INTERSEX IN FOUR SOUTH AFRICAN RACIAL GROUPS IN DURBAN

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'Created half to rise, and half to fall;
 Great lord of all things, yet a prey to all;
 Sole judge of truth, in endless error hurled;
 The glory, jest, and riddle of the world.

                Alexander Pope   (1688-1744)
                  'An Essay on Man' epistle II; I:15.

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INTERSEXUALITY

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INTRODUCTION

Development of the normal individual follows a well-defined series of events
which is initiated when a normal ovum is fertilized by a normal spermatozoon.
The zygote develops rapidly: within a matter of a few weeks the embryo is
recognizable as being of a particular sex and barring mitotic accidents, un-
favourable gene action or insult by teratogens, the gonads and genitalia of
the newborn will be distinctive and typical of its genetic sex.

The years following birth are relatively inactive ones for the sex apparatus,
as growth continues slowly until the onset of puberty. At puberty there is
great activity and the genital organs become sexually mature and functional;
a state that will persist for several decades until the menopause in women
and impotence overtakes the male. The important hormones which are produced
by the newly-matured gonads initiate and control the appearance of secondary
sexual features in the pubertal child and stimulate his erotic interest in
members of the opposite sex.

During the years of childhood parental influence is particularly strong in the
absence of hormonal control of sex determination, and in the course of these
early years a child should be taught that there are 'boys and girls'. Through
education and experience the child becomes socially orientated to life as a
male or female. This social alignment is normally firmly established by the
third year of life and thereafter is continually reinforced until after puberty

the individual is able to assume the full role of his or her sex.

However, the process of growth and development of the human, from fertiliza-
tion to maturity, is fraught with dangers which may in fact even be present
before fertilization has been accomplished. The potential for abnormal de-
velopment begins with gametogenesis, when an irregular meiotic division in
either parent may cause an aneuploid gamete to be produced; or during the
exchange of genes at chiasmata a deleterious pair may be incorporated into
the genotype, to express their effect at some stage of life. A mitotic non-
disjunction in the early divisions of the zygote may result in aneuploidy of
the gonosomes. At any stage during foetal life endogenous or exogenous andro-
gens, or certain drugs, may divert normal development. Thereafter, excessive
or deficient hormone production by the endocrine glands, hormone-producing
tumours, or exposure to certain drugs may produce contrasexual features or a
failure of expected sex characteristics to appear.

Any one or more of these events can result in the birth of a baby whose sex
is ambiguous; in an infant or child whose somatic or psychological progress
is contradictory to its genital or ascribed sex, or in an adult who finds
distressing heterosexual signs appearing.

DEFINITION

An intersexual state is said to exist in the human when any one or more of
the criteria by which sex is assessed do not correspond (DANON and SACHS, 1957
ANDERSON, 1968 amongst others). These criteria are the genetic, gonadal, geni-
tal and somatic (hormonal) sexes; the sex of rearing (ascribed sex), psycho-
logical sex, and gender role.

The first four of the parameters listed above may be considered as definitive
and can be measured objectively, whilst the last three must be assessed sub-

jectively. Extrapolating from this definition it follows that the normal male has an X and Y sex chromosome pair; functional testes located in the scrotum and a phallus which is penile and transmits the urogenital canal to its tip. Secondary characteristics include a muscular physique with wide shoulders and narrow hips; a beard, and excursion of the pubic hair towards the navel. The temporal hair line may recede in later years. The social orientation is with boys and later, men. He regards himself as a male and sexual attraction is towards the opposite sex. Conversely the normal female has feminine contours and genitalia; her upbringing is opposite to, and her attraction towards, males.

INTERSEX IN SOUTH AFRICA

The first, and certainly the most contentious report of an intersex in this country was that of Dr James Barry, Surgeon General to the British forces at the Cape during the period 1817 to 1827, and who in death was found to be an intersex. Controversy regarding this person's true sex still rages (KIRBY, 1970). Although intersexes must have been seen in South Africa during the intervening years only spasmodic reports of cases have appeared in the literature. WULFSOHN (1950) was one of the first modern authors to describe an intersex in the South African literature, and since then reports have been made with increasing frequency. This phenomenon is certainly the result of increased awareness and improved diagnostic methods. Most of the major intersex syndromes have been recognized in South Africans of different racial groups (JACKSON and HOFFENBERG, 1956; DE LA HARPE, 1959; COHEN and THOMAS, 1960; KLEMPMAN, 1964; ANDERSON, 1965; HURWITZ; WILTON and LEVER, 1966; SEGAL et al, 1967; VINIK, 1969; GRACE and SCHONLAND, 1970). One of the noticeable features of several published articles was the vague classification of cases and lack of detail concerning diagnostic cytogenetics. A commonly expressed belief is that hermaphroditism is the commonest form of intersexuality among the Bantu races of South Africa and Rhodesia, and that intersexuality on the

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whole is more prevalent in the Bantu than other races (KLEMPMAN, 1964; FORBES and HAMMAR, 1966; WILTON, 1969). There is, however, no indication that any one author has given more than passing consideration to the great numerical disparity between the four races and no attempt has ever been made to estimate the incidence or prevalence of intersexual disorders in any local community in Natal. For instance, it has been shown that gonadal dysgenesis is the most common intersex syndrome in the Bantu of Natal (GRACE, 1970).

The South African population is made up chiefly of four distinct races; the Bantu, a composite group formed from many smaller tribes of the Nguni stock; immigrant whites of European origin, and Indians from the southern provinces; and the smaller Coloured community which originated through miscegnation between early white settlers at the Cape and their Malaysian slaves and indigenous Hottentots. No population census has been made in South Africa since that of 1960, projections from which estimated that the 1969 population consisted of 18,000,000 Bantu; 3,750,000 whites; 1,500,000 Coloureds and some 800,000 Indians (GOVERNMENT PRINTER, 1966).

Calculation of figures for the national, or even regional prevalence of intersex is virtually impossible at present. It is common knowledge that the Bantu do not readily present themselves for medical attention, and that vast tracts of the country have very meagre medical services. Mission hospitals, which do excellent work in the outlying areas, generally can not make use of cytogenetic services because of financial and transport difficulties. Also, a large number of Bantu confinements occur far from the reach of any obstetric attention and so abnormalities which might have been detected at birth do not come to our notice until many years later, if at all. All of these factors introduce bias into the statistics. The white, Indian and Coloured communities are also not very enthusiastic patients when they are intersexual but, in contrast to the Bantu, their babies are mostly delivered

in circumstances which permit obstetric attention and so gross anomalies of the genitalia may be treated in infancy. Later, examination at school clinics may detect some forms of intersex but again there are many Bantu children who do not attend school, or attend one which is beyond the range of school health services. Data are made the more inaccurate by the migrant labour system of southern Africa: migrant labourers, mostly Bantu males, find their way to cities and towns hundreds of miles from their kraals, and it is impossible to say that, for instance, a Bantu seen at a Durban clinic is not from a kraal in Pondoland, four hundred miles away!

There are a number of intersexual syndromes which are not evident in the newborn; these can only be detected by active screening procedures, or at an older age if the individual is sufficiently motivated to seek medical advice.

A surprizing observation was made during interrogation of the local Bantu -- all questioned were Zulus -- because there do not appear to be any stories or folk tales concerning ambiguously sexed individuals; in fact they have only two words which could possibly relate to such persons. These are 'ncukubile' which can be used to describe a bisexed individual, and 'mpisishane' which applies more to effeminate males than to intersexes. The implications of this poor vocabulary are twofold: the Zulu language, in common with all of the Nguni dialects, has words to cover all varieties of appearance and nuance of thought, and yet it has no suitable term for persons with strange genitalia! This is not what one expects of a culture in which hermaphroditism is said to be so common. The second point is that there are no tribal laws or stories concerning such ambisexual persons: again, this is peculiar because prior to the advent of the white man about 150 years ago there was no written history and all forms of knowledge and tradition were propagated by word of mouth. As a man's phallic prowess was very important it is odd that there are no folk tales to explain the origin of the intersexual habitus.

Similarly, there do not seem to be any traditional explanations concerning the intersexual appearance amongst the Indian and Coloured communities either.

Since the inception of cytogenetic services in South Africa, at Johannesburg during 1962, and at this Institute in 1965, there has been an ever increasing demand for diagnostic cytogenetic investigations. This trend is obvious from the figures presented in Table I. The latest available report of the number of investigations done in Johannesburg shows that from 1963 to 1966 the yearly total rose from 147 to 212 (S.A.I.M.R. Annual Reports, 1962 - 1966). Of the

TABLE I

Number of Patients Investigated

Annually by N.I.I. Cytogenetics Department

Year	Total	Racial Origin			
		B	W	I	K
1965	84	24	34	22	4
1966	98	30	38	21	9
1967	119	45	48	23	3
1968	177	38	94	37	8
1969	240	122	67	35	16

patients investigated at this Institute the number, but not the proportion, of those referred for intersexual problems has increased, as is shown in the next Table. Unfortunately, prior to mid-1967 when the author came to this laboratory, no accurate details of either provisional or final diagnoses were kept and so retrospective analysis of the records is impossible. Similarly, the figures given by the South African Institute of Medical Research in Johannesburg did not include an accurate analysis of their cases. Cytogenetic services are relatively novel in South Africa so that until all medical men are familiar with the facilities provided, it can be expected that there will be fluctuations in the number of patients referred annually to departments such as this.

TABLE   II

Numbers of Patients referred
for evaluation of Sex Status

Year	No	% of annual total	W	B	I	K
1965	13	15	2	6	5	0
1966	31	31	9	7	11	4
1967	35	31	12	12	11	0
1968	43	25	17	17	8	1
1969	36	15	8	22	5	1

The greater Durban complex has a population of approximately 800,000 according to the estimates of the City Planning Office. An extension of the figures given in Table I shows that approximately 1 person in every 4000 of the Durban community was investigated cytogenetically during 1969, and about 1 in 25,000 was referred for elucidation of sex problems. A more detailed analysis of the figures is given in Chapter XV.

MOTIVATION   OF   THIS   STUDY

Patients referred to this laboratory for assessment of their sex status form approximately 25 percent of the total each year (see Tables above) and they are therefore an important group. The distribution of the patients among the four race groups which form the Durban population varies from year to year; retrospective analysis shows no discernible pattern. Over several years it has been claimed by authors (KLEMPMAN, 1964; FORBES and HAMMAR, 1966; WILTON 1969) and clinicians that intersexuality is more prevalent among the Bantu of the subcontinent than in other race groups; and that in the Bantu hermaphroditism is the commonest form of intersex. As a corollary to this, it has also been said that endocrine disturbances are rare in the Bantu (FORBES and HAMMAR 1966; DINNER, 1969) and that the adrenogenital syndrome is unknown in that race. WILTON (1969; 1969b) did not mention any patients of Bantu origin with Turner's syndrome, and also drew attention to the rarity of Klinefelter's syndrome in Bantu. FORBES and HAMMAR (1966) said of the Rhodesian Bantu, who are

mostly of the Matabele tribe - an offshoot of the Zulu nation, that hermaph-
roditism was much more prevalent than male or female intersexes; they did
not mention any of the gonadal dysgenetic syndromes. In contrast to the ex-
periences of workers in the northern centres, Johannesburg and in Rhodesia,
the reverse appears to be true of the Durban population because gonadal dys-
genesis is the most common anomaly of sexual development in Bantu and only a
single hermaphrodite has been diagnosed during the years 1967 to 1969. Only
3 Bantu with chromatin positiveKlinefelter's syndrome have been reported in
the literature: an XXY (ASMAL, 1967); an XXY and an XY/XXY mosaic (WILTON
1969). To balance the rarity of Klinefelter's syndrome, there is a very high
prevalence of chromatin negative hypogonadism amongst the Bantu. Experience
in South Africa is the reverse of that in Europe, where the Klinefelter syn-
drome predominates over the chromatin negative form of hypogonadism (NIELSEN;
FRØLAND, 1969). The triplo-X and XYY syndromes are apparently rare in South
Africa and there are only single reports of each (ANDERSON et al, 1964; WILTON
and LEVER, 1966).

The few available text books on intersexuality indicate that there are many
gaps in our knowledge, particularly where this concerns the karyotypic and
phenotypic variations of the different syndromes. All too frequently there
is an obvious bias in favour of the endocriniological, or cytogenetic or clin-
ical aspects of intersex (for instance OVERZIER, 1963; WILKINS, 1965; BARTALOS
and BARAMKI, 1967) and there is no currently available text which combines the
observations of all disciplines.

Since the first reports, about 10 years ago, of chromosome anomalies in the
aetiology of intersex syndromes there have been countless case reports, re-
views and dissertations published by the medical press of the world. In this
work preferential attention has been given the local literature because of its
immediate relevance to the population under investigation.

One of the most outstanding features of the local publications of recent years is the manner in which some authors have classified not only their own cases, but also intersexes in general (e.g. HIRSCHOWITZ; DINNER, 1969); in most cases incorrectly. That such unqualified classifications continue to appear indicates a very real danger that the terminology of cytogentics will become terribly confused, a fate which has befallen many other medical disciplines. Unfortunately, although two international conventions have been held to determine the nomenclature of individual chromosomes, none has yet been convened to decide the terminology of the clinical aspects and applications of cytogenetic data. The success of such international discussion can be gauged from the congresses on chromosome nomenclature (DENVER REPORT, 1960; CHICAGO CONFERENCE, 1966): the recommendations are now used universally.

In describing clinical cases it is regretable that authors do not use the popularly accepted names for syndromes, instead of conjuring up synonyms (for example, DINNER (1969): 'relative adrenogenital syndrome' for idiopathic female intersexuality) or failing to use a term when a suitable one exists. Some authors appear to be diletantes as far as the terminology of intersexual states is concerned (FRY et al, 1968; HIRSCHOWITZ, 1969). ANDERSON (1968) did not even mention idiopathic female intersexes in his classification; this is a surprizing omission, especially as the author gave no indication of whether they should be included with 'female pseudohermaphrodites' (all due to adrenal or hormonal virilization).

A fault which has reached epidemic proportions in the literature from many countries is the misuse of the eponym "Turner's syndrome". Further discussion of this particular fault is given in Chapter VII.

The cytogeneticist's investigation is not limited merely to the preparation of the patient's karyotype but includes ancilliary studies such as determi-

nation of sex chromatin frequencies, dermatoglyphic analysis and a certain amount of clinical observation and recording. As will be shown in a later chapter there is little, if any, information on the inter-racial variation of these features. Likewise there is no indication of the normal values in South Africans, with the exception of a single report on a small sample of Bantu and Indians handprint patterns (DE VILLIERS and CLARKE, 1969).

Appreciation of the abnormal is only possible after 'normal' has been established and for sex chromatin and dermatoglyphic analysis in South Africa, this has not been done.

This study was motivated by the desire to prove or disprove the many contentions regarding the occurrence of intersexual syndromes amongst the racial groups of South Africa in terms of incidence, prevalence and inter-racial distribution. Case reports of patients are presented to illustrate features of the syndromes in the different races. Dermatoglyphic profiles are given with many of the case reports and although the normal values are not known, it is hoped that this work will stimulate more interest in this diagnostic aid. Since no data concerning the normal range of sex chromatin frequency in the four races was available, a pilot study was done and the results are presented. The classification of intersexual disorders must be appreciated and to this end a system is proposed and discussed. It is hoped that the clinical studies reported here will emphasize the need for an accurate, and early diagnosis.

REMARKS   ON   THE   PRESENTATION   OF   THIS   THESIS

This thesis will give a broad view of the topic, intersexuality. In order to achieve this the preliminary chapters are concerned with the occurrence of intersexes in nature, in the historical record and in the religions and

cultures of many races. Modern attitudes towards the problem are also mentioned. The normal mechanisms of sex determination and embryological development are outlined, and notes on the aetiology of intersexuality are given. The description of the sex chromatin study and that of dermatoglyphic interpretation is given comprehensive discussion because both are relatively unknown in South Africa. A classification has been devised to cater for the known forms of intersex and a large number of case reports is used to illustrate many of the major syndromes. Most case reports are accompanied by photographs or line drawings which demonstrate the features of the case.

All births at three hospitals were surveyed during the calendar year 1969 and were used as a sample from which the incidence of intersexual anomalies is calculated. Estimates of the prevalence and inter-racial distribution of the intersexes are based upon the numbers of new patients seen in Durban during the year under review.

The information presented here will, it is hoped, lead to a better understanding of this complex and very important subject.

INTERSEX IN NATURE

Introduction
Evolution of separate sexes
Intersex in Invertebrates
Intersex in Vertebrates

INTRODUCTION

The concept of sex, which in common usage has a well understood meaning, is
very poorly defined in the biological context. It is generally accepted to
imply a number of properties of genetic, gonadal, endocrine and other features
of the individual; male or female. The term refers to these attributes as
specializations which have a selective advantage over the primitive bisexual
state. Finally, sex may relate to the mating process by which breeding mem-
bers of the species pair; to copulate, and by such random mating produce
offspring who have the advantage of access to the gene-pool of that community.

EVOLUTION OF SEPARATE SEXES

It is obvious that there has been a gradual progression towards separation
of the sexes in the animal kingdom, which is concordant with the principle
of division of labour shown at all levels in communal and multicellular
animals from Volvox onwards.   There has been considerable and protracted
argument, which persists to the present time, over the stage at which verte-
brates became dioecious. A popular misconception is that terrestrial verte-
brates evolved from the Teleosts, but this is not so. The bony fishes were
a well-defined group that appeared during the Devonian period, some 70
million years earlier than the first reptiles. According to COLBERT (1961)
the terrestrial vertebrates arose through the Crossopterygian genus Osteo-
lepis which in turn gave rise to the arch-amphibian, Icthyostega. From

this primitive tetrapod dichotomous evolution produced the amphibia and the amniote reptiles. This phase occurred during the early Carboniferous epoch. Some 60 million years later the five reptilian classes were established: of these the Theraspids (Synaspida) eventually produced the mammalian fauna of the Earth.

It is reasonable to assume that when the vertebrates became terrestrial they were already dioecious. The more than 60 specimens of the coelocanth, Latimeria sp., which have been collected were all distinctly male or female (SMITH, 1953). From our knowledge of modern reptiles and surviving Archisaurs, the fact that reptile eggs have been found in the fossil record indicates that they were dioecious also. Phylogenetic studies have been further confused by the misconception that the cyclostome fishes are functional hermaphrodites. The truth is that the gonads go through an ambiguous developmental phase, after which either male or female elements regress and the remaining cells become mature and functional: in other words they are protandrous or protogynous (ATZ, 1964). A few examples of bisexed cyclostomes were apparently abnormal and, under normal circumstances, the genus Myxine is the only one in which rudimentary hermaphroditism may occur.

INTERSEX IN INVERTEBRATES

The intersexual state is not peculiar to man alone but has been reported in most of the lower animal phyla (BERTIN, 1967). However, the functional hermaphroditic and trans-sexual modes of life are unique to the lower phyla of the animal kingdom, in contrast to mammals where the condition represents abnormal development. Functional hermaphroditism occurs in the phyla Bryozoa, Phoronida, Aschelminthes, Platyhelminthes, Annelida and Mollusca and in some species of Crustacea. Isolated examples of intersexual insects are also known to occur, probably as abnormalities (YOUNG, 1937 quoting Goldschmidt). Transient hermaphroditism, in which a trans-sexual change occurs during the

lifespan is seen in the Isopod genus <u>Rhyscotoides</u>, which begins life as male but in maturity is sexually female; the reverse is true of the fish genus <u>Molienesia</u>. Hermaphrodites may become unisexual: the Chaetonoidea (Aschelminthes) commence life as hermaphrodites but after sperm is cast the male organs atrophy and consequently all mature animals are female.

INTERSEX IN VERTEBRATES

A brief account of intersexual anomalies in the vertebrate phyla follows.

Fishes

The cyclostomata, long believed to be functional hermaphrodites, have been shown to have mixed gonads of male and female elements in the young, which, in maturity, become unisexual through regression of one type of germ cell. Rare specimens were hermaphroditic: these were tabulated by ATZ (1964), who also recorded some very rare examples of intersex in Elasmobranch fishes. A peculiar feature of the Teleost fishes is that normal and abnormal hermaphroditism occurs. Normal hermaphroditism has been found in the <u>Myctoformes</u>, <u>Anguilliformes</u>, <u>Cyprinodontoformes</u>, <u>Perciformes</u> and <u>Synbranchiformes</u>. In the orders <u>Myctoformes</u> and <u>Perciformes</u> many families are functional hermaphrodites and it is said (ATZ, 1964) that some species may even perform self-fertilization.

Amphibia

The amphibia are a particularly labile group and present unequalled opportunities for the study of sex determining mechanism. Abnormalities as well as complete sex reversal can be induced in a number of ways: for instance, parabiotic grafting, hormone treatment, or simply changes in climate. The gonadal sex can be reversed experimentally: and it is possible for genetic females (WZ sex chromosomes) to breed as males. Similarly genetic males (WW) can be bred as females. Mendelian laws apply to the crosses between

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such reversed individuals and both WW and WZ offspring are produced in expected 1:1 ratios. A comprehensive review of this interesting topic was given by FOOTE (1964).

Reptiles

Intersexuality amongst reptiles is not known to be common, possibly because to date not much attention has been paid the cytogenetics of this group. A few uncommon examples of intersexuality have been discovered in Chelonia and Lacertilia, but only rarely in Ophidia and Crocodilia: this apparent discrepancy is most probably due to the poor availability of the dangerous species. Attempts at the experimental induction of sex anomalies in reptiles have met with poor success when compared to other vertebrate phyla (FORBES, 1964).

Birds

Unlike reptiles, birds show marked sexual dimorphism. The female is the heterogametic sex, with WZ sex chromosome complement. Intersexuality in birds has been recognized for many centuries: Aristotle wrote of hens which came to resemble cocks, and vice versa. TABER (1964) related a number of tales which featured intersesual birds. Recent researches have shown that when a female bird is castrated it assumes the coloration of the opposite sex (TABER, 1964). Gonadal dysgenesis has been reported, as also free-martinism of heterosexual twins (JAFFE and FECHHEIMER, 1966) in which chimaerism occurred as it does in mammals, but it was the male gonad which was transformed (MOORE and OWEN, 1965).

Insectivora

Certain moles are known to produce 'super females' but it is not certain if this is a normal event or not (ATKIN and KLINGER, 1962). The normal male vole <u>Microtus oregoni</u> exhibits gonosomic mosaicism, with either XO/XY or XY

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sex chromosomes; the female has the XX complement (OHNO et al, 1963).

Marsupialia

Multiple sex chromosomes have been described in the genera Potorous and Macropus (SHARMAN et al, 1950; MOORE, 1965).

Rodentia

Rats and mice have been studied extensively in laboratory colonies and several anomalies of sex development have been found. Some of the reported sex chromosome complements were XXY (CATTANACH, 1961); the XYY (CATTANACH and POLLARD, 1969); 39,X/41,XYY mosaicism (EVANS et al, 1969) and a hermaphrodite with presumptive 39,XO/40,XY mosaicism (LYON, 1969). A chimaera was reported in a female mouse; thought to be the product of double fertilization of post-meiotic ovum nuclei (RUSSELL and WOODIEL, 1966). Some interesting experimental work in which an embryonic testis was grafted to an embryonic ovary proved earlier experiments, in that the testis suppressed further development of the ovary, but only if it was at a later stage of development than the ovary (MACINTYRE et al, 1959). If this was not the case the ovary might induce changes in the testis. MACINTYRE et al, (1960) showed that if the grafted testis was further than 8 mm from the ovary it had no effect on it, thus demonstrating the presence of a 'secretion' from the testis.

Ungulata

Domestic animals are the major source of intersexes in this class. In cattle the intersexual state has been known since Roman times but the cause was not appreciated until LILLIE (1916) confirmed an earlier report (TANDLER and KELLER, 1910) that anastomoses between the chorionic blood vessels of heterosexual twins might exist in utero. It became the accepted theory that there was a movement of androgens from the male, across the embryonic membranes, to the female co-twin in which masculinization resulted. Several attempts

to prove the theory were unsuccesful (GREENE et al, 1938). Germ cell chim-
aeras were dicovered in bovine tissues (OHNO et al, 1962) and indicated that
cells might migrate between dizygotic twins in utero (GOODFELLOW et al 1965).
In fact, germ cell migration is still in progress after vascular anastomoses
between bovine twins are established (OHNO and GROPP, 1965). HERSCHLER and
FECHHEIMER (1967) tested the theory that freemartins arose through the trans-
fer of Y-bearing cells to the female twin at the time of tissue differentia-
tion: in 13 twin pairs they were able to show a positive correlation between
the degree of masculinization and the male-cell content of the affected female
co-twin. Their findings were later criticised by SHORT et al, (1969) because
there was no proof of a cause-and-effect relationship. Androgens crossing
the placental barrier may represent a secondary virilizing agent. WEISS and
HOFFMAN (1969) reported the loss of XX cells from the previously mixed XX
and XY cell population in the testes of 5 male twins of freemartins. However,
XX/XY chimaerism could still be detected in the blood cells after the elimi-
nation of XX cells from the gonads. To explain this they suggested that XY
testicular cells were antagonistic to their XX neighbours and so eliminated
them. SHORT et al, (1969) determined that the reversed gonads of a free-
martin withextensive XX/XY chimaerism were actively secreting testosterone
and they suggested that it was this and not androgens from the male co-twin
which caused freemartinism, although transplacental movement of such andro-
gens might be a lesser cause. Other bovine intersexes had the normal 60,XY
karyotype; one had apparently normal female gonosomes (60,XX) but had testes.
Two specimens with XX/XY chimaerism were also reported (McFEELY et al, 1967).
Another bovine hermaphrodite was described by DUNN et al, (1968).

Caprine freemartins were not thought to occur until the discovery by ILBERY
and WILLIAMS (1967) of an example in Saanen goat twins. Frequent intersexes
with the XX gonosome complement had previously been encountered (BASRUR and

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COUBROUGH, 1964; McFEELY et al, 1967). Three types of intersex in sheep have been described: males with hypospadias and XY gonosomes; freemartins; and recently a third type which had XY sex chromosomes, undescended testes and female external genitalia (ALEXANDER and WILLIAMS, 1964; BRUERE et al, 1969).

Hermaphroditism, gonadal dysgenesis and intersexes of both sexes have occurred in the roe deer of Europe, and according to KOCH (1963) was the only wild animal in which intersexuality occurred with any frequency. No comment can be made about this assertion at present.

Masculinization of female pigs in utero happens quite often and hermaphroditism is common. Mosaic XX/XY intersexes (McFEELY et al, 1967); freemartins (HUGHES 1929) and female intersexes with XX sex chromosomes and male phenotype (HARD & EISEN, 1965) have been described. More complex cases were reported by McFEELY et al, (1967) of two pigs with female chromosomes and testicular gonads. Familial inheritance of intersexuality in pigs has been noted by several authors (ASHLEY, 1962).

Carnivora

McFEELY et al, (1967) reported 2 rare female intersexes, together with 2 male intersexes, and a hermaphroditic dog.

A number of interesting observations have been made on domestic cats but there do not appear to be any concerning wild cats. Tricoloured males often show a mosaic karyotype: CHU et al, (1964) described such a cat with a normal female (38,XX) and a trisomic (39,XXY) cell line. A similar case was reported in 1967 by McFEELY et al. Males with the 39,XXY karyotype were found by THULINE and NORBY (1961). Equal proportions of XX and XY cells were observed in a tricoloured cat reported by MALOUF et al, (1967); this animal had male gonadal and genital structures but both testes showed a random mixture of normal and sterile tubules. Other intersexual tortoiseshell cats had XX/XY/XXY mosaicism. A

concise discussion of the mechanisms by which such mosaics arose was given by RUSSELL and WOODIEL (1966).

Primata

The only abnormality recorded in the literature concerning the lower classes was sex chromosome mosaicism in marmoset monkeys, the result of migration of cells between heterosexual twins (BENIRSCHKE and BROWNHILL, 1962; 1963).

Writing of intersexuality in mammals, KOCH (1963) maintained that the hermaphroditic way of life seen in many members of the lower phyla and the pathological intersexual states found in vertebrates other than mammals were of no import to the study of human intersexuality. This was rather a pedantic view since no attempt was made to explain the origin of hermaphroditism in the higher phyla. Perhaps, if the subject is seen less from the comparatively restricted medical aspect and more in terms of general biology some possible connections may well be seen.

It is tempting to speculate that the hermaphroditic state in the higher vertebrates represents ontogeny recapitulating phylogeny, as Lamarck first wrote. Whatever the truth of this may be, the intersexual state in all mammals does represent a defect of development. The abnormal appearance of primitive sex features in individual animals has occurred with some regularity throughout recorded history, as the following pages will tell.

INTERSEX   IN   HISTORY,   RELIGION   AND   MYTHOLOGY

Introduction
Intersex in History
Intersex in Religion
Contemporary aspects of
    intersexuality

INTRODUCTION

Before relating some of the legends and historical narratives that have sur-
vived to the present it is necessary to explain the terminology because this
has changed over the years.   In the ancient literature epicene persons were
commonly referred to as being androgynous   (Greek: andro = man; gyne = female),
Later legends ascribed the origin of such persons to Hermaphrodite, and they
became known in classical literature as hermaphrodites.   In recent times the
term hermaphrodite, previously qualified by the adjective 'true', has become
restricted to those with the gonads of both sexes, and other types of sexual
ambiguity are termed intersexes, either male or female.   The term, intersex,
when used without any generic qualification, refers to all forms of abnormal
sex differentiation, including hermaphrodites. It is important to note that
the ancients could make no distinction between persons who might now be known
as hermaphrodites and male or female intersexes and so, in their writings, all
were called hermaphrodites or androgyni.

Hermaphrodites were known to man thousands of years ago and ancient peoples
in diverse parts of the world worshipped intersexual and transvestite deities.
The Aztec divinity Chalchiuhthicue was the first female but could assume male
form, as could the Chinese creator of man, Nu Kua. Similar Chinese gods were
P'an Ku and the fabulous, bisexed beast, Ch'i-lin, who resembled a unicorn. A
number of Hindu deities were also credited with ambisexual natures: Shiwa and

Ardda-Nari were gynandromorphic; Vishnu, or Viraj, was able to assume either sex. The ancient Indians hailed a god named Purusa, a hermaphrodite who had created all life. It is believed that the Hebrew god, Jehovah, was first known as Jahveh to the ancients, in which case he was androgynous: Jah in Hebrew meant male, and havvah, female. Another Hebrew deity, Kether, was the hermaphroditic and omnipotent father of the universe. Kwannon was the Japanese Buddhist god who was originally male but subsequently became female. Amongst the cultures of Mesopotamian basin were several gods with bisexual attributes: Ashtar-Chemosh of the Moabdites, said by YOUNG (1937) to be the oldest of the ambisexual characters in historic cultures. Mut, it was inscribed on ancient Egyptian papyri, was goddess of the moon and was sometimes shown with a phallus; a good indication of the intersexual state. With the exception of Priapus most of the classical Grecian and Roman gods of that era were frequently depicted to be of uncertain sex. Venus, for instance, is usually assumed to have been a fantastically beautiful woman, but nevertheless was quite often depicted with a beard. The seed of Zeus fell upon the ground and gave rise to a strangely equipped child, Agdistis. A Greek citizen named Tiresias was changed from a male into a female for sacriligeously interposing his cane between two snakes that were copulating. The famous Maid Marion of British folklore, in Robin Hood's merry band, was thought to have been a transvestite character known originally as Mad Morion. It is perhaps significant that Maid Marion was dressed as a pageboy in the Robin Hood saga. Mexican folk stories tell of tzequiles who were effeminate males dressed as women. Vathek, once a Mahommedan ruler, was also extremely effeminate. It is a very consistent feature of the 'creators' of diverse races and tribes that they were attributed with ambisexual powers. The same trend is evident in African tribal lore: for example, the sun-moon god, Mawa-Lisa, of the Dahomey natives; Nzambi, the Congo tribes' equivalent; and Gurikhoisib, the Hottentot's supreme creator, were all bisexual. A comparable personage was Ahsonnuthi of the North American Navajo tribe.

A list such as this might be endless if all the beings to whom ambisexual or trans-sexual modes of life were ascribed were to be mentioned; for further detail the reader is referred to the encyclopaedic work of JOBES (1962).

In addition to the references in mythology and historical records, there are a number of religious texts in which mention is made of the androgyni. These individuals of unusual sex obviously occurred with sufficient frequency to warrant the promulgation of laws to guide their treatment and behaviour in society; some of these are to be found in the widely accepted religious text, the Talmud. Other references appear in the Tosefta and the Bible.

Although the origin and causes of several forms of intersex remain obscure to us, numerous theories have been advanced. Possibly the earliest of these was a theological argument based on the following verse:

> So God created man in his own image, in the image of
> God created he him; male and female created he them.
> Bible; Genesis 1:27.

This verse is essentially similar in context, but with one important change, to the comment in the Hebrew text:

> Rabbi Jeremiah ben Elazar said: 'When the Holy One, Blessed
> be He, created the first man, he created him androgynous.
> Midrash; Genesis Rabbah 8:1.

According to YOUNG (1937) the word 'androgynous' used in the above excerpt was derived from the Hebrew characters אַנְדְּרוֹגִינוֹס , and when translated to Greek this then read ανδργυνοσ . The English interpretation of this is androgynous, the use of which was explained earlier.

The above passage from the Bible gave rise to profound debate which lasted for many centuries. Young mentioned that the Catholic priesthood at the time of Pope Innocenti III (1198 - 1216 A.D.) advocated the interpretation that Adam was the original hermaphrodite and only later did God, by taking a rib, create separate sexes.

The Greek writer Diodorus (c. 50 B.C.) wrote of Hermaphroditos who was born to Hermes and Aphrodite. The child was named for both of his parents since he shared the sexual features of both. It was recorded that Hermaphroditos was regarded by some as a god, while others declared such a creature of two sexes to be a monstrosity.

Although the most popular explanation of the term is that given by Diodorus, there was another school of thought: Young mentioned that stone columns used as road markers in ancient Greece were known as herms. Various effigies were carved on to them, so that one which bore the likeness of Herakles was called a hermerakles, while one which bore the head of Aphrodite was, naturally, a hermaphrodite.

Some years after Diodorus the Roman writer OVID (BC 43 - 18 AD) produced a saga of seduction in which the characters were the 15 year old son of Hermes and the water nymph, Salmacis. While travelling the land of Lycia the boy stopped at Salmacis' pool to bathe. Whilst he was thus engaged the nymph approached him and begged him to possess her: perhaps foolishly, the youth resisted the numph's earnest pleas, so that in the face of defeat she inveigled her gods to prevent him from leaving. Salmacis' unnamed deities were quite sympathetic and immediately fused the boy's and the woman's bodies.

> '...so were these two bodies knit in close embrace:
> they were no longer two, nor such as to be called, one,
> woman, and one, man. They seemed neither, and yet
> both.

Some time later MARTIAL (40 - 100 AD) wrote:

> 'Male he entered the fount; he came forth both male
> and female: One part of him his sire's, all else had
> he of his mother.

After a lapse of several centuries AUSONIUS (310 - 395 AD) reaffirmed the Hellenic theory, which Ovid had probably plagiarized, by writing of the two-

sexed offspring of Hermes and Aphrodite, Hermaphrodite.

One of the more amusing theories of the creation of hermaphrodites was that
of Phaedrus, related by YOUNG (1937). After dining one evening with Bacchus,
Prometheus was busy determining the sex on some human bodies which he had
just made. He made a terrible error and

> Aduplicuit virginale generi masculo
> Et masculina membra aduplicuit feminis!

Remarkably, major reference works of today such as the Encyclopaedia Brittan-
ica and the Oxford Dictionary, give Ovid's more lurid version of the origin
of Hermaphrodite in spite of the fact that the Greciantheory existed many
years earlier. With the advent of the term 'hermaphrodite' the religious
description, androgyne, fell into disuse.

Throughout the period covered by written history there have been problems re-
lating to the treatment of intersexes. Several directives outlining the stat-
us of such people were given in the ancient Hebrew texts, examples of which
are given below.

> The androgynos has ways in which he resembles men; and ways in
> which he resembles women; and ways in which he resembles both
> men and women; and ways in which he does not resemble either.
> He resembles men in that he becomes unclean by white emission;
> he marries women and not men. The androgynos must not seclude
> himself with women; he does not receive sustenance from a
> father's estate, like daughters; and he is duty-bound to fulfill
> all of the commands of the Torah, like men. He must not defile
> himself with the dead, and if he happens to be of priestly rank,
> like men, he must not cut the corners of his hair.
>
> He resembles women in that he becomes unclean by the issue of
> blood, and that he must not be alone with men; and that he does
> not impose the levirate marriage on a surviving brother; and
> that he does not share in the inheritance with the sons; nor
> does he share in the sacrifices of the sanctuary; and he is
> disqualified as a witness; and he is disqualified from serving
> on the priesthood.
>
> Bikkurim II: 7.

