim, on seemingly good grounds, that the hereditary trait concerned is dominant, of high penetrance and variable expressivity. Familial incidence has been reported by others: Davidson and Smith (1956) quote two affected "sisters"; Solis and Schwartz (1951) describe Turner's syndrome in twins; Bassöe (1956) cites 2 siblings with familial congenital muscular dystrophy and gonadal

dysgenesis - one was a female with typical ovarian "streaks", the other a male with testicular insufficiency. These case-reports lend support to the hereditary basis postulated by Rossi and Caflisch.

A further argument in favour of a genetic etiology in gonadal dysgenesis is provided by a study of male pseudo-hermaphroditism. Bishop (1954) states that "not infrequently more than one member of a family is a male pseudohermaphrodite" and adds his own personal experience of one family of 6 children, of whom 4 suffer from this intersexual abnormality. This strongly suggests a genetic defect as the cause of male pseudohermaphroditism, and, since gonadal dysgenesis is thought to be an "early" form of this abnormality, indirect evidence exists for the hereditary basis of gonadal dysgenesis itself.

It would seem possible to explain the variability of the general Bonnevie-Ullrich-Turner syndrome by postulating three closely-connected, but distinct, genes situated on the same chromosome; one gene for infantilism (i.e. intra-uterine hypo-gonadism) called "I"; one gene for shortness of stature, "S"; and one gene or gene-complex for the various anomalies of musculo-skeletal, cardiac, cutaneous, renal, ocular and other systems, "A". Evidently genetic factor "A" is very variable in its expressivity, since several different anomalies usually occur together, but never all in the same person. Now, if it is imagined that these three factors ("I", "S" and "A") are not invariably inherited together or, alternatively, that they always occur together but that each is not

capable of full penetrance, the entire syndrome - in complete and partial forms - can be explained. Factor "1" generally acts directly on the developing gonad (resulting indirectly in a high F.S.H. excretion), but occasionally it acts via the pituitary (low F.S.H.). These views, as discussed earlier, accord with the experimental results of Jost.

Thus various combinations might occur :

1 + S + A = Full "Turner's syndrome"

S + A = "Pterygium" and other developmental syndromes with short stature and normal sexual differentiation (Rossi and Caflisch, 1951; Skjelbred 1953; Case C. R. quoted below)

A alone = "Pterygium" and other syndromes with normal stature (Rossi and Caflisch, 1951)

1 + A = "Turner's syndrome" with normal stature (del Castillo et al. 1947; Lisser et al. 1947; Wilkins et al. 1944)

1 + S = "Good-looking Turner's" with shortness and infantilism, but no anomalies (Case VII, J. T.)

1 alone = Apparent females of normal height with amenorrhoea and male or female skin sex and no anomalies (Swyer's

(1955) second case; Sun and Rakoff (1956); Case XII, H. de J.)

1 alone (slightly later action) = Male pseudohermaphroditism (Jost's theory, Grumbach et al. 1955)

1 (slightly later action)
+ S + A = Male pseudohermaphroditism with short stature and anomalies (Grumbach et al. 1955)

Case-report. C. R. aged 49 years.

This patient was seen because of auricular fibrillation and mild cardiac failure. Her menarche had occurred at the age of 14 years; periods had been regular, lasting 4 - 5 days with a 30 - day cycle. Two years previously menses had ceased. The patient had had 3 miscarriages but no live children. Family history was not available, since she had been adopted as a child.

She was 4'10" tall and had marked webbing of the neck with a low hair-line (Figure 15.01). There was considerable kypho-scoliosis. The breasts were small, but normal; the nipples and areolae were normal. Hair-growth was average; the external genitalia showed no abnormality. There were no other congenital stigmata of Turner's syndrome. Skin biopsy showed a female nuclear pattern.

Comment: This female displayed shortness of stature and some of the anomalies of Turner's syndrome (webbing of the neck, a low nuchal hair-line and marked kyphoscoliosis). There was no evidence of infantilism, as judged by normal breast and genital development, normal menstrual history and the three miscarriages.

She appears to suffer from "S" + "A" (above) without "I".