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Homosexuality was forbidden the Hebrews, and for the androgynous:

> The laws of pederasty apply to him.
>
> Tosefta: Yebamot II: 5.

Androgynes of the Hebrew community were fortunate in that:

> If he marries it is binding, and the marriage
> can only be dissolved by divorce.
>
> Tosefta: Bikkurim II: 4.

There is no clear indication of when intersex was first mentioned in the old literature. THEOPHRASTUS (372 - 287 B.C.) was certainly among the first to do so when he described the superstitios man, who

> '..returning spends the entire day doing sacrifices
> to the androgynes and putting garlands around them.

HIPPOCRATES (460 - 357 B.C.) was the father of medicine, and as befits this distinction, made what was certainly the first description of the condition we now call acquired virilization, when he wrote of the wife of Pytheus, who was called Phaetusa, whose body and voice became entirely masculine. A similar fate befell Mamysia, wife of Gorgippus. Both ladies were in their climacteric years when they became virilescent. ARISTOTLE also described a race who had the right breast of a male and the left of a female; these were the Androgyni. PLATO (429 - 347 B.C) approached the basic nature of sex when he wrote in his Symposium:

> 'And first let me treat the nature and state of man; for the
> original human nature was not like the present, but different.
> In the first place the sexes were originally three in number,
> not as they are now; there was man, woman, and the union of
> the two, having a name corresponding to this double nature;
> they once had a real existence, but now it is lost, and the
> name only is preserved as a term of reproach.

A hermaphrodite's fortunes varied with the times in Rome: legend has it that Romulus ordered all to be thrown into the Tiber . LIVY (BC 59 - 17 AD) wrote of a child of uncertain sex born amongst the Sabines, and of another who at the age of 16 years could not be sexed. He also recorded that a hermaphrodite created terror among the people, who believed them to be omens of' great

disaster. They were thus to be carried out to sea, as had been done with a similar monstrosity during the consulship of Gaius Claudius and Marcus Livius in the year 207 B.C.

The Middle Ages were seemingly not well-documented and only a few incidents from the late 17th Century onwards were recorded by YOUNG (1937). One very interesting comment was that attributed by Young to the English explorer, Hamilton, who was in west Africa during the years 1688 to 1723: he reported seeing nine hermaphrodites, 'who are common in this country', performing a dance in honour of the gods.

The deity Hermaphrodite abounds in the classical Greek and Roman solid art forms; many statues, carvings and frescoes may yet be seen in museums all over the world. In these works Hermaphrodite is generally shown reclining or standing but, unlike models of the normal female form, with the pudendal area exposed. It would seem that epicene individuals have not been very in-spiring to poets: Young was only able to quote four examples.

CONTEMPORARY ASPECTS OF INTERSEXUALITY

The volume of information contained in historic records indicates that the problem of intersexuality is as old as man himself and now, as in the be-ginning, is still largely unresolved. Modern attitudes towards the unfort-unate person with ambisexual chracteristics remain, surprizingly, similar to those which prevailed 2000 years ago. The exception is that in these times hermaphrodites are not put to death by our so-called civilized societ-ies. To the layman the intersex is still an exotic freak; there is no fix-ed disposition towards the affected individual because the stigmata of sexual abnormalities are not readily understood. For instance, there is a remark-able fluctuation of reaction between sympathy and vicarious interest when a caption such as 'Sex change girl to marry' appears in the news media. Most

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people can recall instances when suspiciously muscular sportswomen were 'exposed' as impostors but few, if any, of those reports ever contemplated that the subjects possibly were females; genetically, legally, and in some measure, socially. It must be small consolation to an affected person to be a good athlete or a figure of passing renown when the chance of a normal social life is practically nil.

In contrast to physical deformities or those disturbances of metabolism which are accompanied by mental retardation, the intersexual state is not often accompanied by gross idiocy. It is therefore of greater social importance because the affected individual is in the invidious position of having deformities of the body but not the mind, and is capable of appreciating his abnormalities. The grave psychological sequelae of such realization demand very careful treatment.

A serious disadvantage which confronts the intersexual person is that his condition is one that cannot be freely discussed and he must, consequently, bear his problems alone. The instability and reticence of these people is exacerbated when, as frequently happens, associates and even family avoid them. These are all the results of the inculcated secrecy and embarrasment with which sexual matters are regarded in modern society. Until a few years ago these presented insurmountable barriers but there is now a happy tendency to regard such matters more realistically.

A further hazard of the intersexual state is that it may not become apparent until adult life and the subject, unaware of his condition, may have entered into marriage. Subsequent discovery by a couple that their marriage is abnormal and barren can cause serious psychological reaction. Less serious, but nevertheless depressing, incidents may befall an intersexual person. YOUNG (1937) described an excellent example: a man of ambiguous appearance

approached a New York policeman for directions, but was promptly arrested by that official for masquerading. The officer noted his prisoner's high-pitched voice, rounded contours and lack of beard, and not until the unfortunate man had demonstrated his sex was he freed. He was being treated at the time for hypogonadotrophic hypogenitalism. Similarly, the fate of the muscular sportswoman being 'exposed' must give food for thought to other affected women. In fact, physical inspection of female competitors is now a recognized preliminary to the Olympic Games; a precaution to ensure that all women are females! Such events must make an ambisexual person extremely reluctant to seek medical assistance lest details of his case, or worse, his identity, should reach the hungry eyes and ears of the public.

This unhappy state of affairs is due to ignorance on behalf of the public and its legislators. A brief survey of the law shows that there is not a single definition of sex: not even after some 2000 years since the Roman law was established and during which time ambisexual persons have not been uncommon.

"Marriage is a union between a man and a woman" (HAHLO, 1963). In South African law there is no further definition of what constitutes a 'man' or 'woman'. Hahlo understated the fact when he pronounced that 'difficult legal problems arise when there is a 'change of sex'' and according to him, should a hermaphrodite's status only be realized after marriage has been contracted, then it is null and void, ab initio, because it is a union of two people of similar sex. That this is unjust to the couple concerned goes without saying, but the law apparently makes no allowance for this.

The position is more definite when one partner undergoes a sex change operation to make him the same sex as his partner: this constitutes constructive desertion and the marriage is terminated thereby. This eventuality

is much less probable than that in which one partner, invariably the woman, has undergone a change of sex before marriage. At this stage it is desirable to consider the success of such 'sex change' operations. Most of them involve the construction of an artificial vagina, using a segment of colon or grafted skin to line the newly fashioned perineal vagina. In many cases the graft shrinks and is thus unsuitable for coitus. The legal consequences of this are somewhat different to those of other intersexes, as was illustrated by the findings of a British court.

The case involved a normal male who was suing for his marriage to a 'sex change' woman to be annulled because it had not been consumated. In passing judgement the Court found that in law there are only two sexes; male and female, and therefore an individual must belong to one or the other: to the gender to which he is best suited. Biological sex depends upon such criteria as genetic, gonadal, genital and somatic sex and so the respondent in this case was a male despite surgical intervention which had sought to make the person into a female. Furthermore, marriage depends upon sex, not gender: therefore the respondent could not be regarded as a woman because no sort of normal coitus was possible.

This judgement received wide publicity in the scientific (editorial, Lancet 1970b) and the lay press around the world. Protagonists (e.g. DEWHURST, 1970) regarded the judgement as helpful in determining the law's position in regard to such persons; others (editorial, Lancet, 1970) protested that this 'most heartless decision would create a third sex where marriage was impossible', which opinion was shared by other correspondents, for example MILLS (1970).

The salient point of this discussion is that it illustrates the lack of any definition of sex in law and that the law, which is an extension of the public's attitudes, has no clear approach to such individuals or their problems. There have been many similar cases over the years, and there have been many recommendations by interested workers for the law to consider its position (COURT-BROWN, 1962; editorial, Lancet 1970). There is no definition of sex in South African statutes so that one may anticipate the day when similar cases will arise here: as others have done in other countries, the legal profession of South Africa should be urged to consider the definition of sex, particularly as it affects marriage contracts, and declare their position.

CHAPTER   IV

METHODS   OF   INVESTIGATION   AND   THE
CLASSIFICATION   OF   INTERSEXES

Development of cytogenetic techniques
Methods of Investigation
Differential diagnosis of intersexes
Classification of Intersex
Treatment of Intersex
Sources of patients for this study

THE   DEVELOPMENT   OF   CYTOGENETIC   TECHNIQUES

In 1665 Robert Hook* first saw the cellular structure of biological material,

a section of cork, and in doing so initiated the study of cytology. Some

two centuries passed before the human chromosomes were seen for the first

time by Virchow* in 1857, in mitotic cells. At the time he did not appreci-

ate the significance of his discovery and a further 20 years passed before

Von Torok* in 1874 observed the successive stages of mitosis. A period of

intense research followed and in 1882 Flemming* introduced the term 'chroma-

tin' to describe the darkly staining material of the nucleus; this was ex-

tended to 'chromosomes' in respect of the discrete, heterochromatic bodies

present during mitosis. Several independent workers had concluded that the

chromosomes actually carried the inheritable factors from cell to cell during

division (Weissman, 1883[+] ; Strasburger, 1884[+] ; Von Kollicker, 1885[+]). In

1866, Gregor Mendel[+], a botanist, had conducted interesting experiments on

pea plants and had shown that discrete characteristics were passed to sub-

sequent generations in an oderley manner and independently of each other.

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* cited by BARTALOS and BARAMKI (1967)

[+] cited by HUGHES (1959)

Those observations were not immediately acceptable in the face of the then
popular theories of such authorities as Charles Darwin (1859), which were
based on the gradual and progressive evolution of species through continuous
variation. Mendel's work passed into a period of oblivion which lasted un-
til the beginning of the 20th Century. Again it was the botanists who real-
ized the significance of the work done by Mendel: three of them, De Vries,
Correns and Tschermak, working independently, each revived Mendel's theory
(STRICKBERGER, 1968). From this point onwards the study of genetics, and
of cytology, progressed more rapidly than ever in the past. The correlation
bewteen chromosomes and Mendelian genetics was realised (Sutton, 1903;
Boveri, 1904; cited by STRICKBERGER, 1968) and within a few years had been
established beyond any doubt. Soon afterwards the role of the chromosomes
in sex determination was demonstrated (Wilson, 1905[+]).

The human chromosomes appear to have first been investigated by Hansemann[*]
in 1891 but none of his findings are known. Following the revival of int-
erest in Mendelian genetics a number of workers investigated human tissues,
using techniques which by comparison with modern methods were very crude.
Most of their preparations were obtained from cell squashes. However, after
many inaccurate estimates of the human chromosome number had been made, two
came quite close to the now established diploid number of 46: De Winiwater
(1912[++]) and Painter (1923[++]) both decided on 48. In an earlier study the
diploid number was said to be 46 (Painter, 1921[++]) but that was soon retract-
ed in favour of the more widely accepted complement of 48. Wieman (1917[++])
had even recognized the X and Y chromosomes.

Such was the state of human cytogenetics in 1955 when OSGOOD and BROOKE made

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* cited by BARTALOS and BARAMKI (1967)
+ cited by HUGHES (1961)
++ cited by HARNDEN (1961)

known their method for obtaining mitotic chromosomes for study from cultured leucocytes. The following year a method of preparing chromosomes from solid tissue cultures, together with a reappraisal of the human diploid number to 46, was published (TJIO and LEVAN, 1956). With these vastly improved methods at their disposal confirmation of the amended chromosome number was soon provided by a number of independent researchers from the study of many different tissues (FORD and HAMMERTON, 1956; BENDER, 1957; FORD et al; TJIO and PUCK, 1958; CHU and GILES, 1959). Progress was made rapidly and soon it was possible to make chromosome preparations with relative ease and on small specimens of blood (HUNGERFORD et al, 1959; MOORHEAD et al, 1960).

Biologists had discovered sexual dimorphism in many animals, vertebrate and invertebrate, in the form of a small, densely staining intranuclear particle, the sex chromatin. This was found in the interphase nuclei of the female but not the male (GEITLER, 1937). It was not until 1949 that BARR and BERT-RAM applied the technique to humans. Another form of sex dimorphism was found; the pedunculated 'drumstick' appendages of the polymorphonuclear lymphocyte nuclei, which similarly were only present in the female (DAVIDSON and SMITH, 1954).

Before 1959 the genetic features of intersexual disorders were largely matters of conjecture. Nuclear sexing had been applied to a certain extent but the findings were never accepted with conviction: conflicting observations such as 'male' nuclear sex in persons who were quite obviously female (e.g. Turner syndrome and testicular feminization) and female nuclear sex in males with the Klinefelter syndrome caused much scepticism and also some rather odd trends in the classification of those disorders. Of necessity, anatomical, biochemical and histological data, in the absence of modern cytogenetic knowledge, governed the approach to the intersexual problems.

Until 1959 laparotomy was practically a standard procedure in the diagnosis of intersex: an illustrative comment was 'It is noteworthy that the bisexual conditions present were discovered by herniotomy in 7 of the 20 cases; by laparotomy in 6, and by autopsy in 7. All but 4 patients had passed the age of puberty, and 12 were 20 years of age or more before the discovery was made' (YOUNG, 1937).

Apart from the major advances in cytogenetic techniques since 1959 there have also been important advances in the fields of radiology, endocrinology, and the development of endoscopic instruments which permit visual inspection and biopsy of the internal structures without the hazards of major surgery.

METHODS OF INVESTIGATION

The investigation of and individual with anomalous sex development can be best considered under the headings of clinical, biochemical, special tests and cytogenetic studies. In a few unhappy cases post mortem examination has also to be considered.

Clinical Investigations

In this phase of the investigation the subject himself must be examined and interrogated to establish personal and family details. In the introduction it was said that intersexual patients are often loathe to discuss or reveal their unusual abnormalities and so they must be approached with even more tact than usual in order to gain their respect and trust, without which cooperation and attendance by the patient at further clinics will be jeopardized.

Also, in respect of the local population, the approach must be varied to take into account the social customs of the individual's racial group, some

races being more prone to resent the extremely personal examination which is necessary. Interrogation must be conducted in terms which the patient is able to understand, but which do not suggest profanity or familiarity.

Experience has shown that it is helpful to commence the first meeting with a general conversation concerning the patient and his family; their illnesses, and then to make routine measurements of the patient before progressing to a detailed physical examination. To distract the subject from his embarrassment during the actual inspection the examiner should to continue to ask questions. Examination should be as quick as possible, but if the patient becomes very restless then further examination should be postponed until he has had time to regain his composure. It is inevitably the physical examination patients are least willing to submit to.

Examination should include all areas of the body, commencing with measurement of height, arm span, ground to pubis distance, head and chest circumferences, weight, and a note on the general build. Following this the features of the head, face, occiput and neck should be noted. The shape and other peculiarities of the chest, spine and abdomen are of interest. Legs, arms, feet and hands frequently show signs which may be of diagnostic value and these should be noted. A record of the dermatoglyphs of the hands should be made, either by photography or hand printing. Indications of hormone activity should be sought by observing the areas covered by scalp and secondary hair; breast development, the size and aspect of the nipples and the contours of any subcutaneous fat. The pectoral and pelvic girdles should be recorded as masculine, feminine or indeterminate. The voice may reveal changes of pitch, which must be recorded. A detailed examination of the genitalia should be done, and if there are any internal structures, specialized gynaecological opinion should be sought.

It is most useful to make a sketch of the genitalia at the time when the patient is examined: one diagram is worth a thousand words! It is also a very good insurance in case photographs prove to be unusable. The illustration should indicate the size, shape and disposition of the phallus together with the position and number of perineal openings. The size and appearance of the labioscrotal structures is important and the location of any gonads has to be indicated. When photographs are being made the patient should, if he desires, be given a face mask to protect his anonymity.

The information gleaned from interrogation and physical inspection will in most cases suggest a tentative diagnosis and with this in mind further investigations can be planned. In this laboratory it is standard procedure to take blood for chromosomal studies at the first consultation.

Biochemical investigations
The prevailing hormone patterns in intersexual individuals are of interest but with few exceptions are not diagnostic. This will become apparent in later chapters where inter-individual variation in the same syndrome can be seen. Endocrine studies which are of particular interest in the study of intersexes are as follows.

The pituitary gonadotrophin, follicle stimulating hormone (FSH) is produced in the anterior lobe of the gland and is responsible for induction and maintenance of gonadal function. The normal gonads metabolize gonadotrophins so that only a small excess is detectable in the urine, in which it is excreted. In the female, normal excretion of FSH is between 6 and 24 mouse units (mu) per day, and in the male 0 to 6 mu. Excretion of FSH in the prepubertal subject is lower and the levels are quite variable so that no advantage is gained from this assay until after puberty.   Occasionally a defect

of the pituitary compromises the production of FSH the gonads lack adequate stimulation and hypogonadism results. Proof of such hypopituitary hypogonadism can be had by supplying the patient with extrinsic gonadotrophins, as there should then be an improvement of gonadal function. If the gonads are themselves dysgenetic then noFSH is catabolized and there is correspondingly high urinary excretion.

Oestrogens are produced principally in the ovaries but the testes also manufacture these substances, in much smaller amounts. In the male circulating oestrogen is conjugated and thus deactivated in the liver. If the liver is damaged or diseased and is prevented from removing excess oestrogen, then it is possible that oestrogen-dependent contrasexual features may appear. Oestrogen is responsible for the induction of such feminine attributes as breast development, deposition of subcutaneous fat and if a responsive uterus is present, endometrial activity.

Androgens, the male hormones, are also produced by both sexes. Testicular androgens are more copious and have far more biological activity than the androgens of the adrenal cortices. Testicular androgens are extremely important for the induction and maintenance of masculinization of the foetal genitalia and, at puberty, for the development of male secondary development. Secondary sexual changes in the male include growth and spread of beard and body hair; deepening of the voice through thickening of the cricoid cartilage and increase of muscle bulk.

The endocrinological tests most employed in the study of intersexes are the assays of FSH and 17- steroid excretion. Unfortunately there are no facilities for oestrogen assay in Durban.

Special Investigations

Included in this section are those specialities which may be used periodically in the investigation of intersexes.

Contrast radiographic techniques are extremely useful in the demonstration of internal genital structures when these are too small to be palpated and which might otherwise require surgical exploration. Routine radiographic studies are often useful in suggesting a diagnosis, particularly in gonadal dysgenesis where some characteristic changes may be seen.

Endoscopy is a relatively new procedure which has done much to minimise the risk of surgical shock to patients. Using this technique the internal genitalia can be vizualized and, if necessary, biopsied and only two small, stab incisions through the abdominal wall are required.

Histological examination of biopsy specimens is essential to the diagnosis of certain cases, and is desirable in many. Some authors have advocated gonadal biopsy in virtually all forms of intersexuality (for instance, OVER-ZIER, 1963) but the general practice in local hospitals is that surgical intervention is only done when absolutely necessary.

Psychiatric evaluation of patients is often a desirable precursor to clinical treatment when the patient seems to be uncertain of his psychosexual or social orientation.

Cytogenetic investigations

These are the tests by which the karyotype, sex chromatin status and other traits are established. For this work, nuclear sexing and dermatoglyphic studies have been dealt with in separate sections (see Chapters V and XVI).

Routine preparation of mitotic chromosomes for karyotyping only became pos-
sible after the developmental work was done by TJIO and LEVAN (1956). They
devised a method of making remarkably clear preparations of mitotic chromo-
somes from cultured foetal tissues, and were able to reassess the human dip-
loid number, which they established was 46. This was soon confirmed (FORD
and HAMMERTON, 1956) in a number of tissues (TJIO and PUCK; CHU and GILES,
1958). The most important practical development was the discovery of the
method for making short-term cultures of peripheral blood lymphocytes. Such
a method was described by HUNGERFORD et al, (1959) and was a modification of
the gradient technique established by OSGOOD and BROOKE (1955). This method
soon became widely employed and despite many suggested modifications, remains
essentially the same even now. Some of the improvements in culture methods
included the re-introduction of hypotonic treatment of cells prior to fixing
(HSU; HUGHES, 1952) and air-drying of slides (MOORHEAD et al, 1960). The
use of phytohaemagglutinin as a mitogenic agent (NOWELL, 1960) was confirmed.

Many different tissues have since been used for cytogenetic investigations.
Although the lymphocyte technique soon replaced the marrow-incubation method
(FORD et al, 1958), the latter enjoyed the advantage that preparations might
be examined after only 3 hours. These two methods have ousted solid tissue
culture from routine investigation: culture of solid tissues require more
time (MINIMUM of 7-10 days) and labour. Also, the failure rate is high when
compared to the short term methods. However, in the study of conceptuses and
in search of mosaicism when this is not evident in the lymphocytes, solid
tissue culture is essential. The most widely employed methods are those that
use skin fibroblasts (BISHUN et al, 1965; DUGDALE and SIDDAL, 1969) from live
and dead subjects. Fibroblasts recovered from the cerebrospinal fluid have
also been used (SPRIGGS and BODDINGTON, 1963) and foetal fibroblasts obtained
from amniotic fluid are employed in prenatal diagnosis (STEELE and BREG,1966;

SANTESSON et al, 1969; GREGSON, 1970). Other sources of cells for culture are the thymus and spleen (BAIN and GAULD, 1964), foetal membranes (BÖÖK et al, 1968) and lymphocytes taken from cadavers of as old as 85 hours (HARROD and COHEN, 1969).

Despite the wide variety of tissues used in establishing cultures the basic principles are similar. Tissue culture depends upon inducing cells to divide, in vitro, in a growth medium and atmosphere which support metabolism. Many such media are available, in solid or liquid form, and consist of isotonic salt solutions to which essential nutrients have been added. Some incorporate antibiotics and fungicides to combat contaminants. Other formulae incorporate homologous or heterologous sera or tissue extracts. The gas phase is usually 5% CO_2 in air. There are three important phases in the culturing procedure: first, viable cells are used to inoculate a culture; they are exposed to a mitogenic agent such as phytohaemagglutinin (PHA), and finally, prior to harvesting the cells are exposed to colchicine, which is responsible for arresting mitosis at the metaphase.

Phytohaemagglutinin, as its name implies, is a plant haemagglutinin which is extracted from the bean Phaeseolus vulgaris. It was originally used as an agglutinin (RIGAS and OSGOOD, 1955) and was later found to have an unexplained potential for inducing mitosis in certain cells (HUNGERFORD et al, 1959; NOWELL, 1960). It has been shown that lymphocytes are the only cells which respond in cultures of leucocytes (MacKINNEY et al, 1962) although lymphocytes from patients with chronic lymphocytic leukaemia are insensitive to PHA stimulation (NOWELL, 1960). In contrast to this phenomenon, lymphocytes from patients with acute leukaemia will divide even when unstimulated (MOORHEAD et al, 1960).

Colchicine is an alkaloid obtained from the herb Colchicum sp. and was first

used in the treatment of gout by ancient Egyptians (GADDUM, 1959). Apparently it interferes with the formation of the nuclear spindle, but the mechanism by which this is achieved remains undiscovered. The application of colchicine to biological material was first done by BLAKESLEE (1937) who noted that cell volume in treated plant tissue increased and the chromosome number doubled. When this technique was first applied to animal tissue is uncertain. The use of colchicine during the last few hours of incubation of cultures permits a large number of metaphase-arrested cells to accumulate; this is the stage at which the chromosomes are at their maximum bulk and, therefore, the most suitable for examination.

Exposure of the cells to a hypotonic medium for a short while before being fixed enhances the final preparation by plasmolysing the cell wall and thus removing the cytoplasm. The nucleus becomes swollen by endosmosis and the chromosomes are consequently able to separate. Such a turgid nucleus is more readily burst, and its chromosomes more easily spread, when it is dropped or squashed on a slide.

Lymphocyte culture technique and karyotype analysis

Of the many methods advocated by various authors, that of MOORHEAD et al (1960) is the most widely used, and is employed in this laboratory in a slightly modified form.

An amount of venous blood, ranging from 0.1 to 20 ml, was drawn into a plain syringe, from whence it was transferred to a sterile, heparinized bottle. In all cases heparin ('Pularin'; Evans Ltd, Liverpool, UK) was added to tubes in 0.15 ml (150 i.u.) volumes; this was found to be adequate for all specimen volumes, as it did not affect low-volume specimens and yet was adequate for as much as 20 ml blood. Blood was immediately mixed with the heparin by gentle inversion of the container, after which it was taken to the laboratory.

The specimen was chilled for an hour at 10°C before the addition of 0.02 ml

of PHA (Difco Laboratories, USA), protein moeity, In very low-volume spec-

imens the PHA was added directly to the culture medium and whole blood was

inoculated into it. Generally, specimens were allowed to stand for an hour

in the refrigerator after the addition of PHA. Specimens were then centri-

fuged gently to clear the supernatant plasma of excess red cells and then

the plasma containing sequestered leucocytes was aspirated into culture tubes

each containing 5 ml of medium M150 (Poliomyelitis Research Institute, Johan-

nesburg). Experience has shown that no additional serum of any sort was re-

quired; also, determination of leucocyte density was not essential, and so

neither of these steps was taken. Two or 3 tubes, each containing about

2 ml of plasma and cells in culture medium, were prepared for each specimen

and were incubated for between 60 and 72 hours at 37°C.

During the final 2 to 4 hours of incubation the cells were exposed to colch-

icine by adding 0.2 ml of colcemid (Ciba, Switzerland) in 0.2% w/v aqueous

solution. Cells were harvested by transferring the culture suspensions to

suitable centrifuge tubes and spinning them down. The supernate was removed

and replaced by 5 ml of isotonic saline, in which the cells were resuspended.

After spinning again the saline was removed and replaced by 10 ml of distill-

ed water, so that the cells were exposed to absolute hypotonicity, for 15 to

20 minutes. Thereafter the cells were spun down and 9 ml of water was taken

off. Three millilitres of fixer (acetic acid-methanol, 1:3) was added; the

fixer was used cold. Repeated changes of fixer were made until the cell

button was cleared of haemoglobin released by plasmolyzed red cells.

After at least 3 changes of fixer, and a minimum of 2 hours, the cell button

was suspended in sufficient fixer to make a slightly cloudy mixture. Four

drops of this were allowed to fall from a height of 2 inches on to a clean,

chilled microscope slide. The wet slide was ignited by passing it through

a spirit lamp flame and when the excess fixer had burned off, drying was completed in an airstream. Staining was done in aceto-orcein (formula given in appendix 1) for 2 hours. Stained preparations were rinsed briefly in distilled water, dehydrated in alcohols and cleared in xylol before mounting them in DePeX (B.D.H.) medium under cover glasses. Chromosomes were examined and counted with a Zeiss 'Research' microscope and were photographed with the instrument's attached 35mm camera. Photomicrographs were made at a magnification of 400x; the final magnification on prints was in the order of 3000x. Karyotypes were prepared according to the classification proposed at the Denver and Chicago internation conferences (DENVER REPORT, 1960; CHICAGO CONFERENCE, 1966). The modal chromosome number was established by counting a minimum of 20 spreads. If there were any discrepancies a further 10 or more spreads were counted until the amodal counts became insignificant or were confirmed. Missing or supernumerary chromosomes were identified with the aid of a camera lucida and confirmed by preparing 3 or more karyotypes. A mixed cell population was reported if more than 10 percent of the spreads examined had a chromosome number, or an atypical chromosome, different from the majority. Whenever possible a second specimen was obtained from patients with abnormal karyotypes in order to confirm the observations.

Lack of facilities in Durban unfortunately precluded the use of autoradiographic labelling techniques in the identification of abnormal chromosomes and this laboratory has no facilities for making solid tissue preparations.

THE DIFFERENTIAL DIAGNOSIS OF INTERSEX

To the interested investigator the final diagnosis of an intersex condition presents an excercise in correlating a number of observed facts. It is well known that the degree of variation shown by intersexual syndromes is enormous; no syndrome has a specific karyotype, and conversely, no karyotype underlies a specific syndrome. However, diagnosis should not be an insurmountable problem if a logical approach is followed. The procedure used in this laboratory is outlined in the following diagrams.
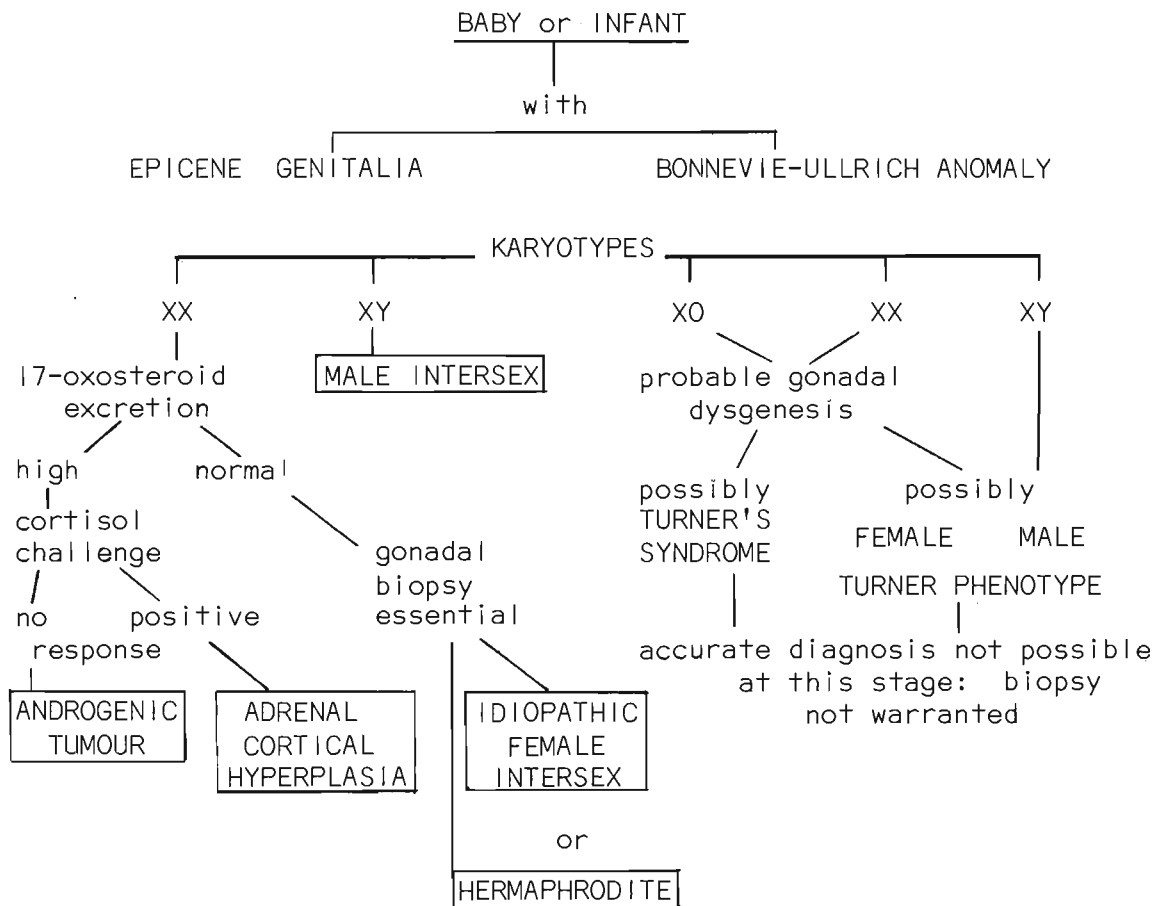
Fig. I: Diagrammatic Explanation of Differential Diagnosis in Babies

ADULT PHENOTYPIC MALES

with

EPICENE
GENITALIA

Cryptorchidism; hypo-
spadia; Delayed puberty;
Infertility; Gynaecomastia

K A R Y O T Y P E

XY

X/XY

XX

XYY

XY

XXY; XX

testes
bilat.   unilateral

POLY-Y
SYNDROME

KLINE-
FELTER'S
SYNDROME

with   without
breast development

ASYMMETRIC
GONADAL
DIFFERENTIATION

PARTIAL
TESTICULAR
FEMINIZATION

MALE *
INTERSEX

17-oxosteroid
excretion
raised

FSH
excretion

high   normal
or low

other cause

ADRENOGENITAL
SYNDROME

* sub-divided as andro- or
gynae-morphic

PRIMARY
TESTICULAR
DYSGENESIS

Fig. 2(a):   Diagrammatic Explanation of Differential Diagnosis
of Intersex in Phenotypic Males

Because the appearance of a patient changes with age, and hormone patterns
are only of use in diagnosing adrenal hyperactivity,babies have been con-
sidered separately (Fig. 1). The differential diagnosis of adults is given
in Figs. 2a and 2b; females with primary amenorrhoea are also considered
separately because they form a rather complex group (Fig. 3).

ADULT PHENOTYPIC FEMALES

with

VIRILIZATION   SECONDARY   PRIMARY
                                AMENORRHOEA

K A R Y O T Y P E S

XY   X   XX   XX   XXX

PURE   GONADAL   POLY-X   SEE
GONADAL   DYSGENESIS   SYNDROME   FIG. 3
DYSGENESIS

with virilization   Ovarian hypoplasia;
                                               mechanical or other
                                               cause

17-oxosteroid
excretion

high   normal

cortisol challenge   INDUCED
                            VIRILIZATION

response
negative   positive

? ANDROGENIC   ADRENAL
TUMOUR   CORTICAL
                HYPERPLASIA

Fig. 2(b):   Diagrammatic Explanation of Differential Diagnosis
             of Intersex in Phenotypic Females

It should be borne in mind that there are exceptions, albeit rare ones,

to the 'ideal' schemes shown in the Figs. 1 to 3 for the differential

diagnosis of intersexual conditions.   Also, there are many further sub-

divisions in some syndromes: for instance, the group diagnosed in Fig.

2(a) as 'Primary Testicular Dysgenesis' was split into more than twenty

clinical entities by JONSEN (1962) in his classification of chromatin

negative male hypogonadism.

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PHENOTYPIC FEMALES WITH

PRIMARY AMENORRHOEA

KARYOTYPES

XY   XO*   XX

Mullerian structures

absent   present   biopsy

TESTICULAR FEMINIZATION SYNDROME

virilization

Gonadal dysgenesis

absent   occurs

stature

short   normal

PURE (XY) GONADAL DYSGENESIS

GYNAE-MORPHIC MALE INTERSEX

with somatic anomalies   without somatic anomalies

PURE GONADAL DYSGENESIS

TURNER'S SYNDROME

RÖSSLE'S SYNDROME

* A number of other karyotypes occur
  (see Chapter VII)

Fig. 3: Diagrammatic Explanation of Differential Diagnosis of Primary Amenorrhoea

CLASSIFICATION OF INTERSEXES

Having correctly diagnosed a patient's disorder it is usually necessary and desirable to store the details of his case. This may be done in notes; on tape recordings or punch cards, but whichever method is employed it is essential that the data be stored under a particular title or index so that it is easily retrievable. This entails a system of classification. The vast majority of diseases are known by a descriptive name: for example, tuberculosis; or, an eponym, such as Paget's disease or Turner's syndrome. Early medical men applied descriptive terms in Latin or its English equivalent to the conditions they encountered and every variation had its own name. An example of the cumbersome nomenclature is taken from the Klebs classification of intersexes (YOUNG, 1937):

'4.   Hermaphroditismus verus unilateralis completus masculinus dexter.

5. Hermaphroditismus verus unilateralis completus masculinus sinister'

Acute confusion arose during the latter years of the 19th Century when the medical journals publicised knowledge from different countries: it was at once apparent that workers in different parts of the world had encountered the same diseases but had applied different names to them. Then, early this century, as the acquisition of knowledge accelerated more and more synonyms arose as authors proposed 'more suitable' names. An excellent example of this is the list of 23 names given the syndrome of testicular feminization (BARTALOS and BARAMKI, 1967).

Fortunately for contemporary medical taxonomists the minutiae of detail used in the Klebs classification have gradually been modified and more practical grouping applied. YOUNG (1937) commented that the older ways were too cumbersome; ontemporary writers have in turn commented on the number of splinter groups named by Young (ASHLEY, 1962).

It has already been observed (p33) that before practical methods for determining genetic sex became available, the approach to, and classification of intersexuality was based on physical features; of anatomical and histological detail. During the decade 1930 to 1940 there was a movement towards restricting the number of categories into which intersexes were classified (as an example, YOUNG, 1937) and this trend has continued. In more recent times a further method of subdivision became available, in the form of nuclear sex, and the basic style of modern classification was established. Most authors at that stage recognized hermaphrodites, male and female intersexes; the last 2 groups were sex chromatin negative and positive, respectively (BISHOP, 1954). Classifications of that period were basically similar but differed in the number of sub-groups. However, the discovery that many females with Turner's syndrome had male nuclear sex, and that males with the Klinefelter syndrome had female nuclear sex, created not inconsiderable confusion. This, seen

in the light of the work done by Jost (JOST, 1958) meant that Turner females and Klinefelter males must represent complete sex reversal. Consequently a group of 'sex reversal' became incorporated into the later classifications (GRUMBACH et al, 1955; MORRIS, 1957). It is interesting that DANON and SACHS (1957) did not accept spermatogenesis in Klinefelter's syndrome as sufficient evidence that they were not females, as was shown by chromatin studies! A few other schemes were evolved in which embryological factors were used to explain intersexuality (WITSCHI et al, 1957). WILKINS (1957) was misled by Turner's and Klinefelter's syndromes to the extent that he related both to hermaphroditism.

The system outlined by WILKINS (1957) was modified by JONES and SCOTT (1958) and they also discarded the term 'pseudohermaphrodite' in favour of male or female hermaphroditism. It is interesting to note that as early as 1933 it had been recommended that 'hermaphrodite' be reserved for those individuals with both male and female gonads, irrespective of the genital or somatic appearance (CREEVY, 1933). More recently still pseudohermaphrodites have come to be called intersexes, male or female. This term, too, was proposed many years ago by Goldschmidt in 1912 (op cit. YOUNG, 1937), who theorized some 'force' which determined the phenotypic sex after the genetic sex had been established. The designation, intersex, is recommended because it is a lot easier to use than 'pseudohermaphrodite', and also is unlikely to be confused with hermaphrodite.

The most important development in the classification of intersexuality was the discovery of underlying chromosomal disorders, and it became necessary to equate these with the classification. Two major groups were recognized, abnormal sex determination and abnormal sex differentiation (MILLER, 1961), together with a sex reversal group for males with ovaries and 'females' with testes, with XX and XY gonosomes, respectively. LENNOX (1961) used a very

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similar scheme but separated intersexes with known endocrine aetiology from other groups which were hermaphrodites, intersexes and sex reversals. Both ASHLEY (1962) and OVERZIER (1963) gave great prominence to the nuclear sex status in their classifications.

It is felt that the use of nuclear sex as a qualification for classifying intersexes is superfluous because, judging from all present evidence, it is totally dependent upon genetic sex: there is only a single possible exception to this rule, the case described by CARLETTI and KEHYAYAN (1968) of a male with an abnormally long Y chromosome and an intranuclear particle that resembled the sex chromatin body. Furthermore, there is known to be variation in the patterns shown by mosaic individuals; for instance, the XX/XY hermaphrodites (OVERZIER, 1963) and in X/XX gonadal dysgenesis (GRACE, 1970): they may be either chromatin positive or negative.

In his chapter on pseudohermaphroditism OVERZIER (1963) claimed that the old concept of pseudohermaphroditism, in which clinically defined syndromes were included, had been abandoned in favour of the (? his) 'new' system by which only disorders of unexplained origin were treated as pseudohermaphroditic. All clinically distinct syndromes of known aetiology were to be classified separately. This is, in fact, the manner in which most authors do treat the classification, but the concept of intersex remains the same: a person who has the gonads of one sex and in whom contrasexual features are present. Unfortunately no international discussion has yet decided the nomenclature of clinical syndromes and it is left to popular usage to establish the names. This is very unfortunate because since the karyotypes commonly associated with some syndromes were discovered it has beome common practice in some circles to refer to, for instance, the 45,X as "Turner's syndrome" (MIGEON and WHITEHOUSE, 1967) but this is in fact not always so. No one syndrome has a specific karyotype, as RASHAD pointed out some years ago (1963) and he

made the suggestion that he existing terminology should be scrapped and replaced by new names. That suggestion was not without merit!

The following classification is based principally upon the genetic and gonadal attributes, with major categories for hermaphrodites, male and female intersexes (including hormonal disturbances) and psychological intersexes.

TABLE III

The Classification of Intersexes

Disorder	Somatic sex	Genetic sex	Gonadal sex
HERMAPHRODITES			
Hermaphrodites	M to F	XX, XX/XY, other	T+O
MALE INTERSEX			
Male intersex	M	XY	T
Partial testicular feminization	M+F	XY	T
Testicular feminiz'n	F	XY	T
Asymmetric gonadal differentiation	M+F	XY, X/XY	T+S
Pure gonadal dysgenesis	F	XY	S
Klinefelter syndrome	M	XXY, XXXY, other	T
Primary hypogonadism	M	XY	T
FEMALE INTERSEX			
Adrenogenital syndrome	F	XX	O
Induced virilization	F	XX	O
Idiopathic intersex	F	XX	O
Gonadal dysgenesis	F	X, X/XX, other	S
Poly-X syndrome	F	XXX, XXXX	O
PSYCHOSEXUAL INTERSEX			
Homosexuality	M	XY	T
Lesbianism	F	XX	O
Transvestitism	M or F	normal	T or O
FALSE INTERSEX			
Various developmental defects, etc.	M or F		

M male T testis S streak
F female O ovary T+O ovotestis

A brief explanation of the syndromes listed in the classification will be given here: for details the appropriate chapters should be consulted.

Hermaphroditism is defined as the coexistence of both testicular and ovarian gonads within the individual. The karyotypes vary; there is a very wide range of phenotypes; diagnosis can only be made conclusively after histological examination of the gonads.

Male intersexes have testicular gonads which may or may not be descended; the gonosomes are usually normal. The phenotype is more or less masculine and breasts never develop. Genital appearance also varies, as does the internal reproductive system: on the basis of these structures the group is sub-divided into andro- and gynae-morphic groups.

Partial testicular feminization is a transitional form between male intersexes and completely feminized males with testes. The habitus is usually masculine, with well-developed genitalia but this is offset by prominent breast development. The karyotype is that of a normal male.

Testicular feminization is a syndrome in which a genetic and gonadal male is completely feminized because of an intrinsic resistance to androgens. Breast development is excellent; the vestibular portion of the vagina is formed and is normally adequate for coitus. There are no Mullerian duct derivatives, which differentiates between this and pure (XY) gonadal dysgenesis.

Asymmetrical gonadal differentiation is, as the name implies, a failure of one testis to develop. The karyotype is commonly an X/XY mosaic and is associated with a variable degree of genital ambiguity: some are ascribed female sex, and others, male sex. Secondary sex development is generally equivocal.

Pure gonadal dysgenesis of genetic males is thought to result from a loss of male determinants and consequently streak gonads are formed. Since no testicular androgens can be produced, masculinization is not induced and the phenotype is identical to that of the female with gonadal dysgenesis.

Klinefelter's syndrome was originally described in eunuchoid, hypogonadal males. They were later shown to be chromatin positive and to have the XXY karyotype. Latterly it has become customary to include all chromatin positive males with this group.

Primary hypogonadism is a poorly described group which probably includes a number of separate disorders. Some are known as 'false Klinefelter' males because all are chromatin negative and have an apparently normal karyotype. Clinically they resemble Klinefelter males in many respects.

Adrenogenital syndrome is caused by a congenital enzyme deficiency which impairs the synthesis of cortisol; loss of inhibition on the pituitary leads to overproduction of adrenal corticotrophic hormone and the target organ becomes hyperplastic. Adrenal androgens lead to virilization of females, which deformity varies depending upon the stage at which male hormones reach a critical level and divert normal female development. The syndrome occurs in males but as it only causes genital precocity and not intersexual deformities, it is not considered here.

Induced virilization results from exposure of a female, foetus or person, to androgenic compunds. These may be hormones produced by the mother in the gestation, or they may be taken as drugs at some stage after birth. Unlike the adrenogenital syndrome, although the deformities are similar, induction of virilization ceases when the source of androgens is removed.

Idiopathic female intersexes are masculinized to some extent although no obvious cause for this can be found. Genetically and gonadally they are apparently normal and only the genitalia are affected.

Gonadal dysgenesis is thought to be due to monosomy of genes located on the short arm of the X chromosome; this causes germ cells in the foetal gonads to degenerate and in the postnatal indiviual the gonads are represented only by connective tissues. In consequence oestrogen-dependent organs and functions remain infantile through lack of stimulation. This defect occurs in a number of forms. The karyotype is frequently anomalous.

Poly-X syndromes involve the addition of one or more X chromosomes into the karyotype. As the number of Xs increases, so do the pathological manifestations. In XXX females there are no remarkable features, only early menopause.

By definition those subjects with contrasexual behavioural changes must be classified as intersexes although there is at present no evidence for an underlying genetic cause. These groups of psychosexual intersexes will not be dealt with in this thesis because their aetiology, investigation and treatment lie almost entirely within the realms of psychiatry, and not within the province of the normal clinician.

The group called false intersexes in the above classification are included because they illustrate an interesting point: what degree of abnormality is required to differentiate between intersexual and not-intersexual? A number of causes; developmental, mechanical, biochemical and others, may result in defects of the genital tract which resemble the deformities of intersexuality but in fact are not so.

Examples and discussion of many of the bizarre disorders listed above will be given in the chapters which follow.

REMARKS ON THE TREATMENT OF INTERSEXUALITY

A detailed account of the methods by which intersexual patients may be treated is not within the scope of this thesis. However, there are a few points which nevertherless must be made here.

At birth a baby should be clearly of one sex or the other. Depending upon the apparent sex at birth the infant will be registered as either male

or female and will be reared accordingly. By school-going age (in fact, by 3 years of age) the sociosexual orientation as male or female is firmly inculcated (WATSON and LOWREY, 1967) and is continually strengthened thereafter. From this it follows that any treatment which may involve reversal of the assigned sex must be undertaken before the child realizes its sex. Failing this, any treatment after the age of 3 years must be designed to reinforce the sex in which the child has thus far been raised. There are instances recorded in the literature where grave psychological consequences resulted from unwise surgery (WILKINS et al, 1955); sometimes ending in suicide (TETER and BOCZKOWSKI, 1965). A number of cases endured sex transformations, only to be changed back to the original sex again (YOUNG, 1937).

The need for an early, accurate, diagnosis and immediate treatment cannot be emphasized too strongly. Some typical examples of untreated and undiagnosed patients will be presented amongst the case reports in later chapters and the significance of these will be considered in the discussion at the end of this thesis.

SOURCES OF PATIENTS

The patients reported in this work came from a number of sources. The majority were seen at the King Edward and Addington Hospitals in Durban, and the Edendale Hospital, Pietermaritzburg. A few were seen at Greys and Fort Napier Hospitals in Pietermaritzburg, and St. Augustines Hospital, Durban. A smaller number of patients was referred for investigation by private practitioners in Durban and Pietermaritzburg. A few patients who had been seen during the past two years were recalled for inclusion in this series: this was felt to be justified because some illustrate certain features of their disorder rather well. No effect will be made on the estimates of prevalence because only patients seen during the year of study are considered in those calculations, and only babies born at the Addington, King Edward and Saint

Augustine Hospitals are used for the calculation of incidence. A crude

summary of the patients encountered in this series is given in Table IV.

TABLE IV

Summary of Cases in This Series by
Diagnosis, Race and Origin

| | n | *No. of patients | | | Race | | | |
		In	Old	Out	B	W	I	K
Hermaphrodite	1	1			1			
? hermaphrodite	3	3			2	1		
Male intersex	3	1	2				3	
Testicular feminiz'n	1			1	1			
Klinefelter syndrome	1		1			1		
Asymmetric gonadal dif'n	1			1	1			
Male Turner phenotype	1		1			1		
Adrenogenital syndrome	1	1			1			
Induced virilization	2	2			1	1		
Idiopathic female i/sex	1	1			1			
Gonadal dysgenesis	8	5	2	1	5	1	2	
Female Turner phenotype	2			2	2			
Hypospadias, male	6	6			4	1	1	
Vaginal defect	2	1	1		1		1	
Primary hypogonadism (males)	8	3		5	5	3		
Totals	41	24	7	10	25	9	7	0

* In   included in incidence and prevalence calculations
  Old patients not seen during year of study
  Out patients from out of Durban area.

Subjects for the study of sex chromatin frequency in samples of the normal

population were taken from volunteer staff and surgical in-patients at the

various hospitals: this is explained in Chapter V.

CHAPTER V

NUCLEAR SEX

Sex chromatin
Nuclear appendages
Methods of investigation
Inter-racial variation
Applications of the test

THE SEX CHROMATIN

Many animals exhibit sexual dimorphism in the form of an elliptical chromatin body which is present in the nuclei of somatic cells in females but not males. Similarly, some polymorphonuclear neutrophil leucocytes of the female have a small lobulated appendage on the nucleus; this is not normally seen in males.

Animal biologists first detected the heteromorphic nature of the sex chromatin (GEITLER, 1937) but it was several years before this method of sexing was used in human biology. SMITH (1945) made the suggestion that this technique could be applied as he had done with insect larvae, for determining the primary sex ratio of humans. Apparently, for several years no notice was taken of his idea and it was not until 1949 that BARR and BERTRAM discovered sex chromatin in the neurones of female cats. The technique was eventually applied to man (BARR et al, 1950) and other animal tissues (GRAHAM and BARR, 1952). After sex chromatin was revealed in human skin cells (MOORE et al, 1953) and other tissues (MOORE and BARR, 1954) many workers verified the method and it soon became routine in cytogenetic investigations (HUNTER et al; EMERY and MacMIL-LAN, 1954, amongst others). The chromatin body became known, unjustly, as the Barr body: this eponym is not justified because a number of others had found sex chromatin a long time before Barr. Very few others names for the chromatin body were used, one of the few being 'chromocentres' (JONES, 1967).

The chromatin body occurs as an ovoid mass about 1μ in length and about half

as wide; it is most commonly found lying inside the membrane of the inter-phase nucleus. It is indiscrete during mitosis. The body is visible under phase contrast microscopy and, with the light microscope, after being stained. Chromatin bodies are first visible in the female embryo at about 12 days (PARK, 1957) and occur throughout all tissues with approximately the same frequency (SOOST, 1962); others have claimed wide variation of frequency between different tissues (BARR, 1963). In the normal female the number of chromatin positive oral mucosal cells is said to increase from birth to day 7, after which it remains stable (CURTIS, 1969). HSU et al, (1967) noted such a change only during the first 3 days of life.

Originally it was thought that the chromatin body was contributed to by both X chromosomes of the normal female cell (GRAHAM and BARR, 1952) but this hypothesis was untenable after the demonstration of chromosomes became possible (TJIO and LEVAN, 1956) and a numerical relationship between the number of X chromosomes and chromatin bodies was seen (HARDEN, 1961b). Usually there is a chromatin body for every X chromosome in excess of one, although the autosomes appear to have an effect on this ratio when the cell is polyploid. To accomodate this, Harnden introduced the formula:

$$B = X - P/2$$

where B is the number of sex chromatin bodies; X the number of X chromosomes, and P the ploidy of the autosomes. The deduction was based on the observation of tetraploid cells (KLINGER and SCHWARTZACHER, 1960).

OHNO et al, (1959) proposed the single X nature of the chromatin in rats. This theory, that the chromatin body is formed by the condensation of only the inactive X chromosome, has come to be accepted in respect of all other animals. Recent studies of chromosome distribution in the mitotic nucleus (COMINGS, 1968) suggest that the chromosomes assume fixed positions and the inactive X is located peripherally; this has been confirmed by autoradio-

graphic techniques (COMINGS, 1967). The Russell-Lyon theory of X chromo-
some inactivation postulated that dosage compensation necessitated the in-
activation of genes on one of the X chromosomes of the normal female (LYON,
1961; 1962; 1963) and that such inactivation was randomly determined in each
embryonic cell so that about half retained the paternal, and half the mater-
nal, X chromosome in the active state. The descendant follows the pattern
set by the parent cell (COMINGS, 1966). However, a number of objections
to the theory were put forward (BARTALOS and BARAMKI, 1967) and it is also
known that in the event of one of the X chromosomes being abnormal, it is
inactivated (SPARKES and MOTULSKY, 1963; KLINGER et al; TAFT et al, 1965).
This was demonstrated by a number of methods which compared the size of the
X chromosome with the area of the sex chromatin in normal and anomalous cells:
the size of the chromatin body is proportionate to the size of the whole X
chromosome (MULDAL et al, 1963). In fact, experienced observers may pre-
dict the nature of the X chromosome by observation of the size of the sex
chromatin: small bodies were seen in cells from a woman with XXp- (JACOBS
et al, 1961) and large ones in cells with XXqi (FRACCARO et al, 1960; 1964).

That some normal female cells have a chromatin body whilst others do not is
an unexplained phenomenon: KLINGER et al, (1967) suggested that it might
be due to functional, physiological or developmental conditions within the
cell. In cells with no visible sex chromatin, it might be that genes from
both X chromosomes are operating: this, if correct, would explain some of
the objections to the Lyon theory. The Lyon theory has been used in an
attempt to explain the so-called phenotypic restriction theory of cellular
immunology, whereby individual lymphocyte parent cells have specific anti-
body-forming potentials. BURNET (1969) suggested that since one set of
genes on either X chromosome was inactivated it is not impossible that a
similar restriction affects autosomal pairs, so that only one allele at
each locus is expressed phenotypically.

NUCLEAR APPENDAGES

Sexual dimorphism of polymorphonuclear neutrophil leucocytes was first seen

by DAVIDSON and SMITH (1954). This dimorphism took the form of a small,

pedunculated nuclear appendage of about 1.5μ in length. These structures

became known as the 'drumsticks' because of the shape. Estimates of the

incidence of such drumsticks in normal females vary considerably and there

is also a variation of incidence at different stages of life (ASHLEY, 1962).

The accepted normal counts are more than 6 drumsticks per 500 neutrophils

in females, and less than that in males. There is a wide range of freq-

uency in intersexual conditions (MACLEAN, 1962).

In comparison to the rapid and easy method of assessing nuclear sex from

chromatin counts, the screening of a minimum of 500 neutrophils is a time

consuming procedure and for this reason is not done at . this laboratory.

Also, the absolute differences between male and female scores are very

small and the test thus has little practical application. For instance,

monozygotic twins with the 45,X karyotype were chromatin negative but had

female drumstick patterns (TURNER and ZANARTU, 1962). MITTWOCH (1964) and

DALLAPICCOLA (1969) reviewed the literature pertaining to drumsticks and

the reader is referred to their works for further details.

METHODS OF INVESTIGATION

Sex chromatin in human tissues can be examined quite easily in smears, thin

sections or cultured cells. The commonest method, which is used routinely

in this laboratory, is the buccal mucosal smear technique (MOORE and BARR,

1955). A wide variety of nuclear stains may be used for demonstrating sex

chromatin, with preparation times ranging from a few minutes to about 1 hour

depending upon the choice of method. Experience has shown that the method

described by GUARD (1959) gives greater definition than most and it is used

in a slightly modified form in the work reported here. The method is given

in detail here.

Scrapings taken from the buccal mucosa are spread lightly, in one movement, across a clean glass slide. The slide is immediately immersed in 95% ethanol to fix for at least 15 minutes; it may be left in fixative for an unlimited time.   The slide is then rinsed in 50% ethanol and transferred into Biebrich scarlet (formula given in appendix 2) for precisely 90 seconds and after passing through 2 rinses of 50% ethanol it is left in fast green stain (formula given in appendix 3) for one hour.   Guard advocated between 1 and 4 hours in fast green with hourly checks on the intensity of the stain: one hour is found to be adequate in this laboratory.   After staining in fast green the slide is rinsed in 50% ethanol and dehydrated by 90-second immersions in each of 75%, 85%, 95% and absolute ethanol, cleared in xylol and mounted in DePeX (B.D.H.) medium under a cover glass.

Cells were examined under oil immersion and the presence or absence of a sex chromatin body was noted. At all times only clear, well stained bodies lying against the nuclear membrane were counted, and only in those cells with evenly stained nuclear plasm. Cells which were rolled or overlapped, or in which the nuclear plasm was heavily granulated, were rejected. Preparations made by the above method showed cells with pale green cytoplasm and the nuclear chromatin stained dark red, although in combination with the green dye this often appeared to be black. This contrast was found to be more distinct than either the Feulgen or Giemsa staining methods. At least 50 suitable cells were examined; scores were doubled and expressed as a percentage. The normal ranges for males and female respectively were taken to be less than 2% and greater than 20% positive.

Estimates of sex chromatin frequency in normal females, especially babies,

vary considerably; in most cases this is probably due to inter-observer bias (CURTIS, 1969). After the first week of life the count remains constant, including during pregnancy (CURTIS, 1969), and there is no decrease with advancing years (LENNOX; DIXON and TORR, 1956), The studies of Curtis and also HSU et al, (1967) negated the earlier theories (TAYLOR, 1963; SMITH et al, 1962) that the sex chromatin was influenced by hormonal changes during the menstrual and gestational periods. Others have suggested that metabolic changes might have influenced the sex chromatin frequency (TAYLOR, 1963; PLATT and KAILIN, 1964).

As Curtis pointed out, most of the published articles concerning the sex chromatin did not give details of the degree of accuracy of the methods employed: she suggested that intra-observer and inter-observer bias together with differences of preparatory techniques were responsible for the diversity of results at different centres.

Although the sex chromatin test is employed at laboratories throughout South Africa there is still no available data on inter-racial variation; nor is there any indication that any laboratory has established its own range of normal values. These shortcomings, and personal experience of two cases in which impossible results were given, initiated the trial which is reported below. On the two occasions a buccal smear was sent to the hospital laboratory and both times the report was "essentially female". This was obviously incorrect since the two patients, who both had frank signs of gonadal dysgenesis, were both found to be chromatin negative by the author and this was supported by the demonstration of the 45,X karyotype in both.

DETERMINATION OF SEX CHROMATIN
FREQUENCY IN NORMAL WOMEN OF FOUR RACE GROUPS

This pilot study was prompted by the lack of information about possible inter-racial variation of sex chromatin frequency and also because there do not appear to be any established normal values for South Africans. Only one publication made mention of inter-racial variation, which was said to be nil, but the authors (DIXON and TORR, 1956) gave no indication of sample size or the origin of their subjects.

Methods

Buccal epithelial scrapes were taken from 10 males and 40 females of each of the four races. Subjects were chosen at random from clinically normal staff members and surgical in-patients at hospitals, the only selection being for age, which in all cases was between 18 and 35 years. Slides were coded and stained, examined and counted by the method described earlier. Fifty suitable cells were scored on each slide; the scores were doubled and recorded as percentage positive. Reproducibility of the method was tested by making 12 repeat counts of 3 slides taken at random. Finally, the slides were decoded and the results gathered into appropriate sets.

Results

The relevant figures for the four races are shown in Table V. Reproducibility of the method was good, as is shown in Table Vb. Only 11 of the initial 200 preparations had to be replaced because of faulty staining. This failure rate (5%) is low, and the majority of preparations were evenly stained and showed the chromatin clearly.

Of the 10 males from each race, there were only 2 with any score at all; a Bantu and an Indian who were scored as 2% and 4% positive, repectively. In these two subjects the bodies counted as chromatin were probably artefacts.

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TABLE V

Results of Estimation of Sex Chromatin
Frequency in Normal Females of four Races

	Whites	Indians	Bantu	Coloureds
n	40	40	40	40
range	18 - 72	6 - 92	12 - 70	14 - 64
mode	36	14	30	30;36
$\bar{x}$	37.45	30.30	38.05	37.00
σ	6.876	9.185	12.62	8.43

No significant differences

TABLE V(b)

Results of Trial to Determine Reproducibility
(Intra-observer error)

	mean	σ^2	σ
Slide A	33.0	11.00	3.3166
Slide B	12.8	4.43	2.1055
Slide C	20.8	8.81	2.9675

Discussion

This method of estimating the incidence of sex chromatin in buccal mucosal cells was technically satisfactory and reproducibility of the observations was good. There was no apparent inter-racial variation, although the Indian females had a wider range and lower mean score than any of the others. This discrepancy was probably due to the small sample size. In contrast to the very small range of scores given by CURTIS (1969) the spread in the present study was wider. The probable reason for this is that her sample consisted of only 25 normal females, the mean score being 40.8 $\pm$ 2.56%. A further possibility is inter-observer bias or technical variation.

A surprizingly high number of subjects were found to be less than 20% positive, which was previously taken to be the lower limit of normal. Of the 160 subjects, 27 (18.4%) had scores of less than 20%. Accordingly, the

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lower limit of normal for female chromatin scores has been adjusted to 10 percent positive.

APPLICATIONS OF THE SEX CHROMATIN TEST

The sex chromatin test offers a rapid and easy means of dividing the population into 'male' and 'female' groups according to the presence or absence of sex chromatin. This dimorphism is extremely useful in screening for sex chromosome anomalies in large population studies, and has been used thus in a number of surveys (FERGUSON-SMITH, 1958, 1959; BREG et al, 1963; MACLEAN et al, 1961,1962,1968; BAIKIE et al; CASEY et al, 1966; CLOSE et al, 1968). Unfortunately the test only indicates abnormal subjects by the fact that a morphological male might be chromatin positive, or a female might be negative; or there might be two or more chromatin bodies per cell. The actual karyotype has to be determined by analysis of chromosomes from cultured cells.

Caution must be excercised in interpreting the results of the chromatin counts in some cases. For instance, if the subject has gonosome mosaicism the chromatin pattern may be either positive or negative: in the syndromes which commonly have underlying mosaicism, the XY/XXY, X/XX and XX/XY patterns have each been recorded as chromatin negative on occasions. In the words of OVERZIER (1963) in respect of hermaphrodites, 'the results (of nuclear sexing) have been dissappointing'. Sampling errors may lead to these contentious observations; for example, JACOBS et al, (1961) reported a woman who was karyotyped as 45,X from peripheral lymphocyte chromosomes but whose sex chromatin frequency in oral mucosal cells was 27 percent. In such a case it is almost certain that cryptic mosaicism was present. Another interesting patient was recorded by CRAIG et al, (1963): a mosaic individual showed a lateral variation in sex chromatin frequency.

Possibly the most valuable application of nuclear sexing is in forensic medicine because this is one of the few parameters by which dead tissue can be sexed (DIXON and TORR, 1956b) and this can be done even on single hair root cells (SCHMID, 1967). Similarly, tissues from pre-gonadal embryos, or from macerated foetuses in which morphological sex is unrecognizable, can be sexed, thereby providing the only means of determining the primary sex ratio. Prenatal sex determination can be done on foetal cells recovered by amniocentesis (SACHS et al, 1956), which has very obvious importance in genetic counselling when sex-linked disorders may be present.

The ideal of of any medical discipline is prevention rather than cure, but in the event of prevention being impracticable, then early detection is preferable to delayed diagnosis. In this respect the sex chromatin test offers the only feasible methods presently available for mass screening of neonates to identify those with numerical gonosome anomalies when these do not cause intersex identifiable by physical deformity. Surveys of this sort have been conducted (PRADER et al, 1958; TAYLOR and MOORES, 1967; MIKAMO and DE WATTEVILLE, 1969) and the results of these and earlier surveys show that about 1:5000 males and 1:23000 females have numerically incorrect sex chromosome constitution. MARQUEZ-MONTER et al, (1968) screened older individuals at a school for the sub-normal and found 5 of 623 boys, and 1 of 377 girls, to have anomalous nuclear sex: this was confirmed by karyotyping.

CHAPTER VI

EMBRYOLOGY OF THE UROGENITAL SYSTEM

Sex determination
The indifferent stage
Specialization in female
Specialization in male
Specialization of gonads
Pathogenesis of Intersex

To appreciate the abnormalities seen in intersexual patients it is funda-
mental that the observer be familiar with the stages of development and
specialization in the normal urogenital tract.   There is not the space
here to indulge in a detailed discussion of the embryology, but a brief
outline of the major developmental milestones is given.

SEX   DETERMINATION

The evolution of separate sex determining mechanisms dates to the late
Jurassic period and almost certainly arose out of a hermaphroditic state.
That hermaphroditic state was, in all probability, the result of male and
female genes being scattered throughout the chromosome set.   Through muta-
tions with selective advantages favouring the localization of the sex genes
on specific chromosomes, determinants became aggregated so that the genes
of each sex were carried on separate chromosomes.   Congregation of the sex-
determining genes on separate chromosomes was followed by a period of con-
solidation during which cross-overs were suppressed in order to retain all
of the sex genes together on what were to become the gonosomes.   In such a
way much of the non-sex content of the special chromosomes was transferred
to the potential autosomes.   The amphibia are said to represent the stage
prior to the removal of non-sex genes to the autosomes because the sex chro-
mosomes are barely distinguishable (SWANSON, 1957).   A similar situation
exists in some Ophidia, where all types from those with indistinguishable,

isomorphic sex chromosomes to those with frankly heteromorphic gonosomes are found (BEÇAK and BEÇAK, 1969). Less is known of the Lacertilia but there is evidence that some species are homogametic and others heterogametic (GORMAN et al, 1967). However, in the higher vertebrate phyla, birds and mammals, the sex chromosomes are quite distinct. There is invariably one large and one smaller chromosome, known as the X and the Y, respectively. In man the male is heterogamous, with the XY combination.

During spermatogenesis the sex chromosomes form a single bivalent in which there is end-to-end synapsis between the long arms of the Y and the short arms of the X. This is suggestive of a short paired segment, a belief that several authors share (ASHLEY, 1962; FORD, 1963; FERGUSON-SMITH, 1965). The male determinants are localized on the Y chromosome (FORD, 1963; GALTON 1966) near the centromere or on the short arms (JACOBS, 1969). In view of this, testicular development in individuals with no detectable Y chromosome is provocative.

The human Y chromosome

The human Y chromosome appears to be only concerned with male-determining genes and none controlling other traits have been ascribed to this sex chromosome although the suggestion has been made (GATES et al, 1962) that it may carry a gene for 'hairy ears'. The chromosome itself is known to show some variation in length and both inter-racial and inter-individual differences have been described; intra-individual variation is slight (BENDER and GOOCH 1961; COHEN et al, 1966; UNNERUS et al, 1967). The action of Y-borne genes commences at about 7 weeks after fertilization (TANNER et al, 1959).

Gametes bearing X or Y chromosomes are produced in equal proportions by the male so that theoretically at fertilization there should be equal numbers of each sex. The secondary sex ratio, at birth, is approximately 106:100

males to females (STERN, 1960). Estimates of primary sex ratio based on
sex chromatin patterns were 160:100 (TRICOMI et al, 1960) and 122:100
(SZONTACH et al, 1961), which are substantially greater than the expected
1:1 ratio. These estimates are interesting in that they indicate that
male embryos must degenerate much more frequently than females.   A few
attempts have been made to distinguish between X- and Y-bearing sperm by
characteristics such as size and shape and by biochemical and biophysical
properties (ROTHSCHILD, 1960; SHETTLES, 1960; 1961) but at present there
is still no proof that this can be done (BISHOP, 1960).

Sex reversal

In some vertebrates extra-genetic factors may control sex determination and
the question arises as to whether similar environmental or physiological
changes can influence the post-genetic sex in man. Amphibia are particular-
ly sensitive to environmental changes; also, parabiotic grafting has shown
the potential for gonadal type to be reversed when the graft involves hetero-
sexual gonads (WITSCHI and OPITZ, 1963).

THE INDIFFERENT STAGE OF UROGENITAL DEVELOPMENT

For a short while after the zygote is formed there are no gonads and the sex
ducts of both sexes are common: this is the indifferent (pre-gonadal) stage
of development.

Urinary system and genital ducts

The nephric and urinary tracts appear slightly earlier than the gonadal
ridges. Bilateral nephric cords arise first (21 days; 3 mm) as folds in
the coelomic mesoderm. They grow craniocaudally; the pronephros arises
the anterior segments, followed by the meso- and meta-nephric structures
in subsequent segments. As each portion is formed the preceeding zone
atrophies. In man the pronephros is vestigial; the mesonephros persists

for only a short time but remnants form part of the vasa efferentia in the mature male, and part of the rete ovarii in the female. The metanephros becomes the functional kidney. A duct is produced on each side of the mid-line by folding of the mesoderm in the region of the pronephros; this is the Wolffian duct. These grow caudally parallel to the nephric cord and as the successive areas of the nephric structures atrophy, so do the adjacent parts of the Wolffian duct. Another pair, the mesonephric (Mullerian) ducts, are formed at the 10 mm (5 week) stage, adjacent the mesonephros and lateral to the older Wolffian ducts. They grow caudally by invagination of the coelo-mic epithelium into the underlying mesenchyme. When the growing points are level with the caudal poles of the mesonepehri, they turn and proceed medi-ally and caudally until the transverse section of each lateral duct meets at the midline, where they fuse.

Cloaca and urogenital sinus

The cloaca is present in the very early embryo (2.5 mm) as a space into which the hind gut and allantois open. It is closed by the cloacal membrane, which on the exterior is surrounded by elevated bilateral labioscrotal and anterior genital eminences. These raised structures surround a depression, the exter-nal cloaca. The cloaca is soon divided by the transverse urorectal septum, which arises from the mesoderm between the hind gut and allantois and grows out to fuse with the cloacal membrane. The resultant anterior chamber forms the urogenital sinus and the posterior space, the rectum. The rectum at this stage is still closed by the anal portion of the cloacal membrane. By 7 weeks this separation of the cloaca into 2 chambers is completed. Concurrent with this phase, the anterior abdominal wall elongates and the tail becomes pro-portionately shorter. As the distance between the umbilicus and genital em-minence increases, the cloaca assumes a ventral rather than anterior position.

The urogenital membrane breaks down during the 5th week, exposing the sinus to

the exterior. Once open, the urogenital sinus becomes continuous with the endodermal urethral plate which adjoins its anterior border. A urethra is ultimately formed by thickening of the plate, which becomes grooved and its edges roll over to fuse and form a canal.

The urogenital sinus is further subdivided by the penetration of the Wolffian ducts into its cranial segment, which includes the opening of the alantois. Ultimately the cranial portion forms the vesico-urethral canal whilst the caudad remainder forms the definitive urogenital canal.

Until the 12th week the external genitalia are epicene and only after this time is further differentiation directed by the now-functional gonads.

The gonads

Swellings appear on each side of the midline: these are the genital ridges. The covering coelomic epithelium degenerates to reveal cords of cells, the primary sex cords, growing down into the mesenchyme of the genital ridge. By 6 weeks (12 mm) the sexless genital ridge is a prominent feature of the embryo.

The origin of germ cells is still controversial: there are two schools of thought. One believes that they arise in situ, from within the genital ridge itself (WILLIS, 1962) whilst the other, and more widely accepted, holds that they migrate to the genital ridge from an origin in the wall of the yolk sac near the allantois. Amongst others, WITSCHI (1948) identified these cells and traced their movement. The germ cells were thought to have an inductive potential because in their absence the genital ridges failed to grow, as was thought to be the case in gonadal dysgenesis (HEMSWORTH and JACKSON, 1963). More recent evidence suggests that this is not so: germ cells are present in the foetal gonads of subjects destined to have gonadal dysgnesis, but

some unknown cause leads them to degenerate and usually by the time of birth all germinal elements have been obliterated (SINGH and CARR, 1966). Between 6 and 7 weeks (12 - 17 mm) the gonads have assumed the nature of one or other sex, as predetermined by the genotype.

SPECIALIZATION IN THE FEMALE

During the indifferent phase the Wolffian and Mullerian ducts differentiate similarly in both sexes. At about 10 weeks (40 mm) the indifferent stage in the female ends when, in the absence of androgenic support, the Wolffian duct regresses.

The lateral Mullerian ducts meet in the midline after growing transversely from the level of the posterior mesonephri and the plug of cells at the growth point of each fuses. Growth continues caudally until the solid cord of cells meets and creates an indentation — the Mullerian tubercle — in the wall of the urogenital sinus. This is completed by the 63 mm stage. Shortly after the transverse Mullerian ducts have joined at the midline (50 mm) the primitive myometrium is formed from the condensation of muscle tissue about the point of fusion; this is quite marked by the 16th week, when the uterine and vaginal areas of the duct are recognizable. Eventually the upper portions of the ducts become the fallopian tubes, their open cranial ends being the internal ostia.

The Mullerian tubercle fuses with the mesodermal wall of the urogenital sinus to form a solid 'vaginal plate'. As growth increases, so does the distance between the caudal end of the vaginal plate and the opening of the urogenital sinus. Ultimately the lower one-fifth of the vagina is formed from tissues of the urogenital sinus; the vestibular portion. During late foetal life the vaginal cord canalizes to form the lower (vaginal) and cranial (uterine) canals. The membrane at the sinovaginal junction , the remnants of

the vaginal plate, persists as the hymen.