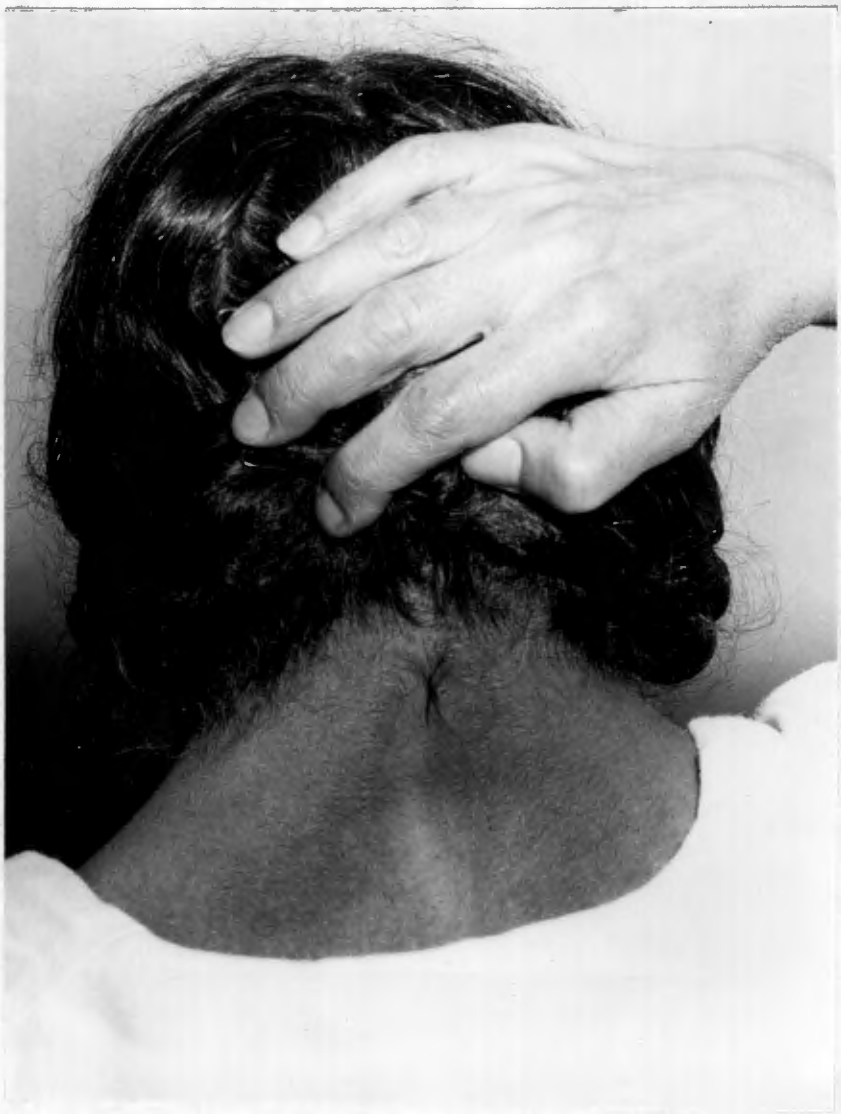


Figure 15.01

Case C. E.

This shows webbing of the neck and a low hair-line.

STATURE IN GONADAL DYSGENESIS

The shortness of stature which is seen in most cases of gonadal dysgenesis conflicts with the tall, eunuchoid proportions generally associated with gonadal failure. The shortness is usually regarded as a distinct genetic abnormality (as postulated above). To test the validity of this hypothesis, the reported cases of gonadal dysgenesis without shortness of stature are reviewed.

Varney et al. (1942) describe a patient 6' 0" tall with "eunuchoid elongation of the extremities". They refer, also, to patients reported by Pela (1935) and Humphrey - the former 5'10" tall with "long extremities", the latter 5' 6½" with "eunuchoid skeletal proportions". Wilkins and Fleischmann (1944) refer to a patient (reported by Kaliga) who was 5' 9" tall with "eunuchoid proportions"; del Castillo et al. (1947) cite a patient, 5' 5½" tall, with the same arm-span; Greenblatt et al. (1956) state that their patient, 5'10" in height, "resembles the tall, eunuchoid male in appearance".

Of Swyer's two cases, the first is stated to have "definitely eunuchoidal proportions", the second to have the general appearance of "a tall, eunuchoid female" (Swyer 1955). Case XII, H. de J., referred to earlier, displays the same eunuchoid habitus.

Thus the majority of tall patients with gonadal dysgenesis show eunuchoidal proportions. This supports the view that the typical shortness of stature seen in gonadal dysgenesis is

genetic in origin (factor "S"). If this particular genetic aberration does not occur, patients show the body-build which is expected in individuals who are deprived of gonadal function before puberty. This argument might be extended: any patient with prepubertal hypogonadism without eunuchoidism or tall stature is likely to suffer from gonadal dysgenesis; prepubertal gonadal failure from other causes should not be associated with shortness of stature.

TURNER'S SYNDROME IN THE ANATOMICAL MALE

On current theories there appears to be no clinical difference between the complete "Turner's syndrome" in a genetic male and that in a genetic female. Both will assume the female body-form.