No marked alteration of the appearance of the external genitalia occurs in
maturation of the female. The basic, unspecialized pattern is retained: the
labial swellings enlarge and surround the remainder of the pudenda, while
the urethral folds of the undifferentiated phase form the labia minora; they
close the entrance to the vestibule. During the second half of intra-uterine
life the vestible gradually becomes shallower until at birth it is little
more than a groove into which the rethra and vagina open. The genital tub-
ercle does not elongate but becomes inclined ventrally, where it is held by
two cords which are continuous with the labia minora. There is thus no homo-
logue of the male phallic urethra.

SPECIALIZATION IN THE MALE

Further specialization of the urogenital structures in the male depends upon
adequate and sustained supply of male-organising substances and other andro-
gens. When the foetal testes become functional as endocrine glands, at 20 mm
(8 weeks), a secretion causes resorption of the Mullerian ducts which by
this time have just begun to grow transversely. The Mullerian ducts have
dissappeared from the male by the 11 week stage.

Extensive changes to the genitalia occur during development of the male. The
genital tubercle elongates, drawing out the primitive urethral plate with it.
Simultaneously closure of the urogenital sinus by fusion of the labioscrotal
swellings commences at the anal margin and progresses forwards. As closure
extends forwards the penile urethra is formed by rolling of the urethral plate
and fusion of its edges. The penile urethra is formed thus up to the level
of the corona: the terminal portion is formed as an invagination of the glans
which becomes continuous with the urethra. The adult urethra therefore opens
at the tip of the glans. Concurrent with these developments, enlargement

of the labioscrotal folds, now fused in the midline, occurs to form the scrotal sac.

SPECIALIZATION OF THE GONADS

Although the genetic sex of the embryo is established at fertilization and the undifferentiated gonads of both sexes are similar, at the 6 week stage a number of very important changes occur. It is essential to the further development of the gonads that the germinal elements arrive in the genital ridges after their long migration from the yolk sac (accepting the theory of WITSCHI (1948) that they originate there).

The testis

The primary medullary sex cords in the genital ridges become separated from each other by interstitial tissue and by 7 weeks they are isolated from the germinal epithelium by the formation of a fibrous integument, the tunica albuginea. During the ensuing weeks the cords become more prominent, forming the seminiferous tubules into which the germ cells are incorporated. Excursions by some of the tubules into the adjacent mesonephric stroma lead to connections being established with the mesonephric ducts, giving access to the Wolffian duct. This system of tubules and Wolffian duct forms the efferent channel for testicular products. At 16 weeks (112 mm) the testis is ready for descent into the scrotum but this migration does not occur until late in foetal life, at about 7 months (240 mm).

The ovary

Changes in the ovary occur less rapidly than in the testis. In contrast to the male gonad it is the cortical area of the genital ridge which proliferates and the few cords which do invade the medulla are soon obliterated. At 8 weeks (20 mm) secondary, cortical sex cords arise from the germinal epithelium. These become fragmented and the cells arrange themselves about

the germ cells to form follicles. Because no tunic is formed about the ovary the germinal epithelium is able to continue supplying the sex cords until late in foetal life. Ovarian stroma invades the prenatal gonad from the mesenchyme near the hilus: when this invasion is completed the primordial follicles are invested with a capsule of stromal cells which then differentiate into thecal cells. Even though a rete ovarii is formed it does not establish connection with mesonephric elements in the way that the testicular tubules do, thus the ovary has no duct system for its products and in adult life ova are shed directly into the coelom.

Thus the individual's sex development is begun. At birth all of the structures should be present, to await final adaptation to functional status when puberty occurs (HAMILTON et al, 1962; AREY, 1965).

PATHOGENESIS OF INTERSEX

Many intersex syndromes are now known to have basic sex chromosome anomalies which, in contrast to most autosomal aberrations, are often compatible with life. A large proportion of spontaneous abortuses have anomalous gonosomes (CARR, 1965; 1966; SZULMAN, 1965) but it is not known why some should abort and others proceed to maturity. That a substantial number does survive the intra-uterine period gives rise to the present study: having survived until birth there is no reason why such individuals should not have normal life expectancy. Other forms of intersexuality are due to biochemical or, otherwise, undetermined causes.

Abnormalities of sex chromosome constitution may take the form of numerical, structural or genotypic changes. These are outlined in the following pages.

Aneuploidy

The commonest cause of aneuploidy is nondisjunction during anaphase (BARTALOS

and BARAMKI, 1967). Present understanding of the mechanisms which control the movement of chromatids during cell division is poor, but it is thought to be a failure of either the centromere or the spindle which causes non-disjunction. This may occur at either the first or the second division, or

TABLE   VI

Possible Gametes resulting from Primary
Nondisjunction at Meiosis I or II (from ASHLEY, 1962)

	Gonocyte	Primary Gametocyte	Secondary Gametocyte	Gametes
Normal Disjunction	XX	XX	X	X	X
			X	X	X
	XY	XY	X	X	X
			Y	Y	Y
Nondisjunction at Meiosis I	XX	XX	XX	XX	XX
			O	O	O
	XY	XY	XY	XY	XY
			O	O	O
Nondisjunction at Meiosis II	XX	XX	X	XX	O
			X	XX	O
	XY	XY	X	XX	O
			Y	YY	O

both. The possible gamete formed by nondisjunction of a normal gametocyte is shown in Table VI and the consequences of double nondisjunction are given in Table VII. Nondisjunction is said to be primary when the gametocyte is normal (Fig. 5) and secondary when the gametocyte itself is aneuploid (Fig. 6). Such nondisjunction may occur in either parent, as was first suspected by POLANI et al, (1954) following their studies of patients with gonadal dysgenesis. Corroboration of this was given by serological investigations using the sex-linked erythrocyte antigen, Xg, as a marker (MANN et al, 1962).
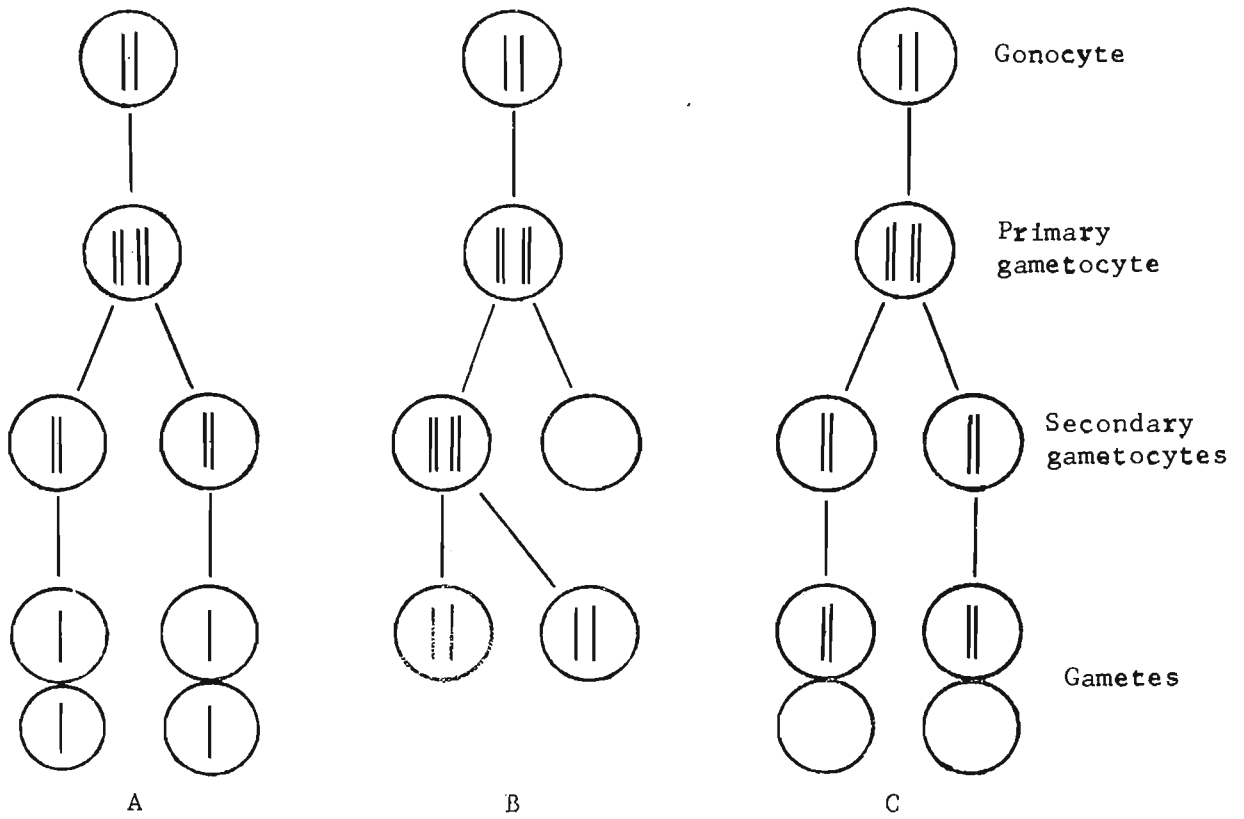
75

Fig. 5: Primary nondisjunction at (B) first meiotic division, and
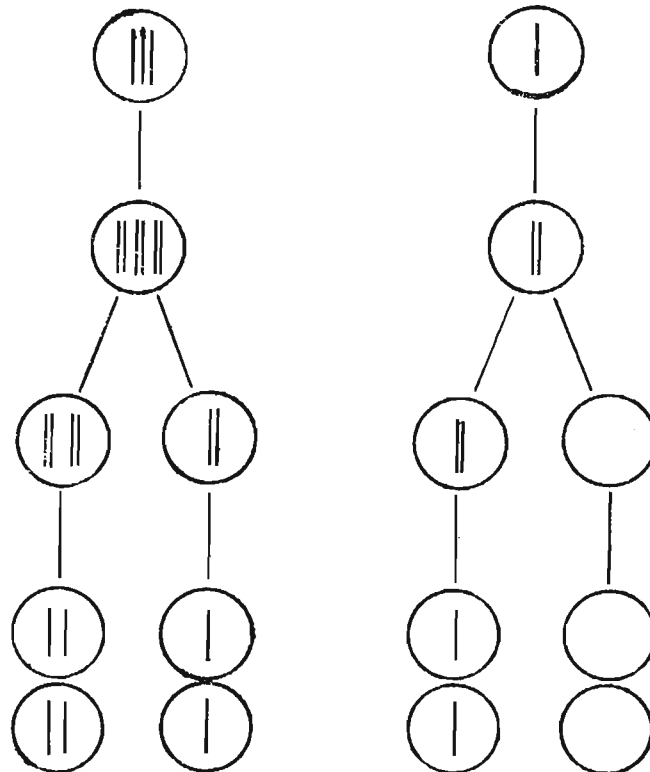(C) at the second division. Normal gametogenesis is shown in A.

Fig. 6: Secondary nondisjunction of trisomic and monosomic gonocytes

TABLE VII

Possible Gametes resulting from Double Nondisjunction

		Males				Females			
Gonocyte		XY				XX			
Gametocyte I		XY				XX			
Gametocyte II		XY		O		XX		O	
Gametes		XXY	Y	O	O	XXX	X	O	O
	or	XYY	X			XXXX	O		
	or	XXYY	O						

Families with 45,X or 47,XXY propositi were studied. Thus FRØLAND et al, (1963) reported a son who inherited an X and a Y from his father. RACE and SANGER (1968) also reported several such cases, together with some in which the mother contributed two X chromosomes to a son. DE LA CHAPELLE et al, (1964) and PFEIFFER et al, (1966) suggested from evidence of two family studies that an XXYY son was the product of a normal ovum fertilized by an XYY sperm. Another two families, whose propositi were XX males, that were investigated serologically led DE LA CHAPELLE et al, (1964b; 1965) to the conclusion that they were derived from XXY zygotes which had lost the Y during somatic cell division. Studies of similar males (FERGUSON-SMITH, 1966) gave rise to the theory that part of one X chromosome had been re-placed by translocated Y material. Such a theory of reciprocal transloc-ation between X and Y was advanced to explain the anomalous inheritance of Xg antigens in families with XX males (SANGER et al, 1964). In about 75 percent of subjects with monosomy-X, the single gonosome was of maternal origin (RACE and SANGER, 1968).

There is no obvious reason why a sperm bearing extra gonosomes should not be viable, since ova with as many as 4 additional X chromosomes are (LEWIS et al, 1964). Possibly there is a limit to the capacity for the smaller sperm nucleus to carry extra material, if this impaired its mobility. How-ever, this argument does not correspond with that of DAY (1965) for the

TABLE   VII

Possible Gametes resulting from Double Nondisjunction

		Males				Females			
Gonocyte		XY				XX			
Gametocyte I		XY				XX			
Gametocyte II		XY		O		XX		O	
Gametes		XXY	Y	O	O	XXX	X	O	O
	or	XYY	X			XXXX	O		
	or	XXYY	O						

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differential infertility of males with trisomy-21, because the bulk of even one additional X chromosome is far in excess of that of an extra G21. It is, possibly, the supernumerary G21 chromosome itself which is deleterious.

Maternal age is a significant factor in the aetiology of autosomal trisomies of E16, D13/15 and G21 (SMITH et al, 1963; SMITH, 1964; MATSUNAGA, 1967) but paternal age has no obvious effect. Several explanations for the maternal age effect have been offered, the most acceptable of which are concerned with post-maturity of the ovum. Generally, aneuploidy is the result of nondisjunction at the second meiotic anaphase and is possibly due to the reduction of cytoplasm in the older ovum (OHNO et al, 1962b) or simply over-ripeness at the time of the second division (WITSCHI and LAGUENS, 1963). These theories are reasonable, considering that the first division is completed before the individual is even born, and it may be 15 or more years until the second is accomplished just before ovulation (KENNEDY and DONAHUE, 1969).

Aneuploidy arising after fertilization can be due to delayed fertilization (JONGBLOED, 1968; 1969).

Mosaics and chimaeras

Mixed cell populations can arise in two ways: mosaicism, when a mitotic accident creates a normal and an aneuploid cell line; or, chimaerism, in which the cell lines are derived from different zygotes. Of these, mosaicism is the more common mechanism, and can be quite complex: as many as 6 cell lines have been found in coexistence. Chimaerism can be the result of a post-meiotic division in an ovum producing 2 nuclei, both of which are fertilized separately; or it may be the result of migration of cells between twins, or the incorporation of a zygote by its twin. These events have been seen on many occasions in cattle and other lower animals (see pp14-19) but less frequently in man. A few hermaphrodites with XX/XY cell lines have

proved to be the result of double fertilization (JOSSO et al, 1965). Post-meiotic division of the ovum is known to occur in man, albeit with very low frequency (KENNEDY and DONAHUE, 1969b). Binucleate ova are said to occur more frequently after gonadotrophic therapy (G.S. JONES, 1968). An unusual cause of chimaerism was reported by KADOWAKI et al, (1965): an infant with severe lymphopenia had XX/XY cells in the lymphoid series and all other tissues were XY; the gonads were testes. This mixture was attributed to the inclusion of maternal cells within the foetus.

Structural changes

Structural alterations of the X chromosome are not uncommon: deletions and isochromosomes of both arms are known and ring-X chromosomes have also been reported on a number of occasions. Recently the effects of various structural anomalies of the X cjromosome were reviewed (FERGUSON-SMITH, 1965) and a less extensive summary of sex chromosome abnormalities was made by JACOBS (1969). The Y chromosome is much less frequently alterred and even then, provided that it is entire, it does not seem to be pathogenic (JACOBS, 1969; GRACE and HARRIS, 1970). Deletions of the Y are pathogenic, the extent of the abnormalities being dependent on the amount of material lost. Masculinization is induced even when only a tiny centric fragment remains (VAHARU et al, 1961) but if the short arms are lost, as in Yqi, (JACOBS and ROSS, 1966) or Yp- (KÖBBERLING et al, 1965) then the phenotype is feminine and gonadal dysgenesis occurs.

Biochemical Disorders

Disturbances of, particularly, hormone metabolism may affect sex development at a number of stages of life. Primary defects such as hypopituitarism lead to hypogonadism, with obvious consequences. A few individuals are insensito androgens, which results in somatic femininity. Hypersecretion in the female of adrenal androgens can lead to extensive virilization because of

excessive production of androgens. A number of other intrinsic or acquired defects can lead to the induction of secondary contrasexual characteristics: for instance, liver disease can obstruct the removal of circulating oestrogens so that in the male gynaecomastia and other oestrogen-dependent contours are produced. In either sex focal teratogenesis can impair gonadal development or function and so cause hypogonadism.

Excessive parenteral administration of androgenic drugs may lead to virilization of a female and masculinization of her unborn female child. Similar deformities are created by androgens produced in certain types of tumours.

Unknown aetiology

There are a number of intersex syndromes in which there is no overt cause; the chromosomal and hormonal patterns are apparently normal and there is no suggestion of any aetiologically significant medical history. This is the case in, for example, idiopathic female intersexuality and certain of the male intersexes and hypogonadal syndromes. Theories have been advanced to explain these phenomena, invoking mechanisms such as 'anti-male' genes, reciprocal translocation of genes between the X and Y chromosomes, mutatant genes etc.. Further discussion of the merits of these hypotheses is given in the final discussion (Chapter XVII).

Examples of many of the causes of intersexuality are to be found amongst the patients whose cases are reported in the following pages.

GONADAL   DYSGENESIS,

TURNER'S   SYNDROME   AND   PHENOTYPES

Introduction
Classification
Pathology
Cytogenetics
Aetiology
Case Reports
Discussion

INTRODUCTION

Gonadal dysgenesis is a generic term for a number of related congenital dis-
orders of development in which the gonads are represented only by connective
tissues and lack germinal elements. Through common usage the term has, un-
less qualified, come to refer to the female; similar defects of the male
should be discussed separately. However, in this work certain of the male
defects will, for convenience, be considered here: the syndrome of pure gon-
adal dysgenesis and the male Turner phenotype, both of which are thought to
have similar aetiology.

The gonadal dysgeneses present a bewildering array of phenotypes, a fact that
has certainly contributed to the confusion of nomenclature and terminology.
In 1761 Morgagni described a disease which he termed congenital ovarian insuf-
ficiency (HAUSER, 1963) and since then many 'syndromes' have been described
which vary only in the slightest from each other. The result is a plethora
of names which all have a common meaning: they describe gonadal dysgenesis
in one form or another. Many of the synonyms were listed by HAUSER (1963).
Most contemporary authors use the term gonadal dysgenesis, which was first
proposed by GRUMBACH et al, (1955) to replace all of the other synonyms, but
a few do not concur; for instance, JONES (1968) refers to ovarian agenesis
or dysgenesis.

Since the discovery of abnormal karyotypes in association with gonadal dysgenesis the taxonomy of these disorders has been further complicated. This is especially true of the 45,X karyotype, which is very prevalent amongst subjects with Turner's syndrome. Incorrect usage has led to the point where persons with that karyotype are automatically referred to as having "Turner syndrome". There has also been an increasing tendency to use the eponym synonymously with the generic term; a most unfortunate and inaccurate practice.

CLASSIFICATION

Affected individuals may be of short or normal stature and they may or may not have any one or more somatic abnormalities. There are also subjects with normal gonads who have many of the stigmata of the gonadal dysgenetic syndromes. The clinical picture of these disorders consists of 3 distinct groups of signs: (a) gonadal dysgenesis, in which the gonadal remnant is devoid of germ cells; (b) stature, which may be short or tall, and lastly, there may be any number, or none, of the somatic abnormalities known as the 'Turner stigmata'. Also, it should be noted that the anomalies may be evident at birth or may appear during childhood, or only after the expected age of puberty, so that the astute examiner must consider the variations at each age. The major categories of gonadal dysgenesis may therefore be summarized as follows:

1. Normal stature, no abnormalities
2. Normal stature with abnormalities
3. Short stature, no abnormalities
4. Short stature with abnormalities

A note on 'short' stature: this is an arbitrary parameter but by common practice is taken to be a height of less than 150 cm. This limit is used in the present work.

The four groups listed above are summarized in the following sections.

1. Pure gonadal dysgenesis is a syndrome in which the gonads are dys-
genetic but stature is normal or tall and there are no extragenital defects.
Slight secondary sex development is often seen; there may be scant pubic or
axillary hair and some subjects show spontaneous breast development. However,
none of these features ever develops fully. The karyotype may be that of a
normal male or female; in respect of the former it is often termed 'XY gonad-
al dysgenesis' to distinguish it from the female version. Phenotypically both
are identical. The syndrome was recognized by SWYER (1955) in chromatin neg-
ative patients and became known as Swyer's syndrome (HAUSER, 1963) but was
later termed pure gonad dysgenesis (HARNDEN and STEWART, 1959). The syndr-
ome was recently reviewed (SOHVAL, 1965).

2. Normal stature with somatic abnormalities is an uncommon combination
in gonadal dysgenesis. Patients with this un-named syndrome have been recor-
ded (HAUSER, 1963; HURWITZ, 1966).

3. Rössle's syndrome is also relatively uncommon; it consists of short
stature and gonadal dysgenesis in females of otherwise normal appearance. A
group called ovarian agenesis appears to correspond with Rossle's syndrome.
POLANI (1969) mentioned that only the absence of webbed neck distinguished
between ovarian agenesis and Turner's syndrome.

4. Turner's syndrome is the most widely accepted name for describing a
syndrome characterized by gonadal dysgenesis, short stature and numerous extra-
genital abnormalities. The somatic abnormalities, known as Turner stigmata,
were tabulated by HADDAD and WILKINS (1959) and reviewed by LEMLI and SMITH,
(1963). They occur so frequently that it is now acceptable to extend Turner's
original definition (females of short stature with infantilism, webbed neck
and cubitus valgus) to include females of short stature with gonadal dysgen-
esis and somatic abnormalities (FERGUSON-SMITH, 1965). Those who do not have

one of the cardinal signs, e.g. pterygium colli or cubitus valgus, may be said to be 'variants' of the syndrome. The karyotype may be normal; a mosaic of 2 or more cell lines; it may involve a structurally altered X chromosome, or it may be entirely 45,X.

Syndromes which are frequently mentioned in connection, or confused, with the gonadal dysgeneses are as follows:

1. Bonnevie-Ullrich syndrome: this is a complex of abnormalities in neonates and infants of either sex. The commonest signs are low posterior hair line, cutis laxa of the neck and peripheral lymphangiectatic oedema of the extremities. In children cubitus valgus, short stature and mental retardation may become apparent. Gonadal dysgenesis is not implied by this syndrome, even though it is a frequent concomitant. The karyotype varies from normal male to normal female. Subjects with this syndrome may develop Turner's syndrome or, in both sexes, the Turner phenotype.

2. Infantile Turner phenotype is the name given recently (GORDON and O'NEILL, 1969) to infant females with the Bonnevie-Ullrich anomaly. The new designation was advocated because so many do have gonadal dysgenesis and the 45,X karyotype, which gives a strong, but not positive, indication that they will develop Turner's syndrome. The new name is recommended because it replaces an eponym which is frequently confused with the condition known as Ullrich's syndrome.

3. Female Turner phenotype describes females of short stature and other Turner stigmata but in whom gonadal development and function is normal. The name was proposed (JONES et al, 1966) in an attempt to clarify the use of the eponym, Turner's syndrome. A few authors, principally of the European

school, use the term Ullrich's syndrome for this disorder (POLANI, 1969).
The karyotype is usually that of the normal female but occasional mosaics
have been described.

4. __Male Turner phenotype__ describes males with Turner stigmata. The name
was given by JONES et al, (1966) in order to preserve the integrity of the
eponym Turner's syndrome, which for many years had been wrongly applied to
affected males. FLAVELL (1943) was apparently the originator of the term
'male Turner's syndrome' but fortunately this has with few exceptions, for
instance POLANI (1969), fallen into disuse since Jones and his colleagues
made their recommendations. Even more recently there has been a move to
incorporate this phenotype into a poorly defined homogenous group, Noonan's
syndrome (KAPLAN et al, 1968). Subjects are phenotypically male and have a
number of Turner stigmata. Testicular dysgenesis is common and anorchia
occurs in occasional cases (HELLER, 1965). As a consequence of testicular
defects secondary sex development is poor. The karyotype is usually that of
the normal male or a mosaic of X and XY cell lines.

The male intersex group known as asymmetrical gonadal differentiation is
mentioned here because of its aetiological similarity to female gonadal dys-
genesis. It is characterised by the presence of a testis and a contralater-
al streak gonad. Patients are frequently of feminine appearance and have epi-
cene genitalia. The commonest karyotype is the X/XY mosaic but a few have a
normal male genotype (ZOURLAS and JONES, 1965). The clinical features of the
syndrome will be given in Chapter XI.

PATHOLOGY OF GONADAL DYSGENESIS

Extragenital abnormalities of the type found in association with gonadal dys-
genesis and the male and female Turner phenotypes are very variable, both in
frequency and in severity, and can affect almost every organ.

Gonads and Genitalia

The cardinal feature of gonadal dysgenesis is that the mature gonads do not incorporate any follicles; they are represented as fibrous streaks of connective tissue which occupy the normal ovarian position. The stroma is reminiscent of that seen in the normal ovary but occasionally patches of hilus cells similar to testicular interstitial cells are found. Some authors, for example HOFFENBERG et al, (1957) and ASHLEY (1962), classified patients with a few follicles as having gonadal dysgenesis. By definition those patients must be regarded, as were similar patients (WILKINS, 1965), as having hypoplastic ovaries. However, foetal and neonatal ovaries of 45,X individuals often have follicles (CARR et al, 1966) but in the older foetuses there is a proportionate increase in the amount of connective tissue and reduction in the number of germinal elements (SINGH and CARR, 1968). The pathogenesis is further obscured by the fact that many individuals with apparent Turner's syndrome have some evidence of ovarian function in the form of menstrual activity. Generally such menstrual activity is short-lived and at best, episodic. An exceptional patient was reported by BAHNER et al, (1960) to have produced a normal child, and yet her karytotype was 45,X. In that case undetected mosaicism was surely present. From the evidence of Singh and Carr, and other patients with the 45X karyotype (which almost invariably implies gonadal dysgenesis (FERGUSON-SMITH, 1965)) the most likely explanation is that the germ cells do in fact complete their migration to the gonadal ridges but some unknown factor prevents their survival there. The rate at which they are obliterated varies between individuals so that some, perhaps the less severely affected ones, still have a few follicles which survive to the age of puberty. These then are responsible for inducing menstruation but once expended, early menopause occurs. BAHNER et al, (1960) described their patient as a fertile example of Turner's syndrome but in view of her menstrual history and fertility she should have been regarded as female Turner phenotype.

The gonads in the female Turner phenotype are essentially normal but there may be slight retardation in the manifestation of secondary sex characteristics. In a single patient (GRACE, 1970) the clitoris was small, there was no axillary hair and the buttocks were devoid of subcutaneous fat (see Case 8).

In the male Turner phenotype the testes may be absent or show varying degrees of dysgenesis (FERRIER and FERRIER, 1967). They may be scrotal or cryptorchid and are invariably sterile. Secondary sex is not well-developed, although in this respect there is wide variation between patients because androgenization is, naturally, dependent upon the testicular competence. Androgen levels in this syndrome are very variable (SCHOEN, 1965).

Asymmetrical gonadal differentiation in the male, as the name implies, is the result of a failure of one gonad to develop. The affected testis may be seen in the form of a streak gonad, or may be absent. The genitalia always show a degree of ambiguity. Details of this syndrome are presented in Chapter XI.

Secondary Sex Development

Hormone-dependent secondary sex development is very poor in all groups. In the dysgeneses there is an almost complete lack of oestrogen; what little is present is of adrenal origin. Thus menstruation does not occur; breast tissue is not produced and the typically feminine contours formed by the deposition of subcutaneous fat are lacking. A very sparse growth of pubic hair is present but axillary hair is usually absent. Infrequently, patients with clitoral enlargement are seen; they were thought by GRUMBACH et al, (1955) to represent a transitional stage between gonadal dysgenesis and proper male intersex.

Endocrine patterns

Originally TURNER (1938) believed that infantilism in his patients, whose ages ranged from 15 to 23 years, was due to hypopituitarism. That contention was negated by the demonstration of raised urinary excretion of FSH (VARNEY et al, 1942) and for a time such raised FSH excretion was taken to be diagnostic of gonadal dysgenesis (DEL CASTILLO et al, 1947). But, a number of women with proven gonadal dysgenesis had normal FSH excretion (HERTZ et al, 1950; SWYER, 1955; JACKSON and HOFFENBERG; BRIGGS & KUPPERMAN, 1956; HAYWARD and CAMERON, 1961), which therefore refuted the earlier belief. Argument presented by ALBRIGHT et al, (1942) suggested that gonadal dysgenesis could lead to changes in the pituitary, in that increased demand for gonadotrophins might be satisfied to the detriment of somatotrophins: this would then account for short stature. That theory however was contrary to the evidence of prepubertal gonadal ablation, which caused increased FSH excretion but not retardation of growth. It appears that increased production and excretion of FSH is the result of the gonadal defect: because FSH is not metabolized the feedback mechanism which would normally inhibit the pituitary is ablated.

Oestrogen deficiency in gonadal dysgenesis is a universal finding (ELLIOTT et al, 1959) which is reflected by the state of vaginal cornification. Patients with normal FSH excretion might be explained by the following theories (HAUSER, 1963): FSH production falls to normal after an initial (undetected ?) rise, as it does during the hypergonadotrophic phase of the climacteric; or, the hypophysis never did respond to the oestrogen deficiency in any event. That the excretion of FSH becomes normal after oestrogen therapy strongly suggests that abnormally high excretion is due to loss of the feed-back pituitary inhibition.

Pure gonadal dysgenesis is less likely to cause over-production of FSH and many subjects have normal, or even reduced, urinary excretion (HERTZ, 1950; SILVER and KEMPE, 1953; HOFFENBERG et al, 1957). Some patients also have secondary sex features compatible with oestrogen stimulation: for instance, slight breast development, feminine contours and vaginal cornification. In resepect of such patients great caution must be excercised to exclude those who have hypoplastic and not dysgenetic gonads.

Urinary excretion of 17-oxosteroids is slightly lower than normal, the reason for this being that all metabolites are of adrenal origin with no gonadal contribution (ZANDER and HENNING, 1963). It remains to be proved that signs of virilization, or oestrogenization, in occasional patients are caused by hormones of adrenal origin.

In most patients the adrenals, thyroid and thymus function normally and only isolated cases have been reported with concomitant disturbances of the other endocrine glands (HAUSER, 1963). However, GUINET et al, (1969) found a high incidence of thyroidopathies and auto-antithyroid antibodies in patients with gonadal dysgenesis

Skeletal changes

Widespread bone changes are often encountered, common signs being generalised osteoporosis, cubitus valgus, micrognathia with highly-arched palate, box-like rib cage and pectus excavatum. Bradymetacarpalism, particularly of the IVth elements, is a particularly significant sign (ARCHIBALD et al, 1959; ACHESON and ZAMPA, 1968), as is buttressing of the outer supracondylar ridge of the humeri (ASTLEY, 1963) and enlargement of the medial tibial condyle with beaked 'rat tooth' exostoses arising from the inferior aspect (KOSOWICZ, 1959; ASTLEY, 1963). Other skeletal anomalies include peculiarly shaped clavicles and epiphyseal dysplasia of the wrists. A number of less common deformities

such as bifid neural arches (FINBY and ARCHIBALD, 1963), missing bones and syndactyly (JACKSON and SOUGIN-MIBASHAN, 1953; KOSOWICZ, 1959) have been found. Diagnostic significance can, however, only be given the features of the hands, knees, elbows and feet, and the radiological appearance of osteoporosis (POTASNICK, 1969).

Rarefaction of the bones is very prevalent. This was considered to be generalized osteoporosis (WILKINS and FLEISCHMANN, 1944) which affected mainly the long bones (WILKINS, 1957; ACHESON and ZAMPA, 1968) or, as others maintained, the axial skeleton (HAUSER, 1963). The significance of oestrogen deficiency in the aetiology of such osteoporosis was discussed by LISSER et al, (1947) who suggested that it was possibly a form of osteogenesis imperfecta, a developmental defect which caused short stature. WILKINS and FLEISCHAMNN, 1944) claimed it was a consequence of a germinal or genetic defect: this was supported by ELLIOTT et al, (1959) but ACHESON and ZAMPA (1968) maintained that it was a sequel of oestrogen deficiency. POTASNICK (1969) concurred and mentioned the analogue of postmenopausal osteoporosis. PRUNTY et al, (1953) demonstrated improved calcium retention after oestrogen therapy in a 16 year old girl. Further proof may be adduced from the fact that after oestrogen therapy some patients show an increase in height (WILKINS, 1965). Others held that short stature was a genetically determined defect (VARNEY et al, 1942; ERSKINE and RANNIE, 1946) but there is little support for that opinion.

Skin lesions

Webbing of the neck, pterygium colli, occurs in some 60 percent of patients with the 45,X daryotype, and in approximately 20 percent of those with other karyotypes (FERGUSON-SMITH, 1965). A similar defect was found to be caused by migrating blebs of cerebrospinal fluid during foetal life in the progeny of irradiated mice (BONNEVIE, 1934) and confirmation of a comparable pheno-

menon in humans has been presented (HIENZ and GROPP, 1968) together with
discussion of the relevance of foetal cystic hygromata in the formation
of pterygium colli.   A number of 45,X foetuses were studied by SINGH and
CARR (1966), who considered cystic hygromata to be intra-uterine manifesta-
tions of webbed neck.   The apparent shortness of the neck in affected per-
sons is not due to any bone change such as those found in the Klippel-Feil
or Friessel syndromes;   the neck retains full mobility.   Pigmented naevi
sometimes occur scattered all over the body but unfortunately these have
no diagnostic value.

Cardiovascular system

Abnormalities of the heart and/or great vessels are the principal causes of
neonatal death in the gonadal dysgeneses.   The commonest are septal de-
fects, valvular stenosis, coarctation of the aorta and congestive left-side
heart failure.   WILKINS (1965) stated that some 25 percent of patients
develop idiopathic hypertension;   unfortunately he gave no indication of
the age of onset of symptoms.

Ophthalmic pathology

There is said to be an increased incidence of strabismus, myopia and lens
opacities (HAUSER, 1963).   The incidence of colour-blindness was investi-
gated several years before the demonstration of the abnormal karyotypes and
led to the prognostication (POLANI et al, 1954) that these women had only
one X chromosome.

Psychosexual attitudes

Mental retardation is uncommon and this is reflected in the low yield of
women with gonadal dysgenesis in population surveys of mental institutions.
The more important symptoms are those of depression, paranoia and, in
Turner's syndrome, reduced cognition and retention (MONEY and ALEXANDER,

1966). According to HAMPSON et al, (1956) the degree of intellectual deve-
lopment corresponds to the physical appearance rather than chronological
age. This tendency is also shown in their personal relationships: women
with short stature are reticent, and lose interest in their appearance be-
cause they do not attract males. A lack of initiative certainly stems
from the realization that they are unattractive and they are more distressed
by short stature than by a webbed neck; less by amneorrhoea, and least of
all by infertility (HAMPSON et al, 1956). Libido is generally absent.
There is no record that because heterosexual contact is unavailable they
turn to lesbianism.

Other organs less commonly involved in the pathology of gonadal dysgenesis
are the kidneys and gastro-intestinal tract (HAUSER, 1963; SINGH and CARR,
1966). There is said to be a high incidence of sex-linked recessive dis-
orders, such as pseudopseudohypoparathyroidism (SCHWARTZ and WALTER, 1962).

Appearance of signs

The appearance and progress of signs in gonadal dysgenesis is such that it
may be detected at birth or it may be suspected only during childhood; if
not, it will present as failure of secondary sex characteristics to appear
at the expected age of puberty.

Suspicion may be aroused if an infant has the Bonnevie-Ullrich anomaly or
the infantile Turner phenotype (GORDON and O'NEILL, 1969). However, an
absolute diagnosis cannot really be made until the subject is older because
of the possibility, albeit a small one, of typical features failing to ap-
pear. A few reports of the infantile signs have been made (JACOBS and
KEAY, 1959; FRØLAND et al; CONEN and GLASS, 1963; CARR et al, 1968).
Short stature is not obvious in babies and although gestation is usually
full term the birth weight tends to be low (WILKINS, 1965). GORDAN et al,

(1955) claimed that short stature was obvious at birth, but this is a minority opinion.

During childhood it may be noted that the subject is stunted; this appears at about 5 or 6 years of age. Stunting is due to an abrupt cessation of growth between 9 and 15 years (LISSER et al; DEL CASTILLO et al, 1947). At this stage some children may also appear to be mentally subnormal.

At the expected age of puberty a sparse growth of secondary hair appears, but this is limited to the pubes; the breasts never develop and the menarche does not occur. Subsequently the appearance changes little; the genitalia remain infantile and the habitus unattractive. In some patients obesity is a further problem.

Growth proceeds in those patients who are destined to be of normal stature and they may even become quite tall. These subjects have pure gonadal dysgenesis and although they may enjoy some slight, spontaneous breast enlargement, the nipples remain hypoplastic and the areolae poorly defined.

Minor variations occur, such as virilization in the form of clitoral enlargement or increased density of secondary hair (GORDON et al; GRUMBACH et al, 1955). Other patients may have any of a number of sex-linked disorders concomitant with gonadal dysgenesis, usually associated with monosomy-X. An extensive review of the clinical aspects was given by DE LA CHAPELLE (1962).

A report of the dermatoglyphic patterns in gonadal dysgenesis and those allied syndromes mentioned above is given in Chapter XVI.

CYTOGENETICS OF GONADAL DYSGENESIS AND
THE TURNER PHENOTYPES

A wide variety of karyotypes has been reported in gonadal dysgenesis: this probably explains the wide diversity shown in the outward appearance of patients. The earlier observation that nuclear sex was sometimes male and in others, female (POLANI et al, 1954; 1956; GRUMBACH et al, 1955; GREENBLATT et al, 1956), was explained when the 45,X and other karyotypes were found. Likewise, the syndrome of testicular feminization was explained by the XY karyotype revealed by JACOBS et al, (1959). The initial report of the XO karyotype (FORD et al, 1959) was soon confirmed and since then some 20 more karyotypes have come to light (BARTALOS and BARAMKI, 1967) and their bearing on the phenotype was discussed in a comprehensive review by FERGUSON-SMITH (1965). In a large measure, mosaicism is responsible for phenotypic variation; the X/XX mixture results in truncated stigmata (DE GROUCHY et al, 1961) and indecisive sex chromatin counts (LEMLI and SMITH, 1963).

The karyotype in pure gonadal dysgenesis is usually either that of a normal male or female; less commonly a mosaic of either and a 45,X cell line. In the female Turner phenotype the pattern is almost invariably that of the normal female (POLANI, 1969) and in the male Turner phenotype, either 46,XY or X/XY mosaicism (HELLER, 1965).

AETIOLOGY

The cause of gonadal dysgenesis and of the 'Turner stigmata' has not yet been established unequivocally. In an endeavour to explain the variable appearance of patients it was postulated in 1957 (HOFFENBERG and JACKSON) that 3 linked deleterious genes controlled short stature, gonadal dysgenesis and extragenital abnormalities. That theory was viewed with caution (HAUSER, 1963) or was rejected because no evidence had accrued to support it (ASHLEY, 1962). GRIBOFF and LAWRENCE (1960) proposed a similar 3-gene

theory to account for Turner's syndrome in patients with the 46,XX karyotype. This excellent idea was later given credence by evidence from the karyotypic data examined by FERGUSON-SMITH (1965), who concluded that it was monosomy of certain genes located on the short arm of the X, or on a small homologous portion of the Y chromosome, that was the responsible factor. This explains the number of different karyotypes which can all produce a similar phenotype; for instance, 45,X; 46,XXqi and 46XXp- all are monosomic for the short arm genes. Mosaicism of normal and monosomic cell lines can, to a large extent, explain the dilution of signs as well as inter-patient variation. The theory put forward by Ferguson-Smith can be used to explain the appearance of Turner stigmata in males, and it is also probable that the series of disorders within this group can be explained in terms of the number of loci lost. Thus, although the female Turner phenotype has apparently normal gonosomes, a small, submicroscopic deletion may exist (NORA and SINHA, 1969). This in turn recalls the idea put forward by HOFFENBERG and JACKSON (1957) by which 3 genes controlling infantilism (I), short stature (S) and somatic abnormalities (A) could be inherited singly or in combination. The possible permutations of the 3 genes are as follows:

ISA   gonadal dysgenesis + short stature + abnormalities (Tuner syndrome)

IS   gonadal dysgenesis + short stature (Rössle's syndrome)

IA   gonadal dysgenesis + abnormalities (un-named syndrome)

SA   short stature + abnormalities (Turner phenotype)

I   gonadal dysgenesis alone (Pure gonadal dysgenesis)

S   short stature alone

A   somatic abnormalities alone

It is remarkable that most of these theoretical combinations have been seen clinically. Possibly the S and A defects, manifested as short stature or somatic abnormalities alone, do occur but have not been recognized as part of this series. However, modern evidence indicates a loss of genes

rather than the presence of deleterious genes as the cause (FERGUSON-SMITH et al, 1964) although the three-unit theory may be correct. Applied to the male, the ISA combination might represent the Turner phenotype with anorchia and the SA defect the more common phenotype in which the testes are present but with variable degrees of dysgenesis. Examples of both types were reported by HELLER (1965), who also described the condition in an American negro (Case 2; E.C): to date no Bantu has been reported with the male Turner phenotype. The familial occurrence of the Turner phenotype in sisters and in 2 brothers and 2 sisters (MIGEON and WHITEHOUSE, 1967) led them to implicate an autosomal recessive mechanism as the cause. This was abnegated by NORA and SINHA (1969) following their study of 3 families: they showed it to be compatible with an X-linked recessive gene, but could not distinguish between that and a submicroscopic deletion such as was proposed by FERGUSON-SMITH (1965). Several reports of gonadal dysgenesis affecting chromatin negative sisters have appeared (DAVISON and SMITH, 1956; IZAKOVIC, 1960) and sisters (HAUSER, 1963). Monozygous 45,X twins were reported, and 14 other such twin pairs reviewed, by SHINE and CORNEY (1966).

The cause of gonadal dysgenesis was thought to be failure of the germ cells to reach the gonadal ridges after migrating from the yolk sac; or, a defect which precluded their further development in the genital ridges (WILKINS & FLEISCHMANN, 1944a,b) but that this was not due to the same genetic control which governed other sex development. The presence of the germ cells in the genital ridge is essential to the further specialization of the gonads (JOST, 1958) and failure of the germ cells to complete migration results in gonadal differentiation being arrested at the unspecialized stage. The older hypotheses have been discredited by the demonstration in the gonads of foetuses and neonates with the 45,X karyotype of primordial follicles and ova (CARR et al, 1968). OHNO et al, (1960) postulated that 2 active X chromosomes are necessary for normal ovarian function in the embryo as

no sex chromatin is visible in mammalian oogonia. In the event of 1 being abnormal, the germ cell aborts (FERGUSON-SMITH, 1965). If this hypothesis is extended to poly-X females, many of whom are fertile and produce normal children (BARTALOS and BARAMKI, 1967), then further explanation is required as to why they, but not monosomic females, should be fertile. In answer to this Ferguson-Smith hypothesized non-disjunctional events during the proliferation of germ cells, thereby permitting their return to normality. There does not seem to be evidence for or against this in the literature.

<div align="center">CASE   REPORTS</div>

Case 1   (Infantile Turner phenotype)

A Bantu baby, G.Z., was transferred to hospital from a peripheral maternity clinic for investigation of 'deformities of the spine, hands and feet'. She was the product of a full-term, uncomplicated pregnancy of a 23 year old primagravida. There was no relevant family or medical history.

The baby weighed 2777 G at birth. She had cutis laxa of the neck, a low posterior hairline, flattened occipital contour and abnormally folded pinnae.The chest was broad and flat with widely spaced, hypoplastic nipples. The dorsal aspects of both hands and feet were markedly oedematous (Fig. 7). There were no obvious skeletal or genital anomalies. Heart sounds were normal and the chest was clear.

Investigations confirmed the diagnosis of infantile Turner phenotype. Analysis of peripheral blood lymphocyte chromosomes revealed only the 45,X karyotype. Buccal mucosal cells were chromatin negative. The baby was allowed to leave hospital after its mother had been advised of the situation.

When aged 10 months the infant was readmitted to hospital with acute bronchopneumonia, to which she succumbed 48 hours later. The marked webbing of the neck which was present at birth, and the peripheral oedema had regressed. A post mortem examination of the internal genitalia was done: this showed a small uterus with thin fallopian tubes and streak gonads (Fig. 8). There was extreme hyperplasia of the left ventricular wall. No obvious cause for this, apart from mild hydronephrosis of the right kidney, could be found. Hydronephrosis was also of unexplained origin. There was no coarction of the aorta or other great vessels. Histological examination of the gonads showed only poor ovarian stroma without follicles (Fig. 9). Dermatoglyphic patterns are shown in Table XIII. There were no radiological signs of abnormality.

Case 2   (Turner's syndrome)

A 20 year old Indian, B.R., was investigated because of primary amenorrhoea. She claimed to have had recurrent abdominal pain 'monthly' since the age of

13 years. However, the patient was of very low intelligence and the veracity of her history is open to doubt.

She was short of stature; 152 cm tall, and tended towards obesity (Fig. 10). Her weight was 41.7 Kg. Armspan was 156.2 cm and ground to pubis height, 73 cm. Her facial appearance was dull, with slack jaw, protruding teeth and noticeable facial asymmetry. She had a left convergent strabismus of 10°; there was bilateral proptosis. There was no ocular hypertelorism. The palate was very highly arched and narrow; several of the upper teeth were maloccluded. Inside the lower lip was a small neoplasm. Mild webbing of the neck was seen. The chest was wide and flat with poorly developed breasts; both nipples were hypoplastic, with poor areolar definition. Cubitus valgus was present bilaterally. The fingers were all of normal length but tapered and showed terminal clubbing; digits V were camptodactylous. The labia were flat and the clitoris small. Secondary hair was limited to a sparse growth over the mons veneris.

Bimanual examination of the internal genitalia was unrewarding; only a very small cervix could be felt. Radiographs of the spine showed early osteoporotic changes; the knees showed overgrowth of the tibial condyles, with rat tooth exostoses. Urinary excretion of FSH was 48 mu per day; of 17-oxosteroids and oxogenic steroids, 5.2 mg and 4.5 mg per day, respectively.

Cytogenetic tests revealed the 45,X karyotype in peripheral blood lymphocytes. Buccal mucosal nuclei were sex chromatin negative. Interesting feature of this case was that the hospital laboratory found the chromatin pattern to be 'essentially female' (cf. remarks on p61).

Case 3   (Turner's syndrome)

G.N., a 36 year old Bantu staff nurse, had never menstruated until she was given oestrogen therapy at the age of 28 years.

Investigation showed a short, obese female: she was 137 cm tall and weighed 68 Kg. Armspan was 130.5 cm. The occiput was flattened with a low scalp margin on the nape, and the neck was webbed. Her chest was wide and box-like, with sternal excavation. The breasts were widely spaced, poorly developed, with hypoplastic nipples (Fig. 11). Both arms were relatively long and there was bilateral increase in the carrying angles. The hands were essentially normal but the fingers were very long (Fig. 72b). The left IVth toe was very short. The external genitalia were infantile. Bimanual palpation detected a small cervix but the uterus and its adnexae could not be felt. The heart and lungs were normal. The patient was intelligent but had never experienced any heterosexual desires.

All karyotypes prepared from cultured lymphocyte chromosomes were 45,X (fig. 12). Radiological studies showed classic signs of gonadal dysgenesis: there was extensive osteoporosis of the cervical spine, buttressing of the supracondylar ridges of both humeri, and overgrowth of the medial tibial condyles with rat-tooth exostoses. Dermatoglyphic profiles are reported in Table XIII and Fig. 72b.

Case 4   (Turner's syndrome)

M.M. was a 22 year old Bantu who presented at hospital complaining of primary

amenorrhoea. She was 154 cm tall, with eunuchoid proportions: armspan was 167 cm and the gound to pubis distance, 82 cm. Her weight was 51.25 Kg. The disproportionate appearance was exacerbated by hemiatrophy of the left side.

Her occipital hair line was low. The neck was webbed. The left shoulder was about 3 cm lower than the right shoulder (Fig. 13). Micrognathia was associated with a highly arched palate. There was no breast tissue; the nipples were small, hypoplastic and widely separated. Both arms were seen to be long, with increased carrying angles. The hands were essentially normal. Her pelvic contour was adolescent. Both feet had wide spaces between digits I and II and the remaining toes were extremely hypoplastic (fig. 14). The external genitalia were infantile: the clitoris was small and the vagina could admit only one finger. Secondary sex development was restricted to a sparse growth of hair on the pudenda. The patient had no libido and was not attracted to men. Her mental state appeared to be normal.

Bimanual examination of the internal genitalia was not possible because of the narrow vagina and so laparotomy was done. A small uterus with long, thin fallopian tubes was seen. The gonads were represented by pale, slender streaks of tissue; biopsies of the gonads were taken.

Histological examination of gonadal tissues revealed scanty ovarian stroma and absence of follicles. There were a few small clusters of cells that were reminiscent of hilus cells. Some vascular hyalinization was evident (Fig. 15).

Urinary excretion of FSH and 17-oxosteroids was low, being 6 mu and 4.6 mg per day, respectively. Mild reduction of bone density was seen in radiographs of the spine. No other abnormalities of the skeleton were noted.

The diagnosis was confirmed by the demonstration of sex chromosome mosaicism, there being equal proportions of 45,X and 46,XX cell lines in peripheral blood lymphocytes. The buccal chromatin count was 27 percent positive. Dermatoglyphic details are given in Table XIII and Fig. 72c.

Case 5   (Pure gonadal dysgenesis)

An elderly Bantu woman, approximately 60 years of age, was admitted to hospital for treatment of acute bronchopneumonia, malnutrition and cor pulmonale. Questioning revealed that she had never menstruated; had never had any heterosexual desires and had lived a secluded life. The patient was 167 cm tall and claimed always to have been of slender build. Her armspan was 168 cm. Pectus excavatum was seen in the wide, flat chest. Breast development and other secondary sex features were absent: there were no other stigmata of gonadal dysgenesis. She had severe kyphosis which, on radiographic evidence, was due to osteoporosis of the vertebrae. It could not be established if this was caused by the osteoporosis of gonadal dysgenesis or senile degerative changes.

Cytogenetic investigation showed X/XX mosaicism (Fig. 16) in the lymphocyte karyotypes. The oral mucosal sex chromatin count was 33 percent. In deference to the patient's advanced years and deteriorating health no further investigations were undertaken. The patient died in renal failure and a post mortem inspection of the internal genitalia was made.

The uterus was small; the fallopian tubes were long and thin and the gonads

were represented only by pale streaks. There were no anomalies of the heart and aorta. Histological examination of the gonads showed only connective tissues; there was no evidence that any germinal elements had ever been present.

Case 6   (Turner's syndrome)

A 27 year old white female was investigated because of gross pterygium colli and primary amenorrhoea. She was referred for examination by a psychiatrist to whom she had complained of her unattractive appearance.

Examination showed an obese female, 154 cm tall and weighing 78.5 Kg. Her scalp margin was low both on the forehead and neck. The ears were low-set. Her chin was small; there was retrognathia and highly-arched, narrow palate. She had a wide, flat chest with marked cleidosternal excavation (Fig. 17). Bilateral lipomastia was present; both nipples were small and there was no areolar pigment. The pubic escutcheon was masculine and an excursion reached the navel. The labia were flat, the clitoris small and the vagina was narrow and dry. Both carrying angles were increased. The hands and feet were normal. Because of steatopygia it was not possible to assess the pelvic contour.

The patient was an intelligent woman who held a responsible secretarial post. She was mildly paranoic about her physical appearance; her chief complaint was the webbing of her neck. An interesting point was the fact that she attributed the 'shape of her neck to an accident when, as a baby, she was dropped on her head'. She had never attracted males although she herself claimed not to be disinterested in the opposite sex.

Analysis of cultured lymphocyte chromosomes demonstrated 45,X/46,XX mosaicism in equal proportions. The sex chromatin count was 18 percent in buccal mucosal cells. Dermatoglyphic findings are reported in Table XIII and Fig.72d.

Case 7   (Pure gonadal dysgenesis)

V.N. was a 25 year old Bantu school teacher who presented at hospital because of primary amenorrhoea.

She was 165 cm tall and slightly obese (Fig. 18) her weight being 63.95 Kg. Armspan was 177 cm. She had no remarkable physical signs. The breasts were slightly developed but with very small nipples. There was a sparse growth of pubic and axillary hair. The clitoris was small.

Bimanual palpation did not detect any internal genitalia. Peritoneoscopic examination demonstrated a very small uterus, 2 cm long by uterine sounding, and thin fallopian tubes. Both gonads appeared to be whitish streaks. Unfortunately no biopsies were taken during thie operation. The dysgenetic state of the gonads was also reflected in the high rate of FSH excretion; a 24 hour urine specimen had the equivalent of 48 -96 mu. Urinary excretion of 17-oxosteroids was 10.5 mg daily.
The karyotype was apparently normal (Fig. 19) and the sex chromatin count was 34 percent. The dermatoglyphic profiles were interesting (Table XIII; Fig. 72e).

The patient said she was attracted towards men but had not had intercourse.

Case 8   (Female Turner phenotype)

A young Bantu aged 24 years was admitted to the maternity ward at 40 weeks
gestation to await delivery of her first infant. On admission she was seen
to be of odd appearance and genetic studies were done subsequent to her con-
finement.

The patient was only 145 cm tall; the ground to pubis height was 77 cm and
armspan 149 cm. A week after the delivery of her baby her weight was 60 Kg
The occipital contour was flat and the posterior hairline was very low (Fig.
20). Clinically, spinal kyphosis was seen but this was not confirmed on
radiographs. The neck appeared to be short and was webbed. Micrognathia
and hemiatrophy of the face gave the patient a peculiar expression: she had
the typica; 'fish mouth'. Both clavicles were abnormally shaped and the rib
cage was wide and had sternal excavation. The breasts were ponderous with
the nipples situated medially (Fig. 21): lactation occurred normally. The
humeri were short and the carrying angle of the right arm was increased. The
pelvis was android. Except for hypoplasia of the right IVth toe there were
no abnormalities of the legs or feet. Secondary sex development was not at
all good, apart from mammary development: the clitoris was small; there
was no axillary hair and the pubic escutcheon, which followed feminine lim-
its, was very sparse and there was no subcutaneous fat over the buttocks or
thighs. The patient was of very low intelligence and was uneducated. She
was not married but claimed to know who was the father of her child.

Karyotype analysis revealed no chromosomal abnormality. The sex chromatin
frequency of 37 percent was normal. The manual dermatoglyphic patterns were
quite remarkable in that the total ridge count was only 12; details appear
in Table XIII and Fig. 72f. Radiographs showed only mild osteoporotic bone
changes and there were no other typical Turner stigmata. Oestrogenization
of the vaginal epithelium was normal. During caesarean section it was noted
that both ovaries were macroscopically normal; no biopsies were taken.

Case 9   (? Female Turner phenotype)

Baby S. was the product of a full term normal pregnancy of a young primipara
(Case 8, above). The baby was delivered by caesarean section because of
cephalo-pelvic disproportion.

At birth the baby's general condition was satisfactory. She weighed 1920 G;
crown to rump length was 23.0 cm and armspan, 34 cm. The head and chest
circumferences were 28.6 cm and 25.0 cm, respectively. The forehead receded
and the occiput was flat. The sagital sutures were widely open. The hairline
was low on the nape. The ears were low-set with oddly folded pinnae. The
palate was arched and narrow; there was no retrognathia. She had a broad,
flat chest with mild sternal depression. No other skeletal abnormalities
were noted. Both palms had aberrant flexion creases. A dimple was located
over the sacral spine. The baby is shown in Fig. 22.

On the 14th day signs suggestive of intestinal obstruction appeared and on
day 18 laparotomy was performed. Complete rotation of the gut was found;
the caecum and vermiform appendix appeared in the left epigastrium. Explor-
ation detected no obstruction of the bowel. The post-operative course was
unsatisfactory and the baby died 4 days later.

Prior to death it was established that the baby had a normal female karyo-

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type and there was sex chromatin in 17 percent of buccal mucosal cells.

A post mortem dissection was done.   The corpse weighed 1727 G and was of aneamic appearance. The surgical wound had healed well. All of the cranial organs were apparently normal, as were the heart and lungs. The stomach was normal but the gut was rotated. A small pedunculated polyp, 4 mm in diameter, was found in the duodenum but it was not thought to have caused an obstruction. The large bowel was coiled irregularly and a 6 cm loop of the sigmoid colon was found in the left iliac area: this, if occluded by pressure of the gut contents, could have caused signs suggestive of intestinal obstruction.   The rectum and anus were normal. Macroscopically the liver, spleen, pancrease and adrenal glands were normal, as were the urogenital organs.

Microscopic examination of post mortem tissues showed signs of liver damage as hepatic cells had fatty infiltration and the nuclei were displaced to the cell walls.   Kupfer cells were very prominent and there were some in-flammatory changes,   Biliary caniculi and ducts contained bile thrombi. Both ovaries were histologically normal and contained many primordial foll-icles (Fig. 23).   The pathologists' consensus was that   liver damage had been caused by anaesthesia administered to the mother for the caesarean section, and exacerbated by further anaesthesia administered when the baby itself was submitted for surgery. The origin of the signs, anorexia and vom-iting, that suggested intestinal obstruction was not determined and there remains the possibility that they were manifestations of a biochemical dist-urbance; a sequel to liver damage.

Case 10   (Male Turner phenotype)

A white male aged 7 years was noted to be of odd appearance; at birth 'Turner syndrome' had been considered as a possibility. At birth he was said to have had severe cutis laxa but peripheral oedema and other signs of the infantile Turner phenotype were not mentioned.   Birth weight was 3798 G.

At 3 months of age idiopathic hypercalcaemia was diagnosed; this has since been controlled well by dietary restrictions and developmental milestones were attained in reasonable time.

On examination the child at 7 years was 102 cm tall and weighed 18.7 kg. His posterior hairline was low; the occipital contour was flattened and the ears were small and low-set (Fig. 24). The palate was highly arched and narrow and there was retrognathia. The eyes were prominent; he had alternating conver-gent strbismus. Ocular hypertelorism was seen, and there were mongoloid epi-canthic folds. Mild webbing of the neck was noted. Both clavicles were oddly shaped and there was severe pectus excavatum of the wide, box-like chest. The humeri were short and the carrying angles were increased (Fig. 25). The hands were grossly normal.   Bilateral pes valgus was due to retroversion of both femoral heads. He had bilateral flat feet. The penis was small, about 3.5 cm in length; both testes were scrotal and measured approximately 1 cm long. Tendon reflexes were present but reduced, and there was mild hypotonia.   The heart was essentially normal; the pulmonary arteries were 'large' but blood pressure was normal.   His full-scale IQ was 75; reading age was 6 years and mental age, 7 to 8 years.

Karyotype analysis revealed only the normal male chromosome complement (Fig. 26) and there was no sex chromatin in a buccal mucosal smear. The dermato-glyphic patterns are discussed on p210.

PLATE   I

Case 1

Fig. 7: The patient, with infantile Turner
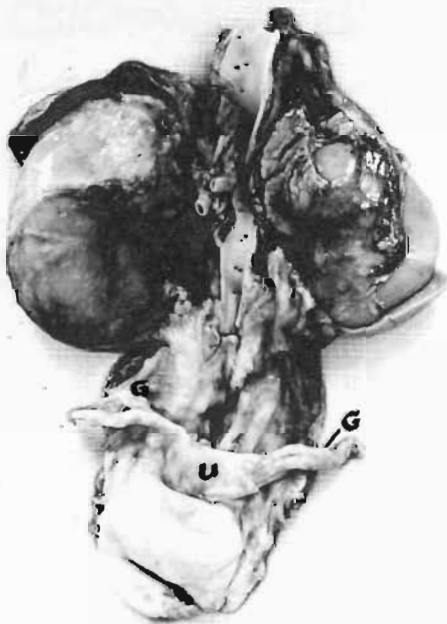phenotype.

Fig. 8: Internal genitalia; note
streak gonads (G), small
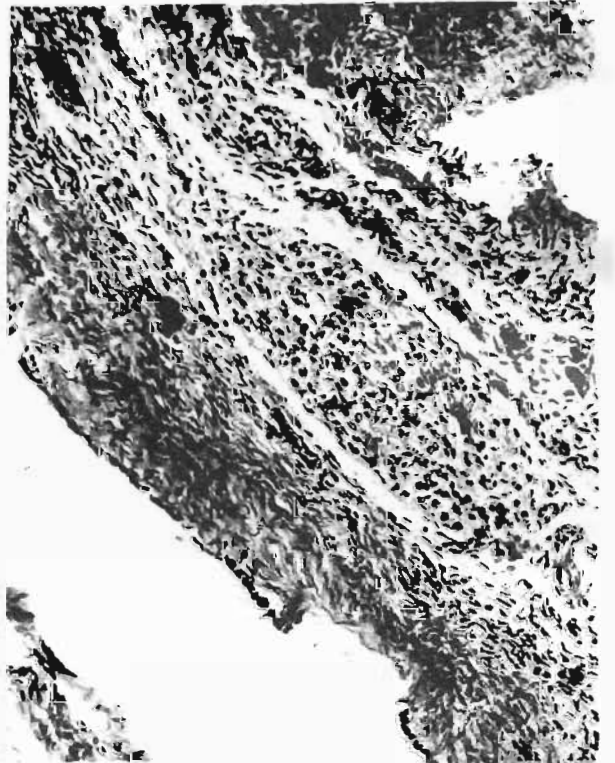uterus (U) and hydronephr-
otic right kidney.

Fig. 9: Section of streak gonad;
note wavy cortical stroma
and absence of follicles.

PLATE II

Fig. 10: Case 2, frontal view.

Fig. 11: Case 3, showing
typical Turner stigmata.

Fig. 12: Case 3, karyotype (45,X).

PLATE III

Case 4

Fig. 13: Typical Turner facies with
many somatic abnormalities.

Fig. 14: Patient's feet; note the
simian space between toes
I and II; also severely
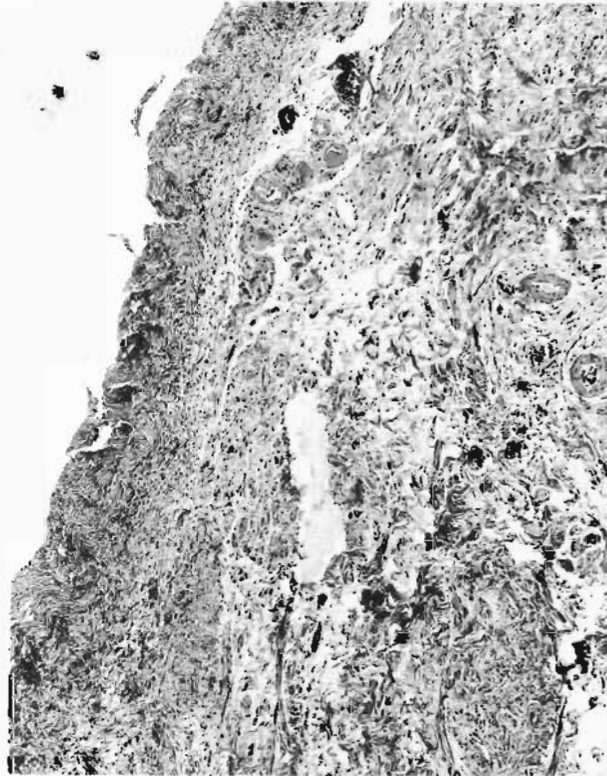hypoplastic IVth digits.

Fig. 15: Section of streak gonad with
wavy cortical stroma; also
note vascular hyalinization.
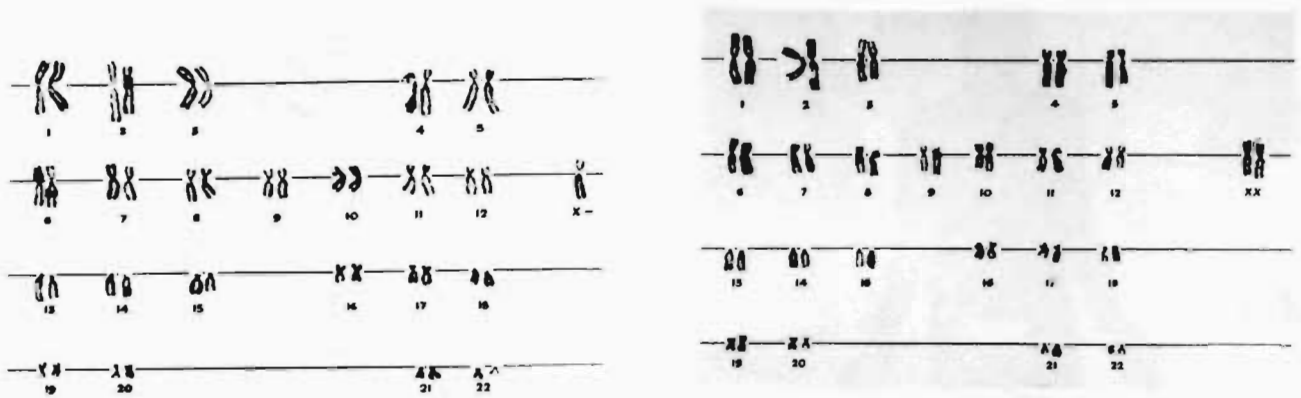
PLATE IV

Fig. 16: Case 5, mosaic karyotype of (a) 45,X and (b) 46,XX cell lines

Fig. 17: Case 6. Note lipomastia and steatopygia

Fig. 18: Case 7, pure gonadal dysgenesis
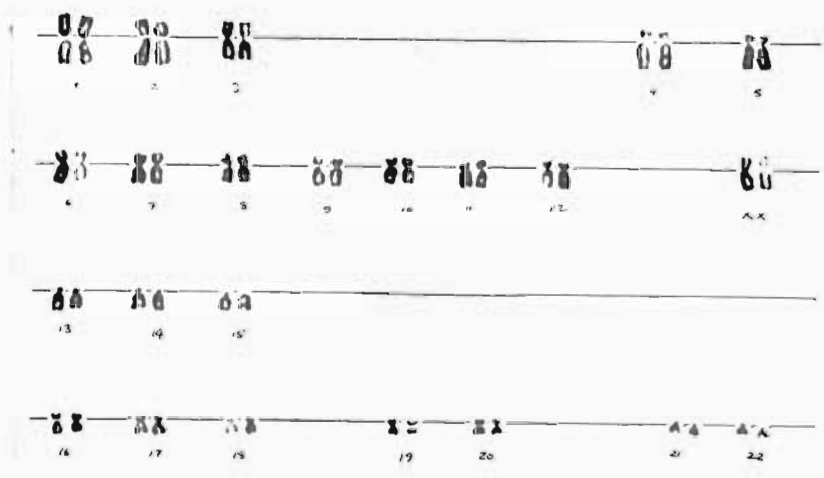

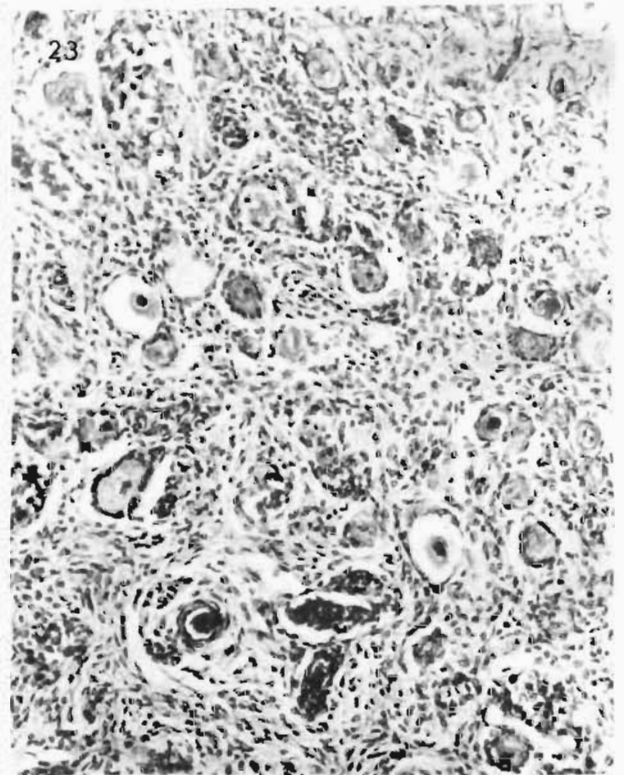Fig. 19: Case 7, apparently normal female karyotype.

PLATE V

Fig. 20: Case 8, note retrognathia, occipital contour, low hairline.

Fig. 21: Case 8, showing numerous abnormalities.

Fig. 22: Case 9, postmortem photograph showing spinal dimple. Note mild cutis laxa of the nape. Head was shaved prior to operation.

Fig. 23: Case 9, normal neonatal ovary with numerous follicles.

'Gonadal dysgenesis' is a collective term for a number of related disorders in which the mature gonad is devoid of germ cells. The term is, by common usage, restricted to disorders of the female. There is a wide range of phenotypes in which gonadal dysgenesis occurs and there are also a number of allied syndromes which share many of the features but do not have defective gonads; some of these allied conditions may also affect the male. They are included in this discussion because they form part of a series but the clinical features are listed in Chapter XI (male intersexes).

Classifications which were used before the advent of present cytogenetic methods regarded 'Turner's syndrome' as sex reversal (LENNOX; MILLER, 1961), which is easy to understand because the investigators were confronted with females who had 'male' nuclear sex. It is now known that nuclear sex does not give an absolute indication of genetic sex, and since the discovery of the 45,X karyotype this phenomenon has been explained. There is now, among some workers, the practice of regarding all with the 45,X karyotype as the Turner syndrome and using the generic and specific eponym synonymously: both are incorrect practices.

In the classification presented earlier (p 82) there are two major features which are used in the subdivision of patients; normal or short stature and the presence or absence of somatic abnormalities. The first group is pure gonadal dysgenesis and this typically shows normal stature with no somatic dysplasias. The un-named group with normal stature, gonadal dysgenesis and a few isolated somatic stigmata have been included with this group because the alternative of isolating them in a new group, which would then require a name, is contrary to the practice employed here of simplifying the taxonomy of intersexual diseases. Thus the type of patient mentioned by HURWITZ (1966) and reported by HAUSER (1963) should be included here, as is

Case 5 of the present series. In deference to those workers who wish still

to distinguish between these tall patients, those with a few Turner stigmata

could be referred to as variants of pure gonadal dysgenesis.

A similar argument may be used in respect of the patients whose principle

characteristics are short stature and gonadal dysgenesis. Those without any

extra-genital anomalies have been variously known as Rössle's syndrome (HAU-

SER, 1963); or, if they lack webbing of the neck, ovarian dysgenesis (POLANI

1969) to distinguish them from those with the other stigmata which go to make

up Turner's syndrome. Neither of the terms is particularly good: the former

because it is an obscure eponym which has not been encountered in any publi-

cation other than Hauser's, and the latter because it is easily confused

with several other synonyms for Turner's syndrome and gonadal dysgenesis in

general. A more acceptable suggestion was made by FERGUSON-SMITH (1965): it

is reasonable to describe persons with many, but not all, of the features of

Turner's syndrome as variants of that syndrome. This system has been adopt-

ed by the author. For many years the eponym, Turner's syndrome, has been

abused: a particularly poor application of the eponym was made by BAHNER et

al, (1960) in describing a woman with Turner's syndrome and 45,X karyotype

who had produced a normal male infant. Obviously she did not have gonadal

dysgenesis and thus could not be an example of that syndrome: she should

have been described as having the female Turner phenotype.

Not all authors are in agreement about the use of the eponym, Turner's syn-

drome. For example, HAUSER (1963) contested the validity of gonadal dysgen-

esis being an integral feature of the syndrome because Turner did not make a

direct inspection of his patients' gonads. That was a sublime argument: the

description given by TURNER (1938) of poor sex development, somatic infanti-

lism, lack of oestrogen dependent secondary sexual features, and his failure

to palpate gonads in any of the 7 women was very convincing. Hauser claimed

that the syndrome should rightly bear Ullrich's name because he had described it earlier (ULLRICH, 1930). The correctness of this is open to question as Ullrich did not mention sexual infantilism, probably because it was not evident in his 8 year old patient (NORA and SINHA, 1969). Whatever the historical precedence to this syndrome's name is, the fact remains that "Turner's syndrome" is widely known in the English speaking world (ULLRICH, 1949) and to change it now would create further chaos. It must, however, be borne in mind that many of the European authors refer to the Ullrich syndrome and that there are some English language authors who have delegated the same title to the female Turner phenotype (POLANI, 1969 for instance).