The anatomical maleness of some cases of Turner's syndrome is difficult to explain. Possibly factor "1" (responsible for the infantilism) strikes late, so that some testicular differentiation and irreversible male changes already have occurred. Possibly factor "1" fails to penetrate completely - the result being not gonadal dysgenesis, but rather an incomplete gonadal disturbance, which permits normal anatomical masculinization. Intermediate between the ordinary or apparently female "Turner's syndrome" and the anatomically male "Turner's" is the "pseudo-hermaphroditic Turner's syndrome" (Grumbach et al. 1955).

WHY ARE PATIENTS WITH GONADAL DYSGENESIS PREDOMINANTLY GENETIC MALES ?

Previously one wondered why "Turner's syndrome" occurred almost exclusively in females, the male counterpart being the rather motley collection referred to earlier. Now it appears that gonadal dysgenesis is predominantly a (genetic) male syndrome. Thus, Hampson et al. (1955) (including 22 cases of Grumbach et al. 1955) report 31 of a series of 37 patients to be genetic males. Polani and Lennox (Lennox 1956) 16 out of 16, Sun and Rakoff (1956) 13 out of 15, Carpentier et al. (1955) 10 out of 12. In the present series 15 out of 23 were genetic males. Thus, of these 5 series, 85 genetic males are found in a total of 103 cases (83%). Davidson and Smith (1956) refer to 139 cases of gonadal dysgenesis in the literature (sources not disclosed) - amongst whom there were 116 genetic males; they add 18 cases of their own, 15 of whom were genetically male, to give an overall percentage of 83%.

Nelson (1956) records oral smears or skin biopsies on 103 patients with gonadal dysgenesis; 87 were "genetic" males, 16 "genetic" females (approximately 84% males).

There is thus, in all series, a preponderance of "genetic" males to females in the ratio of between 4 and 5 to 1. Davidson and Smith accept these figures as support of a genetic basis of gonadal dysgenesis. However, apart from genetic sex

linkage, this male preponderance might be explained in terms of sex-limitation, i.e. something in the general internal environment of the early developing females may be less conducive to the development of this particular disturbance. One striking environmental difference between developing male and female embryos is apparent. In the foetus, up to the 6th week, the gonads are identical in both sexes - the "indifferent period of gonadogenesis". If the embryo is to be male, the gonads start to differentiate in the 7th week; if it is to be female, the first evidence of differentiation is seen in the 10th week. If the particular influence - genetic or acquired - operates between the 7th and 10th weeks, the developing male gonads might be more susceptible, the quiescent female gonads less susceptible. This difference in the time of gonadogenesis in the two sexes might account for sex-limitation.

If, on the other hand, male sex linkage is responsible for the male preponderance, this linkage cannot be complete, since 15 - 20% of cases of gonadal dysgenesis show "genetic" femaleness.

CHAPTER XVI

CONCLUSIONS (PART II)

CHAPTER XVI

CONCLUSIONS (PART II)

The syndrome of gonadal dysgenesis appears to be a variety of intersexual development. Study of other varieties of intersex lends support to this view. During the course of this study, it became apparent that the current concepts of the etiology of hermaphroditism in general are open to much valid criticism. A revised theory of the causation of some intersexual states, including gonadal dysgenesis, has been presented.

The investigation of hermaphroditism in general has shed light on several aspects of the syndrome of gonadal dysgenesis. The lack of body-hair in some of these cases may be attributed to a congenital unresponsiveness on the part of the hair-follicles, as is said to exist in the condition of oestrogen-producing testes. Lack of pituitary gonadotrophic stimulation may account for some cases of gonadal dysgenesis, as well as cases of male pseudohermaphroditism.

Finally, arguments are produced in favour of the hereditary nature of gonadal dysgenesis; it seems possible to explain the complete syndrome and its various partial forms in terms of an incomplete male sex-linked or male sex-limited genetic aberration.

CHAPTER XVIX

SUMMARY (PART II)

CHAPTER XVII

SUMMARY (PART II)

(I) Gonadal dysgenesis is considered in relation to male pseudohermaphroditism. Depending on the stage of intra-uterine or post-natal life at which it occurs, gonadal failure may result in gonadal dysgenesis, male pseudohermaphroditism, some varieties of eunuchoidism or, merely, sterility in the male.

(II) The major types of hermaphroditic development are reviewed and current concepts of etiology are summarised in the light of information derived from nuclear sexing techniques. Illustrative case-reports are presented of the four main types of abnormality.

(III) A reconsideration of these etiological concepts reveals certain discrepancies. One of these is the recent demonstration of female nuclear patterns in individuals with apparent male body-build - that is, Klinefelter syndrome.