In support of Ferguson-Smith's proposal that women with short stature and gonadal dysgenesis should be described as variants of the Turner syndrome even although they lack one or other of the cardinal signs (webbing of the neck and cubitus valgus), it can be pointed out that pterygium colli is not always a permanent feature. In many cases it regresses within the first year of life (as in Case 1) and the mature subject may show only vestigeal signs, or none at all. The cause of this regression appears to be the transient nature of the cerebro-spinal fluid blebs in the subcutaneous layers; some are resorbed and others become sclerosed to cause persistent pterygia (HIENZ and GROPP, 1968).

The position of the female with fewer or more stigmata of Turner's syndrome but who has a history of some scanty, irregular menstruation is problematic. Reports of such patients have been made from time to time: LINDSTEN and TILLINGER (1962) described a 22 year old female with many features of Turner's syndrome but who had had oligomenorrhoea for 8 years, beginning when she was aged 12. She was found to have very few Graaffian follicles. The question is: can a female with the Turner phenotype transform to Turner's syndrome when she ceases to menstruate? It is felt that such reclassification would be valid.

The interesting phenomenon of one syndrome giving way to another is shown by the Bonnevie-Ullrich anomaly, which in time may transform to the Turner phenotype in males (HELLER, 1965) or females (NORA and SINHA, 1969) or it may become the complete Turner syndrome. A diagnosis cannot be made with absolute certainty in patients with the Bonnevie-Ullirich anomaly because of the uncertainty regarding the final appearance of the mature subject. In infants the probable diagnosis becomes more certain as other stigmata can be detected: for instance, the dermatoglyphic patterns may give an indication of the actual condition, as was the case with Baby G.Z. (Case 1) in this series. But, although the 45,X karyotype is usually associated with gonadal dysgenesis a few rare exceptions make dogmatic prognostication dangerous.

Extrapolation from karyotypic data to make a diagnosis is frequently inaccurate, as is shown by MELIN and SAMUELSON (1969). They described a patient as having gonadal dysgenesis because she had X/XXq- mosaicism: this was in spite of her menstrual history! FERGUSON-SMITH (1965) showed that about 8 percent of the 45,X group and 20 percent of the X/XX group had some history of menstruation. This brings the discussion back to the classification of subjects who have had menstrual activity (see above). One of the more startling cases was a woman with X/XX mosaicism who produced a baby girl 'with signs of Down's syndrome'; the baby was not karyotyped (PREDESCU et al, 1969). The significance of the mongoloid appearance of the infant was not commented upon, which is strange because the authors noted that the mother had bilateral epicanthes.

It has been shown that the diagnosis cannot be made from karyotypic data alone, just as the karyotype cannot be predicted from clinical signs.

During the past decade there have been several theories to explain the origin
of gonadal dysgenesis. A similar theory to that offered by HOFFENBERG and
JACKSON (1957) was advanced by GRIBOFF and LAWRENCE (1960), by which females
with chromatin positive gonadal dysgenesis had a deletion of the 'genes for
gonadal development' which were closely associated on the X chromosome with
those for stature and somatic balance. Their theory was contested (STEWART
1960) because the finding of chromatin negative and positive individuals was
indicative of a recessive gene mechanism. Yet another theory held that if
X inactivation occurred randomly, as was proposed by the Lyon theory, then
XXqi and XO cells would be left without the genes of the short arm if the
only normal X was inactivated. This should cause cell death and the authors
suggested that the number of cells which were so obliterated would account
for the variable somatic abnormalities.

There is little doubt now that gonadal dysgenesis, Turner stigmata and short
stature are caused by monosomy of genes located on the X, or the homologous
portion of the Y, chromosome (FERGUSON-SMITH et al, 1964). This evidence
provides some substantiation for the 3 gene theory of HOFFENBERG and JACKSON
(1957) because the syndrome displayed would depend upon the number of genes
lost (NORA and SINHA, 1969). To explain the fact that different karyotypes
with effective monosomy of the short arm of the X (as in XO; XXp- and XXqi)
do not produce constant phenotypes, FERGUSON-SMITH (1965) made the following
suggestions. The abnormal X is always condensed to form the sex chromatin,
but this does not occur until about the 16th day after fertilization; prior
to that time the genes from both Xs might be effective. Alternatively, it
might be that in spite of condensation, some genes remain active. There is
substantial evidence for the latter possibility (KLINGER et al, 1965; 1967).

Surprizingly, Turner did not seem to consider gonadal dysgenesis as a factor
in the pathogenesis of the syndrome which he described although it had been

shown some years earlier that ovarian dysgenesis occurred in this type of female (RÖSSLE and WALLART, 1930). Turner suggested hypopituitary hypogonadism as the cause but this was abnegated by the demonstartion of raised FSH excretion by affected females (VARNEY et al, 1942). At that time it was claimed that the appearance of patients was so convincing that the diagnosis could be made without even assaying FSH excretion (LISSER et al, 1947). In time, however, it became evident that the level of FSH excretion could not be regarded as diagnostic because some patients had normal, or even reduced, levels in the urine (shown for example by JACKSON and HOFFENBERG, 1956). Consequently, no great emphasis was placed on the use of this test during the investigation of the patients reported in this series.

Misuse was soon made of the eponym, Turner's syndrome. It was applied to a male with certain Turner stigmata and the term "male Turner's syndrome" was coined (FLAVELL, 1943). Some authors persist in using the term (e.g. POLANI 1969) despite the attempt by JONES et al, (1966) to clarify and standardise the use of the eponym. This, they suggested, should retain its original meaning and that the designation 'Turner phenotype' should be applied both to males and females with sufficient Turner stigmata as to raise the possibility of Turner's syndrome as a diagnosis. This policy has been adopted here and it dispenses with the terms Ullrich syndrome, Bonnevie-Ullrich syndrome, etc. There are many examples of poor and inaccurate usage of the nomenclature: for instance, BLOISE et al, (1960) wrote of 'gonadal dysgenesis (Turner's syndrome) with male phenotype' in an 8 year old boy with very epicene genitalia but few Turner stigmata. Bloise and associates were soon criticised by their contemporaries (MARTIN, 1960 amongst others) for such blatant misuse of the eponym.

More recently another school (KAPLAN et al, 1968) recommended the inclusion of both male and female Turner phenotypes in a homogeneous new group, named

for one of their colleagues, Noonan's syndrome. This move was advocated in
an attempt to clarify the terminology of the male Turner phenotype but it
seems more likely that this poorly defined 'new' syndrome will also confuse
the female classification. Another remarkable feature of this new syndrome
is that in its female form it is a 'genocopy of Turner's syndrome' (OPITZ
et al, 1965).

In conclusion it may be said that the series of disorders, from the male
Turner phenotype on the one hand, through the gonadal dysgeneses to the fe-
male Turner phenotype at the other extreme, present a complete, graded ser-
ies which demonstrates very well the variability of phenotype with different
karyotypes. It also illustrates the impracticability of trying to categor-
ize syndromes according to the karyotypes, and the complexity of naming each
minor variation of a syndrome. The classification suggested above enjoys
the advantages of restricting the number of groups to a minimum and it also
removes from use several eponyms; the names employed here are unlikely to
cause mutual confusion.

This series
The patients reported here demonstrated most of the salient features of the
gonadal dysgeneses and related male and female Turner phenotypes.

Case 1 showed the classical Bonnevie-Ullrich anomaly, which in females is
termed the infantile Turner phenotype. This patient also showed how variable
the appearance is with age: at 10 months the severe cutis laxa of the nape
had become almost unnoticeable. In such a patient the appearance of Turner's
syndrome would have been almost inevitable, as evidence the typical dermato-
glyphicpatterns. Cases 2, 3, 4 and 6 showed Turner's syndrome; all were of
short stature and had gonadal dysgenesis together with various somatic defects.
In Case 2 neck webbing was not very prominent; this feature was seen more

clearly in Cases 3 and 4, and most spectacularly in Case 6. This shows the degree of variability possible amongst subjects with similar karyotypes: in Cases 2 and 3 it was 45,X whilst Cases 4 and 6 were X/XX mosaics.

Pure gonadal dysgenesis, both with (Case 5) and without (Case 7) Turner stigmata, was demonstrated. Case 7 was regarded as having gonadal dysgenesis although the gonads were not biopsied. It may be argued that she had ovarian hypoplasia and not absolute dysgenesis because she showed slight evidence of osetrogenization: this cannot be contested. Nevertheless, in this series she serves as an example of the tall, sexually infantile female with apparently normal chromosome morphology. These patients again emphasize the karyotype-phenotype relationship: Case 5 was tall and had X/XX mosaicism but she differed markedly from Cases 4 and 6, with similar mosaicism; she was only slightly more affected than Case 7 who had seemingly normal chromosomes.

Case 8 was an excellent example of the female Turner phenotype and paradoxically she had more extensive somatic abnormalities than any of the other females with 45,X and 45,X/46,XX karyotypes. There is little doubt that had her infant survived she too would have had similar features since this is a hereditary defect (NORA and SINHA, 1969). The present patient's family was not available for study and her own recollection of anamnestic details was too poor for serious consideration. The male Turner phenotype was well shown by Case 10 who, as it was explained earlier, was included here because of the aetiological similarity between the disorders under discussion. Since neither of his parents showed similar stigmata it must be assumed that an appropriate deletion arose de novo; this was not visible in his karyotype.

The unreliability of FSH assay as a diagnostic aid was shown: Cases 2 and 7 had raised levels but Case 4, with proven gonadal dysgenesis, had a level of

only 6 mu, which is well within normal female limits. There is no obvious
explanation for such inter-individual differences.

It is of interest that none of the patients reported here had any defect of
colour vision; none had clinical evidence of heart defects or hypertension
and none had any other sex-linked defect, all of which are said to be very
prevalent in gonadal dysgenesis.

Some authorities, for example HAUSER (1963), maintain that the diagnosis of
gonadal dysgenetic syndromes cannot be made without resorting to gonadal
biopsy. This is an extremist view because in the face of such indirect
evidence as typical somatic defects, recognized dermatoglyphic patterns,
karyotypic anomalies and amenorrhoea it is quite unreasonable not to accept
the diagnosis without surgical intervention. Only in the event of an other-
wise typical patient showing signs of oestrogenization should this be nec-
essary.

KLINEFELTER'S   SYNDROME   AND

MALE   HYPOGONADISM

Introduction
Classification
Pathology
Cytogenetics &
        aetiology
Case Reports
Discussion

INTRODUCTION

The syndromes of male hypogonadism present a challenge to the diagnostician

because many of them are of similar clinical appearance and require careful

differential diagnosis. Hypogonadism can result from congenital causes or

from secondary agents such as mechanical trauma, infection or other insult.

In every case the consequences are similar: androgen production is compro-

mised, virilization fails and oestrogen-dependent characteristics can appear.

It should be noted that female intersexes with severe masculinization do not

qualify for inclusion in this section just because they were reared as males;

thus JOHNSEN (1962) was incorrect in doing so. The definition of sex (p2)

makes this point quite clear.

CLASSIFICATION

The exact classification is still very contentious and few authors have ever

given more than passing reference to this problem. As JOHNSEN (1962) pointed

out, there is poor correlation between medical, endocrinological and cytogen-

etic observations and classification cannot be based only on the findings of

any one discipline. Johnsen's work is one of the only recent publications

which attempted the differential diagnosis of this complex of syndromes.

For the present purpose the main subdivision of hypogonadal males is into chromatin positive and negative groups. KLINEFELTER et al, (1942) described a syndrome which had as its principle features gynaecomastia, azoospermia, raised FSH excretion but normal distribution of Leydig cells. Urinary excretion of oestrogens was normal and of androgens, normal or slightly low. Several other features were associated with the original signs by subsequent studies (HELLER and NELSON, 1945). At that time patients were segregated in the classifcation according to the degree of eunuchoidism (HELLER and NELSON 1948). Following the discovery that Klinefelter males might have male or female nuclear sex (PLUNKETT and BARR, 1956) it was believed that they were in fact reversals of their sex (MOORE, 1959) and NELSON (1956) was led into terming them 'true' (chromatin positive) and 'false' (chromatin negative) Klinefelter males. Although he soon withdrew these terms (NELSON, 1957) they have persisted and the chromatin negative subject is still often called 'false Klinefelter' male. There is general agreement amongst contemporary authors that Klinefelter's syndrome should include only chromatin positive males (FRØLAND; NIELSEN, 1969) and that this applies to all karyotypic types.

The chromatin negative hypogonadal male presents a problem of classification and this is reflected in the poor coverage given them in the literature. Even such text-books as those by OVERZIER (1963), WILKINS (1965), BARTALOS and BARAMKI (1967) do not discuss the position of the XY, chromatin negative male who in many respects resembles Klinefelter males. Two recent and extensive reviews of Klinefelter's syndrome (FRØLAND; NIELSEN, 1969) were equally vague about these individuals. One of the few authors to attempt the classification of hypogonadal males was JOHNSEN (1962) but bold as he was, he did not make more than passing reference to the chromatin negative 'false Klinefelter' type.

In an endeavour to escape the problem, FERGUSON-SMITH (1958; 1959) gave the name Primary micro-orchidism to Klinefelter-like males and then sub-divided them according to sex chromatin status. He also suggested (FERGUSON-SMITH et al, 1963) that many XY individuals with the so-called 'false Klinefelter' syndrome were actually Del Castillo's syndrome, which is similar but does not show gynaecomastia. Ferguson-Smith rejected the eponym because it was not applicable to, and nor did it cater for, prepubertal subjects: there is remarkable similarity between this argument and that which led to derivation of the term Infantile Turner phenotype, which was discussed in the previous chapter. Nevertheless, the eponym persists through popular usage and the objection can be refuted because of the newer practice of including all poly-X males in Klinefelter's syndrome. NIELSEN (1969) simply segregated patients into chromatin positive and negative groups. In respect of the synonyms put forward from time to time, it is noteworthy that all have added 'Klinefelter syndrome' parenthetically to ensure correct interpretation of the new name! (OVERZIER, 1963).

The chromatin negative patients reported here cannot be classified accurately because in most cases the clinical studies were incomplete.

PATHOLOGY

Although the physical appearance of hypogonadal males may, at times, be somewhat remarkable, the major lesions are seen in the testes.

Testicular pathology

In Klinefelter's syndrome the testes are small and measure approximately 1.5 cm at the longest axis. The prepubertal testis is not remarkable except for paucity of germ cells and the spermatic tubules are thin walled, without sclerosis of the basement membranes. Many tubules may appear small with irregular lumina. As puberty approaches tubular sclerosis is initiated by

increased density of collagen fibres in the basement membranes, followed by hyaline infiltration; this becomes more severe after puberty, until finally the tubule is reduced to a hyalinized ghost (KLINEFELTER, 1958). The interstitial tissue is hypocellular and Leydig cells appear in scattered clumps. Tubular sclerosis is usually universal but rare exceptions are known and a few tubules may produce a few spermatozoa. In these, spermatogenesis is not prolific and seldom complete (FERGUSON-SMITH, 1958). The cause of peritubular fibrosis is uncertain. It was thought to be a response to excessive FSH secretion (MADDOCK and NELSON, 1952). Such sclerosis is not restricted to Klinefelter males but is also seen as a reaction to diverse insults by hormones, infection or irradiation (ASHLEY, 1962). Very different histology was reported by BUNGE and BRADBURY (1957) in a 10 year old boy who was sex chromatin positive: the lumina of some tubules were invaded by Sertoli cell and in a few, by large cells of ovoid appearance. These they interpreted as being transitional between spermatogonia and ova. Similar cells were found in the ovotestes of hermaphroditic rats (BRADBURY and BUNGE, 1958) and it was postulated that ova might have migrated to the tubules from the ovarian zone.

As tubular sclerosis becomes more extensive there is a relative increase in the number of Leydig cells until they appear to be hyperplastic (FERGUSON-SMITH, 1958). An interesting calculation of the Leydig cell volume showed that it varies widely in XXY males (AHMAD et al, 1969) and their 3 subjects had volumes of 0.4, 1.2 and 3.7 ml; these were both lower and higher than the normal range of 0.5 to 1.5 ml. These observations offer some explanation for the differences of opinion among workers regarding the Leydig cell status in the mature patient. In XY hypogonadal males the Leydig cell volumes of 6 patients ranged between 0.45 and 1.29 ml, thus closely approximating the normal male.

The testicular histology of XY patients is similar to, but not as severe as, that in the poly-X males: the tubule outline is more regular and hyalinization is patchy rather than universal (JOHNSEN, 1962; NIELSEN, 1969). These slight differences are said to distinguish bewteen XXY and XY individuals (FERGUSON-SMITH et al, 1957; OVERZIER, 1963) although FERGUSON-SMITH (1958) reiterated a warning given previously (BUNGE and BRADBURY, 1956b) that the testicular histology was not pathognomic of Klinefelter's syndrome and all other clinical features had also to be considered. In subjects with bizarre karyotypes the testicular elements are usually more completely sclerotic (BRAY and JOSEPHINE, 1963) and cryptorchidism is common (ZOLLINGER, 1969). The XX males, a very small group, present a much more variable picture (THERKELSEN, 1964).

Infertility because of azoospermia or severe oligospermia is universal in Klinefelter and hypogonadal males but Klinefelter males with XY/XXY mosaicism have on rare occasions been reported as fertile (WARBURG; DOWLING and KNOX, 1963; COURT-BROWN et al, 1964).

The syndrome described by DEL CASTILLO et al, (1947b) showed normal testicular histology except for the absence of germinal elements.

Somatic features

Gynaecomastia is the most obvious external sign and is variously reported to affect between 25 and 60 percent of patients; the prevalence differed widely in the many surveys that have been made (FRØLAND,1969). The age at onset may be between 14 and 40 years: initially the breast is small, firm and contoured but with age becomes lipomastic. Presentation is often unilateral, progressing to become bilateral. Gynaecomastia seems to correspond to the relatively high levels of circulating oestrogens, although they are in fact produced normally: there is a concomitant decrease in androgen synthesis

which permits expression of oestrogen-induced characteristics. The pathogenesis was related to the level of FSH excretion, which in turn is dependent on the extent of testicular pathology (OVERZIER, 1963) but FRØLAND (1969) found that endocrine studies could not elucidate this relationship.

Endocrine patterns

The most striking feature of hormone metabolism in Klinefelter males is the raised urinary excretion of FSH after puberty (KLINEFELTER et al, 1942; FRØLAND; NIELSEN, 1969). This was supposed to be related to tubule damage (KLINEFELTER, 1958). Rare patients with normal FSH excretion were mentioned by OVERZIER (1963), thus precluding the interpretation of high FSH excretion as diagnostic of the syndrome. Hypogonadism due to other causes may have hypo-, normo- or hyper-gonadotrophic features. Prepubertal excretion of FSH is normal (JOHNSEN, 1962).

Urinary excretion of 17-oxosteroids is generally slightly less than normal (STEWART et al, 1959) but the significance of these assays is difficult to assess because of the known range of individual variation. These findings were confirmed by GIORGI and SOMMERVILLE (1963), who also reported that the XXY and XY groups had similar levels. The decline in androgen production which is characteristic of the ageing normal male occurs early, usually at about 30 years of age, in Klinefelter males. This is reflected in premature impotence, senility and senile degenerative changes (OVERZIER, 1963).

Skeletal changes

Skeletal disproportion which results in eunuchoidism is the result of an early acceleration of growth rather than delayed epiphyseal closure (TANNER et al, 1959) because this generally occurs even earlier than in girls of the same age (STEWART, 1959). Degenerative changes that occur earlier than in normal males are probably related to sex hormone deficiency (OVERZIER, 1963).

Skeletal defects such as cubitus valgus and clinodactyly (ZOLLINGER, 1969);
orofacial deformities (HUBNER et al, 1969) and other anomalies (RERRICK
1969) are common in the XXXY and XXXXY subjects.

Psychopathology

Psychological disturbances and mental retardation are common in Klinefelter
males (NIELSEN; FRØLAND, 1969), a fact that has been known for many years.
In 1957, PASQUALINI et al, found that only 5 of their 31 patients had normal
intelligence. In contrast to ZÜBLIN (1953), Pasqualini and associates were
of the opinion that the psychopathology of Klinefelter males differed from
other forms of male hypogonadism. This view was verified by NIELSEN (1969)
in an extensive comparative study of psychiatric patterns in poly-X and XY
males with hypogonadism. Nielsen showed that in all respects the XY group
was less severely affected and that the degree of severity depended upon the
percentage of abnormal cells in the individual. The most common defects of
the poly-X males were low full-scale IQ, immaturity and insecurity and other
personality disturbances. There was a high incidence of criminality and
psychogenic psychosis. Few had sexual fantasies although homosexuality,
transvestitism and other psychosexual perversions were reported in the lit-
erature reviewed by Nielsen.

Generally, individuals with more exotic karyotypes such as XXXY and XXXXY
have more serious mental impairment (DAY et al, 1963; ZOLLINGER; HUBNER et
al, 1969).

Clinical course

Klinefelter's syndrome is not remarkable in the newborn and can be detected
only by active screening procedures. During childhood the diagnosis may be
suspected because of mental retardation, behavioural disturbances and, at a
later age, delayed puberty or early signs of hypogonadism.

Puberty usually occurs late, at about 15 years (OVERZIER, 1963), and results
in poor development of secondary sex characteristics: beard growth is very
light, the musculature is poor and eunuchoidal proportions develop. Although
the penis and scrotum attain adult proportions, the testes are small (KLINE-
FELTER, 1958; FERGUSON-SMITH, 1959; FRØLAND, 1969). Sexual activity begins
at approximately the same age as in normal males (PASQUALINI et al, 1957),
and most individuals enjoy some libido with variable potency. This however
declines early, at about the middle of the third decade (NIELSEN, 1969).
Hypogonadism itself, or concomitant mental defect, is not itself debilita-
ting and so Klinefelter males have normal life expectancy (NIELSEN, 1969).

It must be pointed out that although a large number of Klinefelter males are
to be found in mental institutions, there is an equally large body of affected
individuals who are quite able to cope with life outside of an institution;
these men frequently marry and the first sign of their condition may be in-
fertility or gynaecomastia.

CYTOGENETICS
AND   AETIOLOGY

The incidence of colour vision defects in Klinefelter males led POLANI et al,
(1958) to suggest that chromatin positive males might have two X chromosomes.
This hypothesis was corroborated by the later discovery of the XX (FORD et al,
1958) and XXY (JACOBS and STRONG, 1959) karyotypes.

The discovery of sex chromatin positive subjects was a factor which led to
the belief that these were actually females with complete sex reversal (see
discussion of older classifications, p48). However, investigators were con-
founded by the appearance of sex chromatin in only some patients but not in
others, and also that in an individual only some tissues might be chromatin
positive (PLUNKETT and BARR, 1956). For example, PASQUALINI et al, (1957)

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cautioned that 'so revolutionary a conclusion needs further proof before it becomes widely accepted', that these were in fact females. The female sex chromatin pattern was only explained after karyotyping established the numerical relationship between sex chromatin and the number of X chromosomes; also, mosaicism explained the latter observation that an affected person could have chromatin negative and positive tissues. Since the initial discovery of the underlying karyotypic anomalies several others have come to light: some were mosaics with as many as 6 cell populations. The known karyotypes were tabulated by BARTALOS and BARAMKI (1967) and were discussed at length by FRØLAND (1969). An interesting point is that all cell lines except the rare XX males and some mosaics such as XX/XXY, X/XY/XXY and the XXXX/XXXXY have included a Y chromosome.

The commonest mosaic pattern is the XY/XXY: this has puzzled observers for many years. Did the XXY line arise from a normal zygote, or did the XY line represent a mutation back to normal from a previously XXY cell? It was concluded from a study of the Xg(a) erythrocyte antigen frequencies in patients and their parents that such mosaics began life as XXY zygotes and the normal cell line thus arose through the loss of one X chromosome (RACE and SANGER, 1969). In general, gonosome aneuploidy encountered in Klinefelter's syndrome can best be explained by meiotic nondisjunction during gametogenesis in either parent (FRØLAND et al, 1968; RACE and SANGER, 1969). Double nondisjunction would be responsible for the more complex mosaics and cell lines (LEWIS et al 1964). A number of factors are thought to indicate individual or familial predisposition towards such nondisjunctional events: familial Klinefelter's syndrome has been described in siblings (MILLER et al, 1961), including twins, (HOLUB et al, 1958) and others have also had autosomal trisomies (BARTALOS & BARAMKI, 1967). However, HECHT et al, (1969) queried this assumption after testing the hypothesis that individuals with one aneuploidy might have two. They screened 772 male mongols and found only one with double aneuploidy; a

48,XXY,21+, instead of the expected 3.1.

A possible gene-controlled mechanism had to be considered in instances where a chromatin positive individual had a chromatin negative brother with signs of Klinefelter's syndrome (BUNGE and BRADBURY, 1956; GRUMBACH et al, 1957), although chance could not be excluded because the frequency of both types was high (OVERZIER, 1963). The extensive overlap of signs led STEWART et al. (1958) to the conclusion that the causes were related.

Contemporary thought accepts that the defects of Klinefelter's syndrome are due to chromosomal imbalance (OVERZIER, 1963; FRØLAND; NIELSEN, 1969) even though patients with apparently normal male gonosomes are sometimes seen. As yet there is no indication of the pathogenic mechanism in the XY patient; a number of theories exist which postulate a submicroscopic deletion of the Y chromosome so that the male determinants are lost. Or, there may have been a submicroscopic translocation of female genes to the X or Y; the XY karyotype might have resulted from a previously XXY organism, and less likely, cryptic mosaicism might be reponsible. In this connection it would be very interesting to know from which parent the X chromosome in these XY karyotypes originated. Studies of this question have not been done.

Maternal age effect

The effect of increased maternal age in the aetiology of Klinefelter's syndrome has been reported on by several authors. LENZ et al, (1966) found that 19.1 percent of 151 mothers were in their 4th decade at the time of the patient's birth, a five-fold increase over the expected number. Similar observations were made by NIELSEN (1969). PENROSE (1964) and FERGUSON-SMITH et al, (1964b) found the maternal age to be about 32.5 years, but only half of the cases were maternal-age dependent. In more recent surveys a decrease in maternal age was noted: of 25 cases it was only 26.8 years (MIKAMO and

DE WATTEVILLE, 1969) and the question was posed as to whether socio-medical factors have tended to shift maternal age to the left through the increased use of contraception and more frequent use of therapeutic abortion to terminate pregnancy in older mothers. A similar trend was found in the maternal age factor in trisomy-21 (COLLMAN and STOLLER, 1969). In the aetiology of Del Castillo's syndrome FERGUSON-SMITH et al, (1963) found that the maternal age was raised (28.7 years, mean) but it was not as high as in Klinefelter's syndrome.

Incidence

The discovery of the chromatin positive status of Klinefelter males enabled population studies using screening procedures to be made for the first time. From the combined results of MOORE (1959), BERGEMANN (1961) and MACLEAN et al, (1961), which included some 6800 subjects, the incidence was established as 2.65 per 1000. In a larger study that involved 20,000 observations on neonates, COURT-BROWN (1962) reported an incidence of 2.1 per 1000. MACLEAN et al, (1964) identified 21 of 10,725 male neonates as chromatin positive, an incidence of 2.1 per 1000. The collected results of 4 surveys of karyo-types in 8715 unselected male neonates indicated a slightly lower incidence; this was 1.8 per 1000 (RATCLIFFE et al, 1970). It is interesting that in India a similar sex chromatin survey of 2058 male neonates failed to detect a chromatin positive individual (SUBRAY and PRABHAKER, 1962). In an attempt to establish whether or not the incidence in adults was similar to that in neonates KAPLAN and NORFLEET (1961) surveyed 1000 army recruits and found only 2 affected. The prevalence of Klinefelter's syndrome can thus confidently be accepted as being between 2.0 and 2.5 per 1000, and so must be one of the commonest intersexual disorders.

Many workers have capitalized on the fact that Klinefelter males are to be found in mental institutions and have accordingly conducted surveys, also

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using the sex chromatin technique, of institutionalized patients. These surveys have shown much higher prevalences than in random population samples (amongst others, PRADER et al, 1958; MACLEAN et al, 1968) and the majority have shown this to be some 5 times greater than in the normal population (FERGUSON-SMITH, 1958; 1959; STEWART, 1959; NIELSEN; FRØLAND, 1969). An equally raised prevalence was found among subnormal school boys (ISRAELSOHN and TAYLOR, 1961). ANDERSON et al, (1964) conducted an investigation of mental institution patients in South Africa and found 5 of 763 males to have poly-X karyotypes. Unfortunately no details regarding the racial origin of the patients was given.

CASE REPORTS

Case 11   (Klinefelter's syndrome)

A white male was first seen during 1967, aged 24 years, for attention to a number of complaints which included ear-ache, lower abdominal pains and anorexia. He was found to have gynaecomatia of the right breast and so was referred for cytogenetic and endocrinological assessment.

He was 170 cm tall; armspan and other measurements were not recorded. No note was made of any eunuchoidal appearance, but the hands were said to be long and narrow. The penis was of adult size but both testes were small and soft. Investigations done during 1967 led to the diagnosis of Klinefelter's syndrome: the karyotype was 47,XXY; two sperm counts were negative and FSH excretion was more than 48 mu per day.

The patient was discharged for psychiatric treatment but during the next 2 years he presented himself repeatedly at hospital for treatment of a plethora of complaints. These then included vertigo, asthma, catarrh and severe abdominal pain. He was readmitted to hospital during June, 1969.

Examination showed a phenotypic male with bilateral gynaecomastia, scanty axillary hair and a poorly delineated pubic escutcheon. There was only a trace of beard growth and the patient had never had to shave. His voice was soft and high pitched. Extensive investigations failed to detect any causes, or even the reality, of his complaints. The earlier karyotypic findings were confirmed. Urinary excretion of 17-oxosteroids was 18.3 mg per day. Testicular histology was typical of the syndrome: the tubules were fibrotic with irregular lumina and generalized hyalinization. There was no evidence of spermatogenesis. Moderate interstitial fibrosis and apparent Leydig cell hyperplasia were seen in some areas. Dermatoglyphic patterns were essentially normal except for slight reduction of the TRC; details are given in Table XIV and Fig. 73a.

During the course of his protracted, and sometimes hysterical, stay in the ward the patient expressed his desire and preference for membership of the female sex. He denied any attraction towards women and had never enjoyed any social intercourse with them. He also denied homosexual inclinations and was not a transvestite. Psychiatric evaluation of the patient is proceeding.

It is interesting that in spite of his stated aversion for the male sex he worked in an all-male environment as an office clerk. His mental capacity was low-normal: he had passed form VIII before leaving school at the age of 16 years.

Case 12 (hypogonadism)

A 14 year old Bantu, A.N., was admitted to hospital in a catatonic state of some 12 hours duration. His parents stated that he had complained of head aches for the preceeding 48 hours; also that he was emotionally labile and suffered frequent episodes of mental confusion.

The patient (Fig. 27) was tall and thin, his height being 170 cm and weight, 60.3 Kg. His voice was unbroken and unsteady. Armspan was 173.5 cm and the ground to pubis height, 92 cm. There was bilateral early gynaecomastia of some 8 months duration. The nipples were small and were surrounded by prominent areolae. Axillary and pubic hair was distributed in the male pattern but was very sparse. There was almost no facial hair. His penis was adult in size; the scrotum was well developed and contained small, soft testes. Evaluation of the mental capacity was difficult because of his often vapid attitude towards questioning. There was no record of any formal education.

Karyotype analysis revealed only apparently normal male chromosomes and he was sex chromatin negative. Dermatoglyphic patterns are shown in Table XIV and Fig. 73b. The parents refused permission for testicular biopsy.

Case 13 (hypogonadism)

A Bantu male, A.Nc., was brought to hospital in a manic state which resisted all but the heaviest sedation. He was aged approximately 40 years. Relatives who accompanied him to hospital told that the patient suffered from recurrent episodes of acute mania; there was no suggestion that he smoked dagga (Cannabis) or used alcohol excessively.

On examination under anaesthesia, the patient was 173 cm tall with bilateral gynaecomastia; the breasts were not greatly enlarged, however. The penis was large but the testes were small, about 2 cm in the longest axis.

Karyotype analysis showed only the normal male chromosome complement and the buccal mucosa was chromatin negative. Dermatoglyphic profiles are reported in Table XIV and Fig. 73c. The patient could not be restrained and so was transferred to a mental hospital: further investigations could not be done.

Case 14   (hypogonadism)

W.M. was a 15 year old Bantu who presented at hospital for treatment of bilateral gynaecomastia.

Physical examination showed a tall, eunuchoid youth (Fig. 28), 178 cm tall and armspan, 180 cm. The lower segment measured 77 cm. His hands and feet were long and narrow. Gynaecomastia was more pronounced on the left than the right side, and had become progressively worse over the previous two years. The penis was well developed and the testes, by palpation, were of normal size but with some reduction of firmness and sensitivity. No disturbances of pituitary or thyroid secretion could be detected by hormonal investigations.

Genetic studies showed only normal male karyotype and sex chromatin pattern but the dermatoglyphic patterns were unusual (Table XIV, Fig. 73d).

Bilateral mastectomy was done; at the same time biopsies of the testes and mammary tissue were taken. Histological examination showed normally sized, regularly spaced seminiferous tubules with Sertoli cells. There was no tubule sclerosis. Only very rare spermatids were seen; none of these were mature. Scattered Leydig cells were seen throughout the interstitial tissue (Fig. 29). The mammary tissue contained well formed secretory elements together with areas of fatty tissue (Fig.29b)

Case 15   (hypogonadism)

A young white male, B.v.G., was remanded by the magistrate's court to a mental hospital for psychiatric evaluation following his third conviction for fraud.

The patient was of low intelligence, with a full scale IQ of 85. His mental state was confused, with severe inferiority complex and hypochondria which was rooted in his having gynaecomastia. Since the onset of bilateral gynaecomastia at the age of 11 years he had been teased mercilessly by school fellows and later, contemporaries at an army training centre. Consequent to the ridicule to which he had been exposed for most of his post pubertal life, the patient was extremely introverted and uncertain of his social rank. He had left school at the age of 16 years with only the Std. VI examination to his credit and had since worked in many jobs as an unskilled labourer, until the time of his arrest.

Examination showed a strongly built, 24 year old male (Fig.30). He was 183 cm tall and weighed 84.36 Kg. His span was 182 cm and ground to pubis height, 91.5 cm. When aged 20 years he had had a complete dental clearance without any prosthetic treatment, a fact which did little for his appearance. There was prominent bilateral gynaecomastia with heavily pigmented areolae. The penis was normally sized but the testes were palpably smaller than normal.

Investigations demonstrated only normal male karyotype and sex chromatin patterns, and the dermatoglyphic features were unremarkable.

Case 16   (hypogonadism)

A 5 year old white boy had been diagnosed as having Klinefelter's syndrome

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PLATE VII
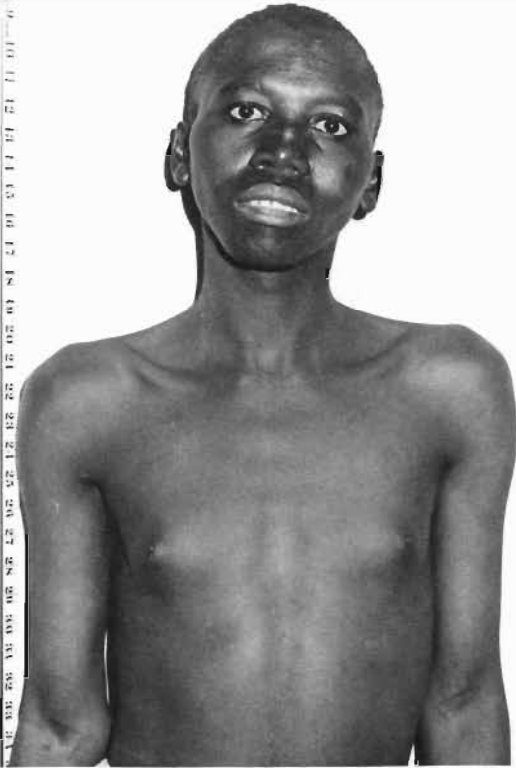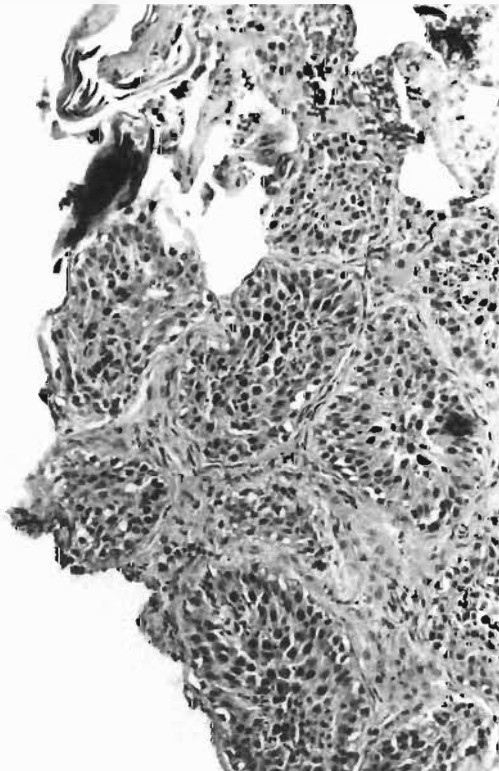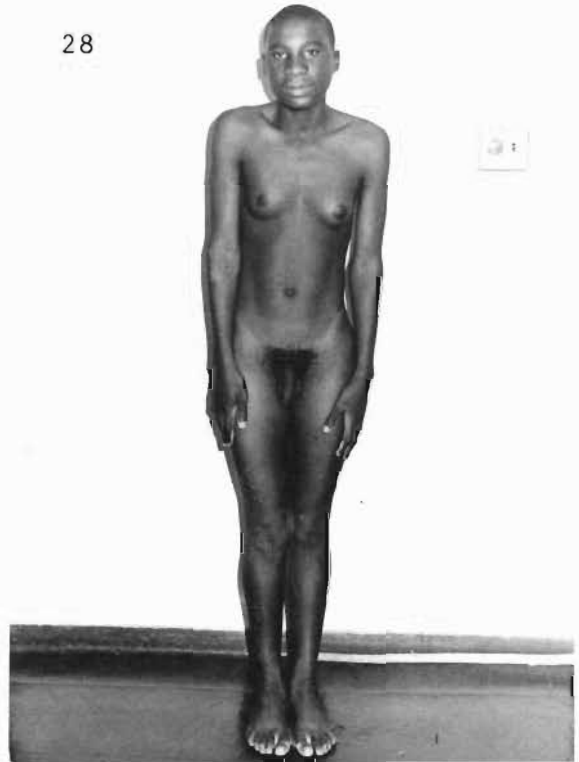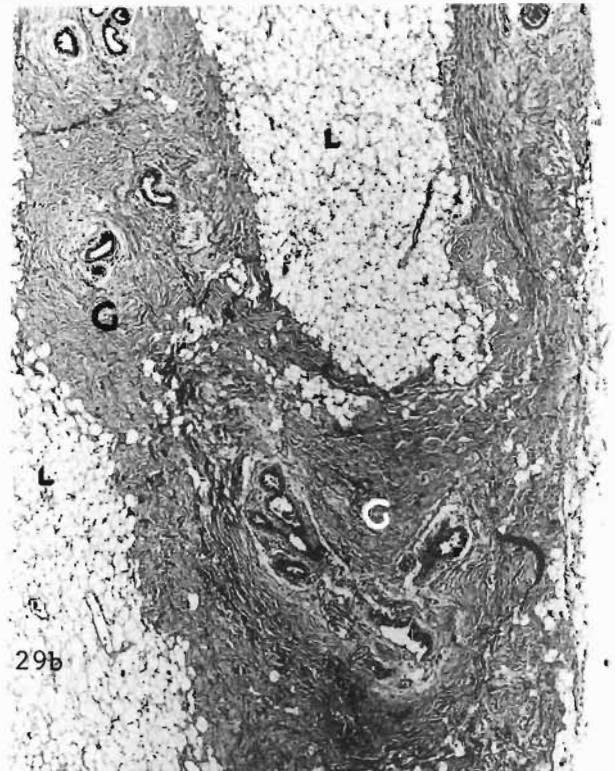
Fig. 27: Case 12, showing early gynaecomastia.

Fig. 28: Case 14; well-developed genitalia offset by prominent gynaecomastia.

Fig. 29: Case 14. (a) testicular histology: note regular tubules, normal Leydig
cell distribution, arrested spermatogenesis and absence of fibrosis.

(b) section of mammary tissue showing glandular (G) and fatty (L) areas.

PLATE VIII
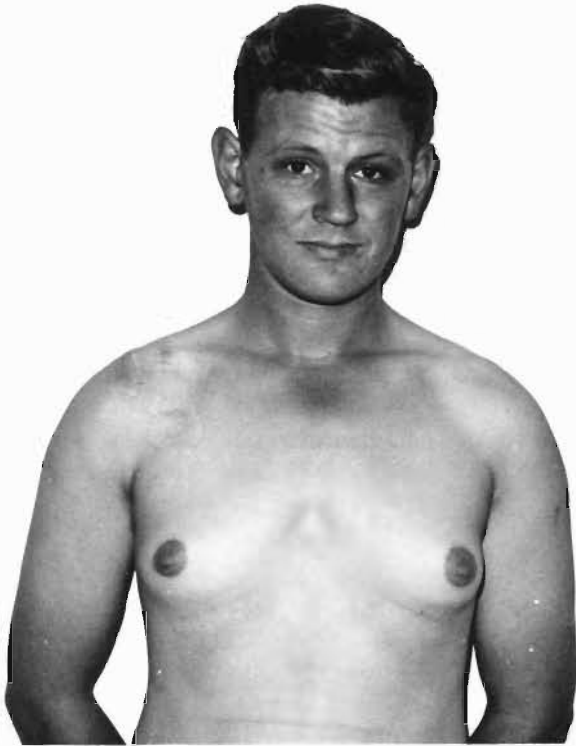
Fig. 30: Case 15, with bilateral
gynaecomastia.

Fig. 32: Case 16. Note torticollis
and retrognathia.
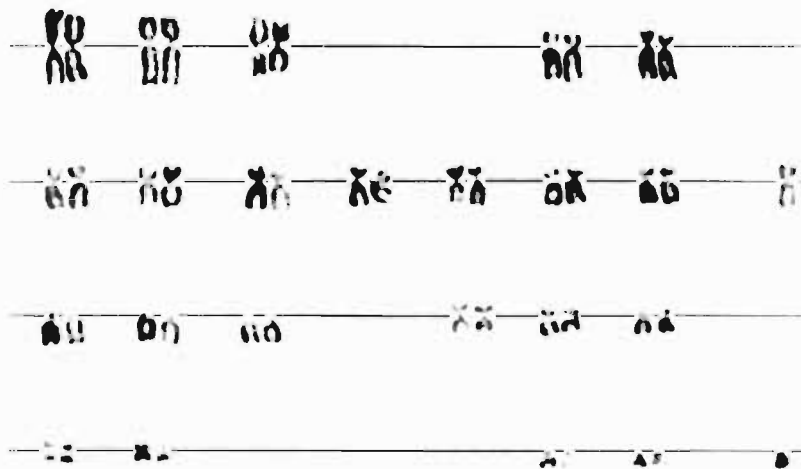
Fig. 31: Case 16, normal male karyotype.

but later examination when the patient was 10 years of age disproved the earlier karyotype analysis, which had been interpreted as being XXY. It was in fact apparently normal (46,XY, see fig. 31).

The child had been slow to develop and was mentally subnormal; he was a poor scholar and had reduced cognition and retention. He was small for his age and was only 124 cm tall at 10 years. His weight was then 21 Kg and armspan, 122 cm. He was born of a 28 year old mother whose previous child was a normal female. At 3 months gestation the pregnancy had been saved from aborting and the patient was born at full term. No relevant medical history was given and there was no family history. The patient had torticollis which was corrected surgically when he was aged 8 years (Fig. 32). Both testes had descended partially but at no time had they been felt in the scrotum; they were palpable in the inguinal canal.

There was no sex chromatin in oral mucosal nuclei. There was bilateral reduction of the TRC (see Table XIV, Fig. 73g).

DISCUSSION

Many of the syndromes of male hypogonadism are very poorly defined and few, if any, currently available texts consider them in detail. The majority of authors regard syndromes separately. It is impractical to discuss the complexities of the classification here and so the following discussion will be limited to Klinefelter's syndrome and those chromatin negative syndromes of congenital hypogonadism which mimic it so closely.

Modern terminology, established by popular usage, accepts as Klinefelter's syndrome any chromatin positive male. This acceptance effectively disposes with the invalid distinctions made by some earlier authors: for instance, 'true' and false' groups suggested by NELSON (1956), and it over-rides the objections raised by FERGUSON-SMITH (1958; 1959) to the use of the eponym in describing prepubertal subjects. Therefore, the major problem is to identify and describe those males with apparently normal gonosomes and yet who have features in common with the chromatin positive individual. The severe lack of consideration, apart from passing reference, given this type of patient in the literature has already been commented upon earlier in this chapter and is almost certainly, at least in the English literature, indication of a paucity

of knowledge concerning the aetiology and classification of the group. Regretably, there was not enough data from the XY patients reported here to enable all the features to be correlated, or to make accurate diagnoses of the syndromes. One of the most interesting findings of this work was that there are two distinct groups within the 6 patients with the XY karyotype. The segregation is apparent in the dermatoglyphic patterns, the one group having very low TRC and the other a more nearly normal TRC: this topic is discussed at length in Chapter XVI.

There can be little doubt that the pathogenesis of Klinefelter's syndrome is related to chromosomal imbalance. Testicular changes and mental defectiveness have been ascribed to this (OVERZIER, 1963; FRØLAND; NIELSEN, 1969) but other features, in particular the abnormal hormone metabolism and gynaecomastia, have not yet been related conclusively to either chromosomal aneuploidy or testicular pathology. Nielsen found no correlation between the extent of testicular changes and the prevalence of gynaecomastia, although Overzier had previously suggested such a relationship. It seems likely that skeletal disproportion is consequent to testicular insufficiency because bone growth is largely controlled by the prevailing sex hormones.

In common with all intersex syndromes phenotypic variation between individuals occurs, although in this case it is not as extensive as in others. A possible explanation of this variation is mosaicism or idiosynchrasies of hormone metabolism which might, for instance, affect the development of gynaecomastia. Similarly the extent of pubertal virilization might be dependent upon autosomal factors. For example, the commonest psychiatric defects are immaturity and insecurity, both features of the adolescent. In those affected individuals who are capable of maintaining a position in society; who marry, and who are usually capable of holding employment, there are less serious psychiatric disturbances such as reduced drive and labile

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nature. Their complaints are generally more personal and relate to infert-
ility, gynaecomastia and loss of libido. However, it is significant that
there are many more XXY males than XO females who are so mentally deficient
that they require institutionalization.

The finding of so many common features in Klinefelter males and XY males with
idiopathic hypogonadism is quite problematical. There are several possible
explanations, none of which can yet be proved, such as a submicroscopic loss
of male determinants or addition of X chromosome material; the reverse, in
fact, of the theory for the origin of gonadal dysgenesis in XX females (see
Chapter VII) proposed by FERGUSON-SMITH (1965). Thus, because there are so
many more superfluous genes in the XXY genotype than in the XY, the pheno-
typic derangements are so much more severe. Nevertheless, although there
are so many similarities there are sufficient discordant features to class-
ify chromatin positive and negative subjects separately. Others have con-
cluded that because of the similarities between the two, they must have an
aetiological relationship (STEWART et al, 1958). These theories regarding
the origin of Klinefelter's syndrome are discussed at length in a later
chapter (p226 et seq.).

Earlier the very noticeable inter-racial variation of prevalence of inter-
sex syndromes was mentioned (p 7-8) and this is illustrated dramatically
by the occurrence of Klinefelter's syndrome in South Africa. There are
only 3 reported Bantu cases: ASMAL (1967) and WILTON (1969) reported, re-
spectively, an XXY and an XXY and XY/XXY. In contrast to this very small
number, Wilton reported 16 whites, and several whites have been diagnosed
at this laboratory during the past 5 years. The syndrome is known to af-
fect Coloureds and Indians, but very infrequently: a single Indian was
found to be XXY at this laboratory, unfortunately before the author's time.
In the light of this is might be significant that SUBRAY and PRABHAKER

(1962) failed to discover any chromatin positive neonates amongst the 2058 which they screened in India. As notable as the rarity of non-white Kline-felter males is the number of chromatin negative hypogonadal patients. They are mainly of Bantu and white origin: during the years 1965 to 1969, both inclusive, 20 whites and 14 Bantu have been referred for investigation, but during the same period only 1 Indian and 1 Coloured were seen.

No reason is readily found for this marked inter-racial difference in the prevalence of male hypogonadism but some possibilities are considered in the discussion which concludes this thesis.

This series

The single patient with Klinefelter's syndrome was, for various reasons, not thoroughly investigated and no photographs were permitted. The testic-ular histology was typical of the disease; hormone excretion was equivocal and the patient was not as tall as is usually expected of the XXY male. The handprints were not quite typical of the syndrome because the TRC was rather low (see Table XIV).

None of the 5 hypogonadal males had any obvious cause for his defects. This is particularly important to note because there is a known high incidence of hepatic disease amongst the Bantu, as siderosis and haemochromatosis; and as cirrhosis in whites. It was said earlier that the clinical investigations were in most cases incomplete. Hormone patterns were not investigated and only a single patient (Case 14) had testicular biopsies taken for histologi-cal study. In this patient the picture was typical of XY hypogonadism as it was described by OVERZIER (1963) in that no peritubular sclerosis or hyalin-ization was evident and spermatogenesis, which occurred in a few tubules, was not completed.

The most interesting finding amongst these patients was that they could be separated into two groups according to the dermatoglyphic profiles. One group, comprizing Cases 12 and 15, had subnormal TRC whilst the other group consisting of Cases 13, 14 and 16 had extremely low TRC associated with long, narrow hands (see Table XIV and Fig. 73). It is thought that this distinction may indicate a difference between the aetiology of the two; this is discussed further in the section on dermatoglyphics (p 211). There was insufficient information about the testicular histology in these patients to permit correlation of the two dermatoglyphic 'types' with gonadal pathology. A more extensive, long-term investigation into this question is being undertaken.

UNREPRESENTED   SYNDROMES

Poly-X females
Poly-Y males
Agonadism

THE   POLY-X   FEMALES

The triplo-X syndrome has not been encountered with any great frequency in South Africa.   A survey of 899 institutionalized females detected 4 with supernumerary X chromosomes (ANDERSON et al, 1964).   The syndrome was recently reviewed by BARR et al, (1969).

THE   POLY-Y   MALES

This is also a syndrome which has been widely reported in countries other than South Africa, although most subjects were discovered in surveys of males in institutions for the criminally insane.   There appears to be but a single case report from South Africa (WILTON and LEVER, 1966).

AGONADISM

Complete agenesis of the gonads is a very rare disorder (OVERZIER, 1963) and has not been reported from South Africa.

HORMONAL   AND   DRUG   INDUCED   INTERSEXES

Introduction
Congenital adrenogenital syndromes
Acquired adrenogenital syndrome
Induced virilization
Feminizing tumours
Pathology
Aetiology
Case Reports
Discussion

'You should be women, and yet your beards
forbid me to interpret that you are so.'
Macbeth,   I: iii.

INTRODUCTION

Because the female develops normally in the absence of any inductor substance

the presence of androgenic hormones or compounds during foetal or post-natal

life will induce masculine features to develop. The male, on the other hand,

is largely insusceptible to the presence of female hormones unless there   is

concomitant insensitivity to androgens.

The majority of females with signs of virilization, either at birth or later

in life, have a history of exposure to androgenic substances preceeding the

onset of signs; those with seemingly unexplained, idiopathic masculinization

are quite uncommon (see Chapter XII). The disorders considered in the present

chapter include the adrenogenital syndrome in its various forms;   acquired

adrenal hyperplasia, and induced virilization of endogenous   or   exogenous

origin. Androgen resistant males with the syndrome of testicular feminiza-

tion are not included here since they are, by definition, male intersexes.

The rare males with oestrogen-producing tumours and feminization will be men-

tioned here, briefly. Adrenogenital hyperplasia also occurs in the male but

since it results only in macrogenitosomia and precocious pseudopuberty and no contrasexual features are produced, it is not considered here.

In females each form of the adrenogenital syndrome and of induced masculinization share similar features of pathogenesis, in that all are caused by exposure of the individual to excesses of androgenic substances; hormones or drugs. Masculinization affects the external genitalia only, and if the onset of signs occurs after birth then the genitalia are not affected but secondary sex characteristics may follow the male pattern and clitoral enlargement is found. The extent of masculinization in each of the syndromes is dependent on the time at which the androgens reach and maintain a critical concentration sufficient to divert normal female development.

THE SIMPLE ADRENOGENITAL SYNDROME

The simple form of adrenogenital syndrome is immediately recognizable in the newborn female because of ambiguous external genitalia. Masculinization is rarely complete and is usually characterized by clitoral enlargement together with some degree of labial fusion.

Pathogenesis and endocrine patterns

The defects of this syndrome are directly related to hormone metabolism, so that they are considered together. The primary defect of this syndrome is a disturbance of corticosteroid metabolism: deficiency of the adrenal cortical enzyme 21-hydroxylase prevents conversion of 17-α-hydroxyprogesterone to desoxycortisol. In consequence there is an accumulation of the precursor substances; progesterone compounds. Through alternative metabolic pathways these are converted in the adrenal cortex to pregnanolone or pregnanetriol: as there is no further obstruction to the conversion of these compounds to androgens, this occurs. The resultant androgenic compounds and their metabolites can be detected in the urine, in greatly increased amounts, as

17-oxosteroids and 11-oxy-17-oxosteroids. Conversely, the diversion of the corticosteroid precursors to androgen synthesis results in an effective shortage of plasma cortisol and thus there can be no feed-back inhibition of the pituitary production of adrenocorticotrophic hormone (ACTH). There is consequently a vicious circle in which the pituitary over-secretes ACTH in an attempt to establish normal concentration of circulating cortisol; as this is impossible more unwanted androgenic steroids are made, without any reduction in the demand for cortisol. In response to the great demand for ACTH the pituitary becomes hyperactive and so the scene is set for the continued hypersecretion of ACTH and undesirable androgens. Since the degree of pituitary hyperactivity is variable between individuals the biochemical and physical manifestations may also vary accordingly (ZANDER and HENNING, 1963; WILKINS, 1965).

Hormone excretion patterns are usually diagnostic of the disease and can be regarded as conclusive if there is a positive response to treatment with cortisol or dexamethasone compounds. Urinary excretion of 17-oxosteroids is raised at birth, a feature which persists and becomes more prominent in time. Serum cortisol levels are low (WILKINS, 1965) and serum ACTH concentration is raised (KELLEY et al, 1952). Urinary excretion of FSH is depressed to the point of being indetectable (ZANDER and HENNING, 1963) although not much is known of FSH metabolism in this disorder. It is thought that FSH production is compromised by the demand for ACTH and this, perhaps, is the cause of suppressed ovarian function. Patients do not menstruate and nor do oestrogen dependent secondary attributes appear (ZANDER and HENNING 1963), but following treatment they attain normal ovarian rhythm and thereafter may even become pregnant (MASON; SWYER and BONHAM, 1961).

In response to prolonged ACTH stimulation the adrenal cortices become hypertrophic and may exceed the weight of the normal gland by 3 or 4 times. The

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gonads remain immature and the primordial follicles become atretic. Secondary follicles fail to mature and ovulation is thus suppressed: this therefore resembles hypogonadotrophic hypogonadism. Large polycystic ovaries with thickened tunica albuginea, similar to those seen in the Stein-Levental syndrome, have been seen in older patients.

THE   SALT-LOSING   ADRENOGENITAL   SYNDROME

This accounts for some 25 percent of all cases of adrenogenital syndromes (BIERICH, 1963),   although WILKINS (1965) noted the prevalence to be more than 50 percent. In contrast to the simple form the enzymatic block is more complex (BONGIOVANNI, 1961) and Wilkins suggested that a partial block of the 21-hydroxylase pathway caused the simple form whilst a more complete blockade would preclude synthesis of sufficient aldosterone to counteract renal salt loss. In support of this theory is the fact that salt-losing infants will tolerate high doses of desoxycorticosterone (DOC) acetate without signs of intoxication.

The sequelae of this biochemical disturbance are more severe: adrenal hyperplasia is more prominent and masculinization more complete. Clinically, the loss of salt produces severe hyponatraemia which if untreated is fatal. Early signs include vomiting and dehydration and, in turn, irregularities of cardiac function. A degree of cyanosis becomes evident. When plasma electrolytes become more concentrated by progressive dehydration, acidosis and potassium intoxication result. This is followed by nervous dysfunction, tachycardia and circulatory collapse until death by cardiac failure supervenes (BIERICH, 1963).

THE HYPERTENSIVE ADRENOGENITAL SYNDROME

This is a rare form of the disease which is associated with salt retention and the attendant dangers of circulatory hypertension, generalized oedema and heart failure. Virilization resembles that of the simple form of the syndrome (BIERICH, 1963; WILKINS, 1965).

A few uniformly fatal cases of adrenogenital syndrome were due to deficiency of the enzyme 3β-hydroxysteroid dehydrogenase, which is a basic enzyme in the synthesis of cortisol and DOC. Because androgen production requires the presence of 3β-hydroxysteroid dehydrogenase, there may be less virilization of females and males may even be intersexual. This is in direct contrast to the other forms of the disease in which males present with macrogenitosomia.

ACQUIRED ADRENOGENITAL SYNDROME

Contrasexual features appear in some women at a later stage of life because of adrenal insufficiency similar to that seen in the simple form of the disorder. In these subjects virilization is limited to those features which have not already been established, and existing functions may be disrupted. Clitoral enlargement, hirsutism and, if the patient is post-pubertal, secondary amenorrhoea are the common presenting signs. The gonads and genitalia are unaffected because they are established before the onset of virilization.

It is impossible to establish whether or not this group is separate from the simple group, or if in fact they represent a very mild form of it. Possibly, minimal clitoral hypertrophy at birth could often go undetected: BIERICH (1963) suggested that the degree of hypersecretion of androgens might be so low that the critical level would not be attained until some time after the subject was born. Alternatively this might be a distinct group in whom the

adrenals function normally up until a certain point when a pathogenic event causes subsequent over-production of androgens.

The biochemistry of such women is not grossly disturbed: urinary excretion of 17-oxosteroids is raised, but not to the extent found in the congenital varieties of the disease. Mild adrenal hyperplasia occurs in some patients. Relief of signs can be had from cortisone therapy.

INDUCED VIRILIZATION

At any stage of life females are very susceptible to the action of androgens even if they are received from a source outside of the body. The effect of such foreign androgens is essentially similar to those of the adrenogenital syndrome and also, the extent of virilization depends upon the time at which exposure to androgens commenced, and the quantity available. Induced virilization can be differentiated from congenital adrenal hypersecretion by the fact that there is no progressive virilization after the source of androgens is removed; growth is normal and excretion of hormone metabolites is not altered. Virilizing substances produced in the mother and which pass the placental barrier to affect the foetus are said to be endogenous; those which are supplied to the post-natal female from an outside source are exogenous.

Endogenous causes

These maternally-produced androgens are usually from tumours. Common androgenic tumours are ovarian arrhenoblastomata, adrenal carcinomas and Leydig cell tumours. Although such tumours may be responsible for causing intersexuality, they are not invariably so: in many cases a woman known to have such a tumour produced a normal female infant (WILKINS, 1958; COHEN & THOMAS 1960). Tumours of this sort may also cause virilescence in the mother.

Exogenous causes

In the same way that natural androgens may virilize a female, so may those given therapeutically. Most are hormones or their derivatives; for example, testosterone and progesterone compounds (JONES, 1957; OVERZIER, 1963). That some mothers received massive doses of one or more of the androgenic preparations during pregnancy and yet still produced normal female infants led OVERZIER (1963) to write of the 'individual sensitivity of man'. There are many stages at which idiosynchrasies of metabolism may affect the fate of a drug; maternal catabolism of the drug may be incomplete; it may or may not pass the placental barrier, or the foetal circulation and response to it may vary.

FEMINIZING ADRENAL HYPERPLASIA

This is an extremely rare form of adrenal malfunction. Lipoid degeneration occurs in the adrenals and all cases are fatal. In males the condition results in feminization of the external genitalia (ASHLEY, 1962). A number of comprehensive reviews of hormone producing tumours are available (JONES and SCOTT, 1958; OVERZIER; HOFFMAN, 1963; GABRILOVE et al, 1965) for the interested reader.

CLINICAL PATHOLOGY OF VIRILESCENT FEMALES

In the previous sections the defects of adrenal function have been described but in spite of the several forms which the disease may take, or the several extracorporeal causes of masculinization, the effects are similar.

In all cases virilization only affects the external genitalia and secondary sex development; genetic and gonadal sex remains unaltered. Internal genitalia are of the female type, and defects are found only in occasional extreme cases. Since masculinization of the foetus is consequent to androgen stimulation it follows that the degree of deformity will depend upon the

time at which androgens reach the foetus and maintain the critical level of concentration to divert normal female ontogenesis. According to BIERICH (1963) the only variable in the pathogenesis is quantitative: since foetal adrenal cortices begin hormone production soon after they are differentiated, the rate of androgen secretion will determine when the critical threshold is attained.

Simple virilization presents in the newborn as enlargment of the clitoris, usually accompanied by the formation of a redundant hood, or prepuce. The glans is distinct and frequently has a dimple which is analogous with the male external urinary meatus. The labial folds may be fused; such fusion always proceeds from the anal margin of the vestibule, forwards, as occurs during specialization of the male genitalia. Intensity of the androgen stimulus governs the extent of labial fusion and the degree of phallic enlargement. In the most severe cases the phallus may be penile with total labial fusion to form a closed urogenital sinus with a hypospadic opening at or on the ventral surface of the phallus. The commonest presentation is that of a small penile phallus bound down by chordee to obscure a funnel shaped introitus; both urethral and vaginal openings may be obvious or be hidden, if labial fusion has reached the base of the phallus. When, in a few extreme cases, a penile urethra is formed, it may be transmitted to the tip of the phallus (MATHIESON and WARD, 1954; BENTINCK et al, 1956) or more commonly, it is associated with a second, functional urethra which opens via the vagina. In such an arrangement the penile urethra is vestigeal (REILLY et al, 1958; PERLOFF et al, 1953). The internal genitalia are differentiated before the adrenal cortices become functional and thus escape alteration.

The most remarkable aspect of females with congenital adrenal hyperplasia is the continued virilescence. The phallus grows, becomes erectile and

may attain 6 or 7 cm in length, and some 3 cm in diameter. Precocious puberty occurs at about 3 years of age when a fine growth of pubic hair appears but it must be realized that this is a pseudo-pubertal change because the gonads do not become functional. Within a few years, by about the age of 12, both beard and axillary hair are present. All secondary hair grows in the male pattern and at the expected age of puberty there are no feminine developments because the gonads are non-functional: thus there is no mammary enlargement and the menarche does not occur.

Skeletal disproportion is a prominent sign. This results after an early, rapid phase of growth promoted by androgens. But, the same hormones then stimulate premature closure of the epiphyses and elongation is stopped. In the long bones this is particularly noticeable, so that the limbs are short in relation to the trunk. Patients are generally short, being between 145 and 155 cm tall. Androgenization is also responsible for the heavy muscle development seen in these females; invariably they are physically many years in advance of their contemporaries.

In the adult these anomalies are consolidated and the thick-set, muscular physique remains devoid of any feminine contours; beard growth becomes an increasingly vexing problem and during the late twenties and early thirties temporal recession of the hair line begins. Balding may be complete in old age (BIERICH, 1963).

By contrast, females with induced virilization do not show progression of signs after birth and there are no further changes. If signs only present at a later stage of life, there is disruption of menstruation and secondary feminine features, such as breast tissue, regresses. Beard growth and loss of scalp hair may appear.

Psychosexual attitudes

Females with adrenogenital syndrome do not show intellectual development parallel with accelerated somatic growth. Intelligence is similar to the normal individual but they show socio-sexual immaturity and tend to be reticent and shy. Such introversion is almost certainly the result of their unattractive appearance and some have been known even to commit suicide. Sexual relationships, if formed at all, are usually not well established and masturbation and homosexuality occur with relative frequency (BIERICH 1963). In common with all intersex states the assigned sex and sex of rearing have a more profound influence over genetic and gonadal sex; consequently those patients reared as males are more likely to be socially well adjusted than those reared as females, since the latter must suffer the tribulations of obvious virilization.

The greatest cause of distress is the menarche in those patients who are raised as males, and belive themselves to be men. To a lesser extent amenorrhoea is a source of worry to those who are reared as females. This is common in all intersexual individuals who have such unexpected experiences.

Treatment and Fertility

Adequate and sustained cortisone therapy can alleviate and prevent the reappearance of stigmata by relieving the pituitary of the demand for ACTH. After a short while on therapeutic amounts of cortisol acetate or dexamethasone compounds the level of 17-oxosteroids in the urine falls dramatically and with prolonged therapy FSH becomes detectable in the urine (WILKINS, 1965). When FSH is available, ovarian function can be established and then conception is possible. Treatment must be maintained because signs reappear after withdrawal of cortisol.

AETIOLOGY

In the case of induced masculinization the cause is usually obvious and is

therefore of no further concern here.   There is very little known of the

pathogenesis of the congenital adrenal defects: CHILDS et al, (1956) were

of the opinion that a non-sex-linked recessive mutant gene was responsible

and from their survey of 798,118 live births of both sexes, incidence was

estimated to be 1:67,000. They further reckoned that heterozygous carriers

of the trait should occur with a frequency of 1:125. A revised estimate

by WILKINS (1965) put the incidence at about 1:40,000. PRADER (1958) made

the incidence to be approximately 1:5,000 after finding 8 affected subjects

in a survey of 40,329 infants. It is impossible to gauge the actual pre-

valence from such widely differing figures. Attempts to identify carriers

of the disease were unsuccesful (CHILDS et al, 1956; CLEVELAND et al 1962).

CASE   REPORTS

Case 17   (? Induced virilization)

A 7 year old Bantu girl, T.Z., was referred for examination by a Zululand
mission hospital. She had gross enlargement of the clitoris, which was said
to have been noticed at birth. There were no details available of family or
medical history. At the time of admission the child had active pulmonary
tuberculosis.

The patient (Fig. 33) was well nourished, 128.3 cm tall and weighed 24.96 Kg.
Her armspan was 127 cm, and ground to pubis height, 63 cm. No abnormalities
apart from the enlarged clitoris could be found. Her mental state and intel-
ligence were normal. The clitoris was enlarged and measured 37 mm in length
and 18 mm in diameter. A hood of preputial skin covered a well-defined glans
The phallus was erectile on excitation but was held down by chordee. A short
funnel-shaped vestibule was formed by labia which were fused for a short dis-
tance from the anal border. The vaginal introitus was obscured by the fusion
but not the urethral opening. There was no abnormality of the internal geni-
talia and there was no pseudo-puberty.

All laboratory tests gave normal results: the karyotype was that of a normal
female and sex chromatin was 26 percent positive. Urinary excretion of 17-
oxosteroids was 2.27 mg per day. Serum cortisol was 18μg percent; serum el-
ectrolytes were within normal limits. Radiography showed temporal and bone
age to correspond. A sinogram outlined a normal vagina, uterus and tubes. An
intravenous pyelogram demonstrated normal kidneys and excretion of dye. The
dermatoglyphic patterns are reported in Table XV.

No cause of virilization could be found. As there was no indication of progressive virilization occurring, cosmetic repair of the genitalia was done. The phallus was resected, preserving the glans, and excised tissue was used to reconstruct the labia. The short sinus was opened.

Case 18   (Exogenously induced masculinization)

A 6 year old white girl was investigated because of a number of congenital defects, including masculinization of the external genitalia. Both parents were of low mental capacity but denied consanguinity; they could not give an accurate history of family matters.

After extensive questioning it was established that the mother had had a number of wasted pregnancies; 3 had resulted in the premature births of a normal male, female and the patient (Fig. 34). The doctor who attended the mother during her last pregnancy, which terminated in the premature birth of the patient, was traced: he recalled having prescribed 'Epister-one' in an endeavour to salvage the pregnancy when it threatened to abort at the end of the first trimester. He could not recall the dosage, but it was taken until the baby was born after 7 months gestation. The mother was then aged 24 years.

At birth the patient weighed 1185 G, and was noted to have clitoral en-largement. There was also evidence of cerebral damage, probably as a result of birth trauma.

Examination at the age of 6 years showed a slightly built child weighing 15.8 Kg and 104 cm tall. Armspan was 99 cm. There was moderate ocular hypertelorism and the facies was similar to that of trisomy-21, with the jaw slack and tongue protruding. She was described as having cerebral palsy.

Inspection of the genitalia revealed a 3 cm phallus, 1.2 cm in diameter, with a prominent, dimpled glans and prepuce. The terminal dimple was deep and could be separated (Fig. 35) to reveal a blind pit. There was no outward sign of a phallic urethra. There was a single opening at the base of the phallus; this was the funnel-shaped urogenital meatus. The labia majora were well developed and the mons veneris had adult contours. A liberal amount of fine pubic hair occurred in the female trigone; no axillary hair was present and there was no evidence of breast budding.

Laboratory investigation confirmed that masculinization was induced: 17-oxosteroid excretion, serum cortisol and electrolytes were all normal and the karyotype and sex chromatin patterns were also of the female pattern (Fig. 36).

Case 19*   (Simple adrenogenital syndrome)

A 24 year old Bantu staff nurse complained of increasing facial hirsutes of several years duration. She had also been dysmenorrhoeic for 3 months. The menarche occurred late, at 18 years, and menstrual cycles had become progressively more irregular and at times she was amenorrhoeic for 2 or 3 months at a time. Her clitoris had 'been large since birth'. She had

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* This patient is reported by courtesy of Dr A. Vinik

PLATE IX

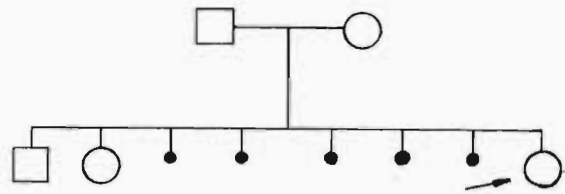FIG. 34 : CASE 18; FAMILY PEDIGREE

Fig. 33: Case 17. Note enlarged phallus;
normal body proportions.

Fig. 35: Case 18; induced masculinization. Note
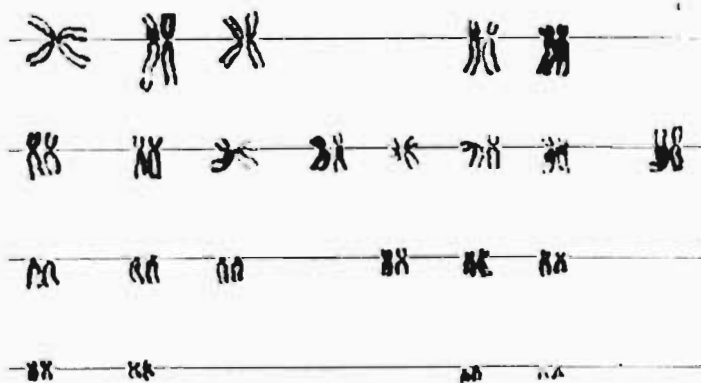grossly enlarged, hooded phallus.

Fig. 36: Case 18, normal female karyotype.

married when aged 23 years and enjoyed normal sexual activities.

Physically the patient was well nourished and of normal bodily proportions.
She had noticeable facial hirsutism and the breasts were small and atrophic.
The pelvic contour was feminine. Pubic and axillary hair were present, in
normal female distribution. The external genitalia consisted of a 1.5 cm-
long clitoris; this was 1 cm in diameter. The urethra was hypospadic and
opened about 8 mm from the introitus, on the anterior wall of the vagina.

The investigations undertaken to establish the cause of virilization incl-
uded cytogenetic, endocrine and gynaecological studies. The karyotype was
normal; the sex chromatin count was 42 percent. Urinary excretion of 17-
oxosteroids was monitored over a 3 month period (Table VIII), and FSH ex-
cretion was also determined. Serological studies showed no electrolyte
disturbance, but for some reason serum cortisol levels were not recorded.
Contrast radiographs showed normal female internal genitalia and this was
confirmed at examination under anaesthesia when the uterus was sounded to
a depth of 6.5 cm.

Excretion of 17-oxosteroids was persistently high and the patient was given
dexamethasone 2 mg q.i.d. for 2 days without any appreciable decrease in
17-oxosteroid excretion. Stilboestrol was added to the regimen and an im-
mediate, dramatic improvement was seen. Continued improvement and relief
of signs was had by giving the patient cortisone acetate 12.5 mg daily.
After 8 weeks beard growth had stopped and breast tissue had reformed; her
voice softened and menstrual activity became regular. The patient's libido
also improved.