- (IV) This -

(IV) This anomalous demonstration of "testes in a genetic female" is discussed and a case-report is presented.

(V) A revised theory of sexual differentiation is proposed. In order to overcome some of the discrepancies mentioned, it has been necessary to postulate the existence of two "evocators", which are responsible for the development of a definitive gonad from the primitive genital ridge. This hypothesis provides a possible solution to some of the problems in this complex field.

(VI) The syndrome of oestrogen-producing testes - a rare form of male pseudohermaphroditism - is discussed separately. The differentiation of these subjects into anatomical females is attributed to lack of male hormone - not, as heretofore, to an excess of feminizing hormone. The analogy is drawn between this condition and some cases of gonadal dysgenesis. The lack of body hair in patients with oestrogen-producing testes is considered to be an example of a congenital end-organ failure (on the part of the hair-follicles). The absence of sex hair in some cases of gonadal dysgenesis might be attributed to a similar mechanism.

(VII) The rôle of the pituitary gland in sexual differentiation is discussed in the light of Jost's animal experiments. It is suggested that failure of this gland is responsible for some cases of hypogonadotrophic gonadal dysgenesis.

A case is presented which, it is felt, provides a link between the pituitary gland, gonadal dysgenesis and male pseudohermaphroditism.

(VIII) "Turner's syndrome" in the anatomical male is considered and 3 case-reports follow.

(IX) A genetic theory is presented, which attempts to explain the syndrome of gonadal dysgenesis and the disturbances which are related to it.

(X) An analysis of tall patients with gonadal dysgenesis lends support to the view that the shortness of stature in this syndrome is due to an associated congenital aberration.

(XI) The overwhelming preponderance of genetic males to females with Turner's syndrome is discussed. This may be explained in terms of genetic sex-linkage, or sex-limitation.

CHAPTER XVIII

GENERAL SUMMARY

CHAPTER XVIII

GENERAL SUMMARY

This thesis is divided into two parts, to each of which a summary is appended. The following paragraphs consist of a recapitulation in abstract form of the salient features of the treatise.

The first part of the thesis is devoted to an investigation of 23 patients with gonadal dysgenesis. The evolution of our concepts of this syndrome is traced from Turner's description in 1938 to the present time. Several facets - clinical and investigative - are discussed in detail. Particular attention is drawn to the occurrence of gonadal dysgenesis in tall, normal-looking females, and to the existence of a state of "ovarian hypoplasia" which simulates it. The diagnosis and treatment of gonadal dysgenesis is reviewed.

The second part considers the place of gonadal dysgenesis in relation to hermaphroditism. Current views on the classification and pathogenesis of various types of hermaphroditism are reconsidered; certain discrepancies are revealed and an attempt is made to reconcile these in a revised theory of sexual differentiation. The rôle of the pituitary gland in relation to gonadal dysgenesis and hermaphroditism is discussed. Brief

allusion is made to "Turner's syndrome" in the anatomical male. A theory is presented to explain gonadal dysgenesis in its multifarious guises on the basis of a genetic aberration.

CHAPTER XIX

METHODS

CHAPTER XIX

METHODS

The following methods were used in the investigation of the patients :

(1) Soffer Test: As described by Soffer and Gabrilove (1952), using 1500 ml. water orally. In a few cases, 20 ml. water per kilo. body-weight was given.

(2) Insulin Tolerance Test: Method described by Fraser et al. (1941). Insulin was administered intravenously in full dosage, i.e. 0.1 units per kilo. body-weight.

(3) Thorn Test: The modification of Renold et al. (1951) was used, 20 mg. A.C.T.H. in 500 ml. sodium chloride being infused intravenously over an 8 - hour period. In all cases eosinophil counts were done, in some 17 - ketosteroid determinations as well.

(4) Urinary 17 - ketosteroids: These were estimated according to Callow's method, as modified by Holtorff and Koch (1940).

- (5) Plasma -

(5) Plasma Cortisol: Method of Lewis (1957); the normal range is stated to be 6 - 12 micrograms per 100 ml. plasma.

(6) Follicle-stimulating Hormone: Two methods were employed. The first is dependant upon increase in mouse uterine weight (Bloomberg et al. 1955); the urinary excretion is expressed in terms of positivity at a given number of "mouse units". The second method (Albert 1956) depends on the increase of rat ovarian size and is expressed in units.

(7) "Nuclear Sexing" Technique: Skin sexing was performed as described by Moore et al. (1953); biopsy specimens were taken from glabrous portions of the skin.

Polymorphonuclear leucocytes were sexed in the manner described by Davidson and Smith (1954).

CHAPTER XX

ACKNOWLEDGEMENTS

CHAPTER XX

ACKNOWLEDGEMENTS

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