TABLE VIII

Urinary Excretion of Steroids by
P.M. (Case 19)

| Date | Daily excretion of | | |
| | 17-oxo- | 17-oxy- | FSH |
	mg/day		mu/day
11.iii	24.6		
12	26.0		
13	27.0		6 - 12
29.iv	32.0		
2.v	34.0		
8	40.0	34.0	Dexamethasone given
9	33.0	33.0	Stilboestrol added
10	3.8	7.9	

DISCUSSION

As a group, masculized females demonstrate the inductive nature of androgens

in the development of male-type external genitalia. The extent of masculin-

ization can be readily interpreted in terms of embryological development to

determine when the diversion from normal female specialization occurred. The

bipotential nature of post-natal somatic growth is also shown by these women

in that virilization can occur at any stage if androgens are made available in sufficient quantities.

In contrast to other intersex groups the classification of females masculinized by known agents is quite straightforward and requires no comment here. The classification of the congenital disorders of hormone metabolism also is unequivocal: the differential diagnosis between the varieties of adrenal hyperplasia is based upon set biochemical parameters and the only possible problem is in deciding between simple or acquired adrenogenital syndrome. There is close clinical resemblance between all of these syndromes because, whatever the cause, the effect is similar: a genetic, gonadal female shows masculinization of the external genitalia and secondary sexual attributes. This is so even if androgens are supplied from without.

Although the pathogenesis of these disorders is well understood, the actual genetic defect is still obscure. One of the more interesting possibilities is that the acquired form of the adrenogenital syndrome is in fact a milder expression of the simple defect. In this case it is likely that penetrance is variable and so demonstrates the 'individual variation' of which OVERZIER (1963) spoke. There is, at this stage, insufficient data to determine the prevalence of this disease. It is not unknown in South Africa, but all of the patients seen by the author (3 during 3 years) were whites. Patient P.M. (Case 19) is believed to be the first report of congenital adrenal virilization in a Bantu: WILTON (1969) stated that the disease was at that time unknown in the Bantu, a view which was shared by DINNER (1969). It is unfortunate that no photographic record of the case was kept, and she had already been treated when seen by the author.

The first patient reported in this group, Case 17, presented a problem of diagnosis. The possible alternatives were induced virilization or idio-

pathic female intersexuality. There were no features suggestive of progres-
sive virilization, which thus excluded the congenital adrenal hyperplasias.
The size of the phallus was such that had she been a female intersex, much
more extensive labial fusion would have been expected: as it was the labia
were fused only along the posterior margin for about 1 cm. However, there
was no available medical history to explain what might have induced clitoral
enlargement late in foetal life and the assignment of the patient to this
category was arbitrary. By contrast, the young white patient was a classical
example of induced masculinization by exogenous androgens.

MALE   INTERSEXES

Introduction
Classification
Predominantly masculine types
Intermediate phenotypes
Feminized phenotypes
Pathology
Aetiology
Cytogenetics
Case Reports
Discussion

INTRODUCTION

A male intersex is defined as an individual with male (XY) gonosomes, sex

chromatin negative nuclei and testicular gonads;   intersexual features are

limited to the genitalia and secondary sex development. The phenotypes of

male intersexes cover an extremely wide range, from 'male' to 'female' in

appearance, with all gradations in between. The consequences of this are

reflected in the nomenclature and classifications which have been applied

to members of this group, more of which will be said later. A basic com-

plication of the classification is the extent of abnormality necessary to

qualify as intersexual: the very minor defect of the penile urethra, hypo-

spadias, was included (SERFLING, 1956) but OVERZIER (1963) objected to this

and excluded them from the group. The majority of authors have avoided the

issue. However, ASHLEY (1962) did discuss it but concluded that it was not

of practical importance and thereafter ignored it. HOWARD (1948) reported

an enlarged prostatic utricle (a Mullerian remnant) in all of 10 patients

with perineal or penoscrotal hypospadias, and a normal utricle in 4 with

penile hypospadias. Two of his 4 patients with perineal hypospadias had

rudimentary uteri and fallopian tubes. It can be argued from this that

simple penile hypospadias is probably due to a local failure of the ureth-

ral plate to fuse, whilst perineal hypospadias is evidence of defective

male differentiation. By this logic penoscrotal hypospadias is an inter-
mediate defect. In order to define intersex, hypospadias at or below the
penoscrotal border will be considered as a failure of masculinization and
so, intersexual.

CLASSIFICATION

The diversity of phenotypes found amongst male intersexes makes the classi-
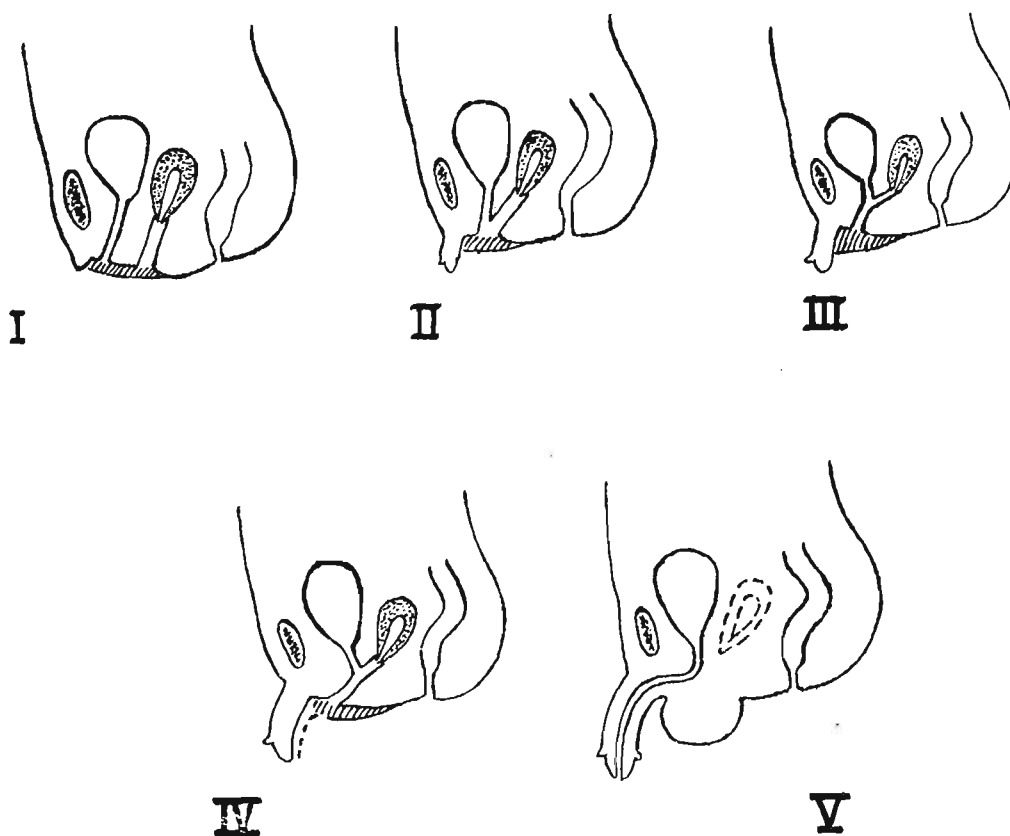fication difficult, especially as the taxonomic systems are based upon the

Fig. 37: The five major urogenital patterns (after OVERZIER)

outward appearance and the internal genital architecture. Any of the five
urogenital patterns described by OVERZIER (1963) may be encountered (fig.
37), and the habitus may be completely masculine or feminine. The follow-

ing system is proposed to cater for the group:

Male Intersexes

All have XY or mosaic karyotypes;
gonads are testes, or indifferent;
nuclear sex male; genital and
somatic appearance is variable.

Predominantly male phenotype

A. with andromorphic external genitalia
    external genitalia types III to V; Mullerian
    structures prominent; male physique and hair
    distribution; NO breast development.

B. with gynaemorphic external genitalia
    genitalia types I to III; Mullerian development
    poor; adult habitus masculine; feminine hair dis-
    tribution; NO breast development.

Intermediate phenotypes

C. asymmetrical gonadal differentiation
    phenotype variable, many reared as females; one
    streak gonad and contralateral testis that is
    usually dysgenetic to a degree. Karyotype often
    X/XY, others XY.

D. Incomplete testicular feminization
    feminine habitus with good breast development
    offset by well formed male external genitalia.

Feminine habitus

E. testicular feminization
    completely feminine habitus; karyotype XY; has
    bilateral intra-abdominal testes; insensitive
    to androgens. No Mullerian structures.

F. pure gonadal dysgenesis
    outward appearance identical to dysgenetic female;
    karyotype XY; streak gonads; rarely virilized by
    clitoral enlargement.

From the above it is obvious that there are three distinct morphological

groups: those with more or less masculine build and who never develop any

breasts; two syndromes which show characteristics of both male and female

and the third group which is outwardly entirely feminine. Recently it was

suggested (PHILIP and TROLLE, 1965) that an intermediate category should

be placed between the gynaemorphic and incomplete testicular feminization

syndromes to accomodate a familial defect seen in 5 males of a family and

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two other unrelated males. However, the small number of subjects and the very strong resemblance to incomplete testicular feminization preclude the adoption of a new group. As a general principle if new groups were to be created for all atypical patients the taxonomy would soon become chaotic. The patient who does not have all the features of any one syndrome must be placed in the most appropriate niche, unless the number of observations warrants the naming of a new syndrome.

PREDOMINANTLY MASCULINE PHENOTYPES

A. ANDROMORPHIC MALE INTERSEXES

Patients of this group are generally unmistakeably male and have a build that is muscular, with wide shoulders and narrow hips. Pubic hair and beard growth occurs in the male pattern, although in some subjects it only endures for a few years. Breast development never occurs. The testes may or may not be descended and range in size from pea-sized nodules to normal. If located in the scrotum spermatogenesis can occur normally and fertile patients have been reported (WULFSOHN, 1950; YOUNG, 1951). In the vast majority the testes are severly dysgenetic (JONES and ZOURLAS, 1965).

The external genitalia range from normal male, with Mullerian structures internally, to those with severe hypospadias and type III internal genital disposition. The Mullerian structures are usually well formed: in those with type V anatomy the vagina is blind and does not communicate with the urethra; in the others - types III and IV - the vagina leads into a common urogenital sinus (ASHLEY, 1962; OVERZIER, 1963). The uterus is often quite large and is frequently bicornuate. It is commonly contained in an inguinal hernia together with the tube of one or both sides (ASHLEY 1962): this state is termed hernia uteri inguinalis (YOUNG, 1951). When associated with normal male external genitalia such a hernia is usually only discovered during herniotomy.

An important feature of this group is that there is never any mammary enlargement. Virilization at puberty depends on, and is proportionate to, the competence of the testes for secreting androgens. Similarly the excretion of hormone metabolites is governed by the testes: in the prepubertal subject FSH and 17-oxosteroid excretion is normal, but after puberty if both gonads are dysgenetic then FSH excretion rises and the androgenic fractions decline. However, there is wide individual variation and hormone studies are of no diagnostic significance.

B. GYNAEMORPHIC MALE INTERSEXES

The attributes of this syndrome are slightly more feminine than in the previous one. Although they have wide shoulders and narrow hips the musculature is lighter and secondary hair follows female limits; beard growth is rare (OVERZIER, 1963). As in the previous syndrome, there is never breast formation. Ambiguity is the main feature of the external genitalia, where the structure is of types I to III, the majority being type II. The phallus is always small and resembles an enlarged clitoris or, at best, a minute hypospadic penis. Chordee is universal and binds the phallus down so that its prominence is further reduced. The labioscrotal folds are more or less fused to form a urogenital sinus of variable depth. The vagina is small and hypoplastic. Surprizingly, the internal genitalia are less perfectly differentiated than in the previous 'masculinized' syndrome. The uterus is rudimentary or absent and the fallopian tubes are thin and irregular. Testes rarely remain at the upper position but descend for a short way: in spite of this, they seldom reach the scrotal folds and their histology is commensurate with the cryptorchid station (ASHLEY, 1962).

Most patients of this sort are reared as females, with obvious consequences at puberty: there is neither menarche nor thelarche (ASHLEY, 1962; JONES & SCOTT, 1958; WILKINS, 1965).

INTERMEDIATE PHENOTYPES

C. ASYMMETRICAL GONADAL DIFFERENTIATION

In this syndrome only one testis develops and the other is represented by a streak, or is absent. SOHVAL (1963) defined the syndrome separately from other types of male intersexuality and termed it 'mixed gonadal dysgenesis' ZOURLAS and JONES (1965) favoured the term asymmetrical gonadal differentiation, proposed by BERGADA et al, (1962) as the former might imply hermaphroditism. A few others (for example, BAIN and SCOTT, 1965) still favoured Sohval's original term.

In a review of the literature ZOURLAS and JONES found that only 6 of 22 patients were raised as males: one had first been regarded as a male and then changed to female, as had happened in their Case 3. All patients had a single testis which, in most, was incapable of suppressing Mullerian development but was able to induce some masculinization of the external genitalia. In about 25 percent of patients Mullerian structures were found only on the side of the dysplastic gonad. All had a uterus and vagina but these organs might be hypoplastic. The adult habitus has mixed features: secondary sex characteristics are always minimal, if present at all. In those regarded as females amenorrhoea and 'clitoral' enlargement are common complaints. Those reared as males have ambiguous pudenda.

Since the review by ZOURLAS and JONES (1965) further observations and discussion was presented by GUINET et al, (1968) and GUINET (1969). It is of interest that the commonest karyotype was the X/XY mosaic, and that certain Turner stigmata such as cubitus valgus and short stature were seen in many patients.

D. 'INCOMPLETE' TESTICULAR FEMINIZATION

Following the work of MORRIS (1953) which drew attention to the male with an entirely feminine body and intra-abdominal testes, a number of patients with frank or partial masculinization were grouped by some other authors with Morris' syndrome of testicular feminization (e.g. DE LA HARPE, 1959). Subsequently it was suggested that such patients should not be included as they had obviously masculine genitalia and, frequently, descended testes. In a later review of the syndrome MORRIS and MAHESH (1963) stated that the partial and complete forms of testicular feminization did not occur in the same families, whereas each was known to occur familialy by itself: this was taken to indicate different aetiology.

The genitalia are usually male, of type IV or V and the testes descend to the inguinal position or into a normal scrotum. The diagnostic features of this group are that (a) they respond normally to androgens and become virilized; (b) the phallus is large and penile; (c) the habitus usually is more masculine, with wide shoulders and narrow hips. A good example of such a patient was given by SCHWABE et al, (1962) although they did not recognize it as partial testicular feminization.

FEMININE PHENOTYPES

E. TESTICULAR FEMINIZATION

This category is the ultimate form of male intersexuality: the body and genitalia are completely feminized, but the gonads are testes. Subjects are of normal or tall stature, sometimes with eunuchoid proportions; they have typically feminine fat distribution and contours and breast development is excellent. The nipples remain small; the clitoris and labia are sometimes infantile, but the vagina is usually adequate and dyspareunia is rarely a problem. The vagina ends blindly and there are no formed

internal Mullerian structures. Testes are always located within the abdomen somewhere along the inguinal canal; inguinal herniae are found in about 50 percent of patients. Secondary hair growth, when it occurs, is in the female pattern.

The syndrome is frequently familial and may affect several siblings (ILIYA et al, 1965; STENCHEVER et al, 1969) in successive generations (PION et al, 1965) but the actual mode of inheritance remains obscure. All of the observations made by Morris were confirmed in a review of the syndrome (ZOURLAS and JONES, 1965b).

F. PURE GONADAL DYSGENESIS

Clinically this syndrome is identical to that which occurs in genetic females, and has been mentioned earlier (cf. pp 83ff.). The phenotype is that of a normally tall woman with little or no secondary sex development and who is always amenorrhoeic. There is bilateral gonadal dysgenesis and poorly formed Mullerian elements (SOHVAL, 1965). Approximately equal numbers of patients with pure gonadal differentiation are male and female (HURWITZ, 1966). The syndrome can easily be differentiated from testicular feminization because this group has no secondary sex features; they respond to androgens and have internal Mullerian structures whereas the testicular feminization syndrome is due to androgen insensitivity and has no internal genitalia. Pure gonadal dysgenesis also occurs in sibships (GUINET, 1969).

PATHOLOGY

Although the above syndromes are distinct, they share certain common characteristics; these will be considered in the following.

Testicular histology

In andro- and gynae-morphic subjects the testes are typical of the intra-abdominal situation and are identical to the cryptorchid testes of other-wise normal males (ASHLEY, 1962; WILKINS, 1965). They may show some Leydig cell hyperplasia but this observation is more typical of the partial (LUBS et al, 1959) and complete (MORRIS, 1953; HAUSER, 1963; ZOURLAS and JONES, 1965b) forms of testicular feminization. The scrotal gonads of the few andromorphic patients with type V genitalia are histologically normal and some even show complete spermatogenesis (WULFSOHN, 1950; YOUNG, 1951).

Spermatic tubules usually have smaller diameter than normal and usually are lined by Sertoli cells and rare spermatogonia (ASHLEY, 1962; HAUSER, 1963). Hauser contested the 'Sertoli' cells reported by so many authors (ATKINS & ENGEL, 1962 for example): he maintained that there were few typical Sertoli cells, as are found in the normal testis, and that this was important since the mature Sertoli cell has been credited with a distinct endocrine function (HAMBLEN et al, 1951). Tubules in testicular feminization are all of simi-lar diameter and do not become sclerotic whilst in the other syndromes the cryptorchid state leads to collagen hyalinization and so all stages of mat-uration and degeneration are seen together (HAUSER, 1963). Testicular size is variable. The histology of the streak gonads found in asymmetrical and pure gonadal dysgenesis is similar to that reported in dysgenetic females.

Endocrine patterns

Because of individual variation of the state of the testes it is not sur-prizing that there are no typical hormone excretion patterns in male inter-sexes. There are nevertheless some interesting features.

In andro- and gynae-morphic subjects FSH excretion may be slightly raised (ASHLEY, 1962) but in partial or complete testicular feminization it can be

either normal or greatly elevated (LUBS et al, 1959; HAUSER; MORRIS and MAHESH, 1963; WILKINS; ZOURLAS and JONES, 1965; 1965b) as it is in pure gonadal dysgenesis. Because of variable testicular competence in asymmetrical gonadal differentiation the picture is even less constant. Following castration there is an enormous increase in FSH excretion by patients with testicular feminization: this indicates that the gonads did in fact respond to gonadotrophic stimulation (JONES and SCOTT, 1958; SPELLACY et al, 1965).

Excretion of 17-oxosteroids by the andro- and gynae-morphic groups is at the lower range of normal; in prepubertal individuals the values appear to be normal because all 17-steroids are of adrenal cortical origin (JONES and ZOURLAS, 1965). After puberty in the testicular feminization syndrome the excretion of 17-oxosteroids tends to increase, but without evidence of virilization (MORRIS and MAHESH, 1963; SHARMA et al, 1965). Castration produces a marked decline (PION et al; WILKINS; SHARMA et al, 1965) which indicates some gonadal contribution (MORRIS and MAHESH, 1963). However, some idiosynchrasies have been noted: SOUTHREN and SAITO (1961) in their Case 1 found that the levels remained unchanged after castration.

Androgen production in the masculine types is usually a reflection of the state of the testes insofar as it is lower than normal but does vary from patient to patient. This is also true of the intermediate forms. In the group with complete testicular feminization androgens are produced normally (MORRIS and MAHESH, 1963) and the plasma concentration and urinary excretion of testosterone confirms this (ROSNER et al, 1965; FRENCH et al, 1966). Testosterone anabolism is normal (HORTON et al, 1965) and studies by SHARMA et al, (1965) confirmed that the testes produce much greater amounts of testosterone than of oestrogens. The latter authors theorized either the presence of an anti-androgenic substance or, alternatively, a

failure of the target organs to respond to androgen stimulation as possible causes of the syndrome.

The production of oestrogens in testicular feminization is normal but in the other male intersexes it is subnormal (ASHLEY, 1962). Others have shown that the testes of the completely feminized subject are capable of converting androgens to oestrogens (KASE and MORRIS; SOUTHREN et al, 1965; FRENCH et al, 1966). Despite oestrogenization these individuals do not menstruate and reports of such events in any male intersex can be discounted as faulty observation (OVERZIER, 1963).

Psychosexual status

The social and sexual affiliations of male intersexes depend entirely on the assigned, an thus the rearing, sex. Unfortunately many patients are incorrectly sexed and such an error made at birth becomes compounded when, at puberty, those raised as females may suffer deepening of the voice and beard growth; or, in the feminized syndromes, amenorrhoea. There is less likelihood of such confusion in patients with asymmetrical gonadal differentiation because even those reared as females are unlikely to suffer obvious virilization (ZOURLAS and JONES, 1965). In pure gonadal dysgenesis and testicular feminization the sex of rearing is invariably female and the only complaints relating to these syndromes are amenorrhoea and, in the former, lack of secondary sex development. Those with testicular feminization are completely orientated as women and as such, marry (SPELLACY et al 1965). The majority are of above-average intelligence (HAUSER, 1963), which is in contrast to most other forms of intersexuality; the few reports of patients with testicular feminization having low intelligence (JACOBS et al, 1959) were refuted by HAUSER (1963) as being unconfirmed.

It is remarkable that the study of intellectual development in other male

intersexes has been ignored completely in the literature (e.g. ASHLEY, 1962; OVERZIER, 1963; HAUSER, 1963; JONES and ZOURLAS; ZOURLAS and JONES, 1965; HURWITZ, 1966). There is therefore the urgent need for information concerning the mental and social development in these patients.

AETIOLOGY

The aetiology of male intersexuality is particularly interesting because the individuals concerned are not affected by contrasexual hormones, as are females. A male organising substance was postulated by JOST (1958) as being responsible for suppression of the Mullerian ducts and induction of Wolffian duct differentiation: this theory was supported by the work of MACINTYRE et al, (1960) which showed that a testicular secretion could only inhibit Mullerian development within a small radius. ASHLEY (1962) and WILKINS (1965) suggested that andromorphic intersexes might be due to lack of the Mullerian suppressor, and gynaemorphic types to a deficiency of testicular androgens. It has been shown that certain types of intersexuality in males are inherited: in pigs some 50 percent of the males in affected sibships are intersexual, which suggests an X-linked recessive mechanism, and it is possible that a similar mechanism underlies the deficiency of one or other testicular product in humans.

The partial, or incomplete, form of testicular feminization has a different cause since, in contrast to the complete variety, there is usually a considerable degree of genital masculinization: they are sensitive to androgens. Possibly, a later failure of androgen production leaves the way open for oestrogenization to occur at puberty; in fact, a form of secondary hypogonadism.

The other syndrome of mixed appearance, asymmetrical gonadal differentiation, can readily be explained by the almost constant karyctypic anomaly:

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most are X/XY mosaics. The few with apparently normal genotypes can more than likely be ascribed to undetected mosaicism (ZOURLAS and JONES, 1965).

There is incontrovertible evidence that the testicular feminization syndrome is due to target-organ failure (SHARMA et al, 1965) since androgens are produced normally and even massive therapuetic administration of testosterone cannot elicit a response (MORRIS and MAHESH, 1963). Failure to respond to androgen is generalized and affects metabolic activity also (FRENCH et al, 1966). The latter authors suggested that from conception the target organs were insensitive although foetal testicular androgens were produced normally and can inhibit differentiation of the Mullerian tract. At puberty the male target areas are still insensitive to androgens but respond to oestrogens. It was postulated that failure of the testosterone feedback to control pituitary production of FSH led to over-secretion of gonadotrophins; this in turn caused Leydig cell hyperplasia. Other theories, which have since been abnegated, were proposed at different times. For example, ASHLEY (1962) suggested that the foetal testes became abverted and produced contra-sexual hormones.

The causes of pure gonadal dysgenesis, with consequent development along unspecialized female lines, were discussed at length in Chapter VII.

Family studies of male intersexes, of testicular feminization (BOCZKOWSKI, 1968) and gynaemorphic types (WALKER et al, 1970) have thus far been of little help in establishing the mode of inheritance.

CYTOGENTICS OF MALE INTERSEXES

The majority of male intersexes with the exception of asymmetrical gonadal differentiation have apparently normal male karyotypes. In the asymmetric syndrome the X/XY pattern is very common (ZOURLAS and JONES, 1965). In

some of the other syndromes occasional atypical chromosome patterns have been recorded (BARTALOS and BARAMKI, 1967; BOCZKOWSKI; JONES, 1968). An unusual male intersex was reported by JACKSON and MARINE (1970): their patient had XX/XY mosaicism in lymphocytes and the skin was only XY. In another interesting case, BOTTURA et al, (1962) recorded the 45,X karyotype in a patient with asymmetrical gonadal differentiation.

CASE REPORTS

Case 20   (Gynaemorphic male intersex)

Baby M, aged 5 weeks, was investigated to determine the sex: the external genitalia were very ambiguous. At birth the baby was registered as a female and so the parents regarded it. The baby was born at home, the full term product of an unremarkable pregnancy in a 23 year old Indian primagravida. The parents were unrelated and there was no contributory history.

Examination showed a health, active baby. Birth weight was 3120 G. There were no obvious abnormalities apart from the genitalia. The external genitalia (Fig. 38) consisted of a tiny dimple-like phallus which measured about 8 mm in length and diameter. The dimple was surrounded by a hood of skin and the glans was divided at the probable site of the male urinary meatus. Urine passed freely from a single meatus at the base of the dimple. The labioscotal area was flat, empty and fused along the midline to form a prominent raphe. No gonads were palpable.

Cytogenetic investigation determined that the patient was a genetic male by karyotype and chromatin pattern. The main palmar flexion creases were normal; no details of ridge patterns were obvious.

No further tests were done at the time and the parents were instructed to bring the infant back to hospital in 12 month's time: to date they have not done so.

Case 21   (andromorphic male intersex)

A 3 year old Indian child was brought to hospital by his parents, who were very agitated about his epicene external genitalia. The child was the result of a normal pregnancy and delivery and there was no contributory medical or family history. The mother was 22 years of age when the patient was born. She had had a normal boy and a girl in 2 previous pregnancies.

The patient was 89 cm tall; the gound to pubis measurement was 40 cm and armspan, 86 cm. He was well nourished and weighed 15.42 Kg. His mental state seemed to be normal and he enjoyed playing with other children. His developmental milestones had been achieved normally. There were no other abnormalities except those of the genitalia.

The external genitalia (Figs. 39, 40) consisted of a prominent penile phallus of 2.8 cm length and 1.5 cm diameter. A preputial skin fold surrounded the glans, which was dimpled. Extensive chordee bound the phallus down and so concealing a single hypospadic opening between the labioscrotal folds. The folds were rugose but were empty and no gonads could be palpated within them or the surrounding areas.

The karyotype (Fig. 41) was apparently normal 46,XY; buccal mucosal nuclei were chromatin negative. Endocrine investigations were not done because of the patient's young age and radiographic and other investigations had to be postponed because the child could not remain in hospital.

Because of the genital structure the diagnosis is fairly certain.

Case 22   (Andromorphic male intersex)

C.G. was a 9 year old Indian boy who was investigated for evaluation of his external genitalia. His parents were unrelated; there was no relevant medical history, and two siblings, a boy and a girl, were quite normal. At the time of the patient's birth the mother was 22, and the father 23, years old.

Examination showed a quiet, shy child (Fig. 42) who was quite alert. He had failed the Standard I examinations in school 3 times. His parents told that he enjoyed playing with other children of the same age group. He was well developed, 113 cm tall and weighing 31.7 Kg. Armspan was 109 cm. There were no extragenital abnormalities.

His genitalia consisted of a well developed, erectile phallus of 3.5 cm long and 1.4 cm diameter. The glans was prominent with prepuce and a deep, blind dimple. There was extensive chordee. The urethra was hypospadic and opened just below the penoscrotal border between the two halves of the deeply divided scrotum (Fig. 43). Both gonads were palpated in the scrotal sacs: each was small, approximately 1 cm long. Palpation of the perineum did not detect a cryptic vagina.

Karyotypes were all 46,XY and there was no sex chromatin. The dermatoglyphic profiles were grossly normal (Table XV). A contrast radiographic study of the internal urogenital tract did not reveal any Mullerian structures. The excretion of 17-oxo and 17-oxy-steroids was normal, at 3.1 mg each per day.

Case 23   (Testicular feminization)

An 18 year old Zulu woman, G.B., presented at hospital complaining of amenorrhoea. She was the eldest of 6 females in a sibship of 8; the last two siblings, both females, had died shortly after birth from unknown causes. There was no family history of menstrual problems.

Physical examination showed a tall, well devloped girl, 165 cm in height and with armspan of 178 cm. Her hands and feet were noted to be large. Breast development was good (Fig. 44) but the nipples were small. The pelvic contour was feminine. The external genitalia were underdeveloped: the clitoris (Fig. 45) was small and the vagina only admitted 2 fingers to a depth of 4 cm. There was secondary hair.

Investigation of karyotypes prepared from cultured lymphocytes revealed only

PLATE X

Fig. 38: Gynaemorphic male intersex
with dimple phallus.
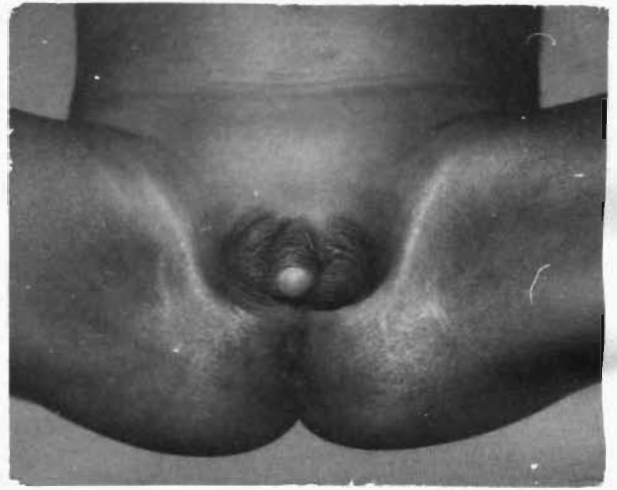
Fig. 39: Ambiguous genitalia of
Case 21.

Fig. 40: Case 21, showing hypospadic
urogenital meatus.

Fig. 41: Case 21, normal male karyotype.

PLATE XI
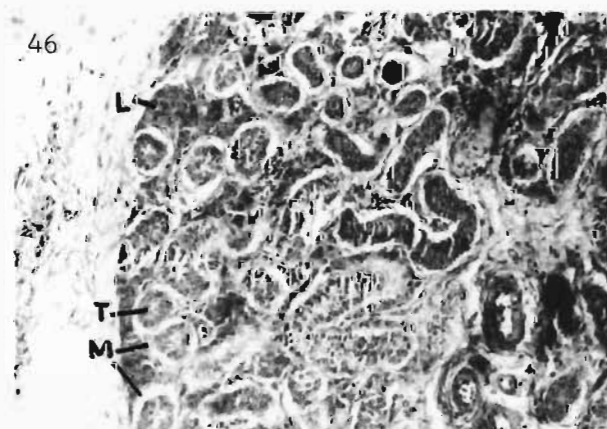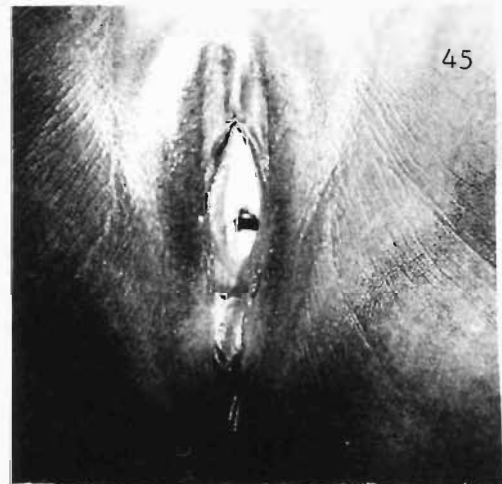
Fig. 42: Case 22, andromorphic male intersex. Note small phallus.

Fig. 43: Case 22, deeply divided scrotum and hypospadic urogenital meatus.

Fig. 44: Case 23, breast development in testicular feminization.

Fig. 45: Case 23. External genitalia; note small clitoris.

Fig. 46: Case 23, Testicular histology: numerous irregular tubules (T) with
hyalinized basement membranes (M) and focal Leydig cell hyperplasia (L)

PLATE XII

Case 24
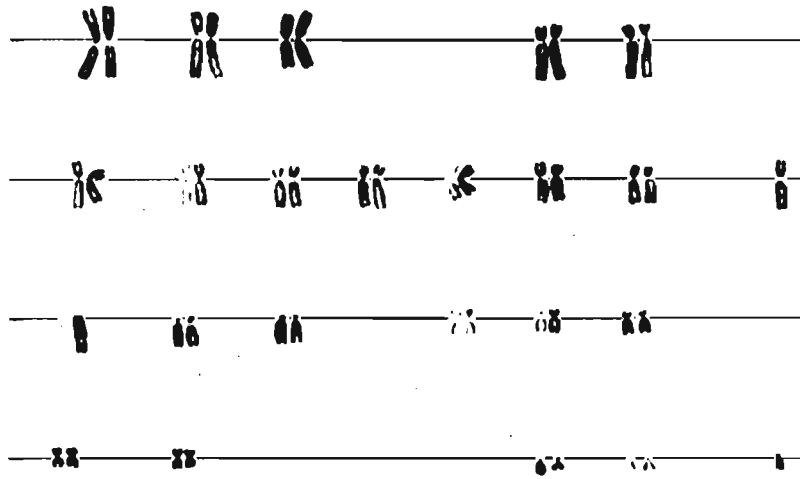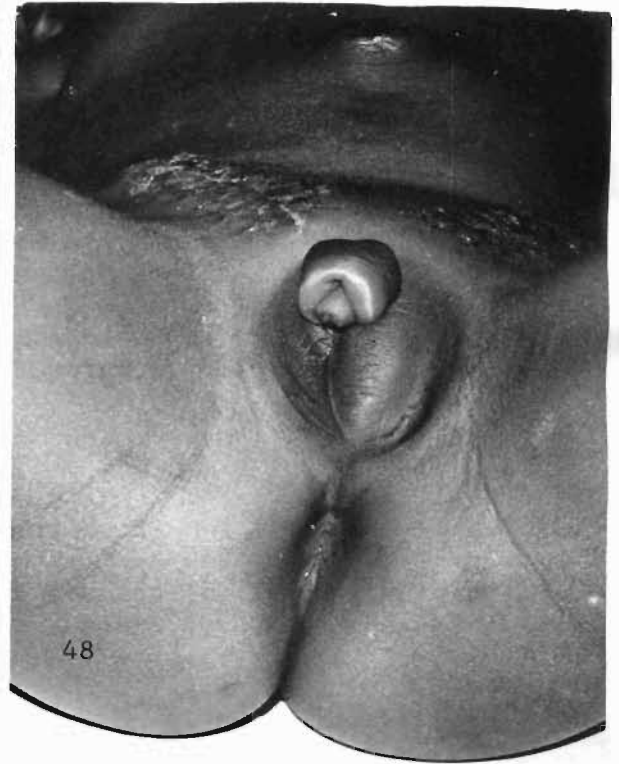
Fig. 49: Apparently normal male karyotype.

Fig. 47: The patient; note small phallus and swollen leg.

Fig. 48: External genitalia after orchidopexy of the left gonad. Preputial phimosis is due to post-surgical oedema. The right gonad was absent.

apparently normal male chromosomes; there was no sex chromatin in buccal epithelial nuclei. Urinary excretion of 17-oxosteroids was 12.9 mg per day.

At laparotomy bilateral intra-abdominal testes were removed. There were no internal genitalia. A pellet of oestradiol benzoate 20mg was implanted in the rectus abdominis muscle.

Histological examination of the testes showed hypoplastic tubules without any evidence of spermatogenesis and there was marked Leydig cell hyperplasia (Fig. 46); there was no suggestion of malignancy.

Because of the known familial tendency towards this disorder the number of females in the sibship was regarded as suspicious. Screening of the family was, however, unproductive.

Case 24   (Asymmetrical gonadal differentiation)

A 6 year old Bantu child was admitted to hospital with his right leg swollen and painful. The symptoms were of several years duration: he was diagnosed as having Milroy's disease.

The boy was cheerful and alert and seemed to be of normal intelligence. He was 111 cm tall; his armspan was 113.5 cm and the ground to pubis height, 58 cm. There was pitting oedema of the right leg (Fig. 47), due to congenital lymphangiectatic oedema. Incidental to the presenting complaint it was seen that the child had ambiguous genitalia.

The genitalia consisted of a penile phallus 4 cm long and 17 mm in diameter; this was bound down by chordee and obscured a single meatus near the base of the shaft. Labioscrotal swellings surrounded the base of the phallus; they were rugose with a prominent median raphe. No gonads could be palpated in either the scrotal, inguinal or perineal areas. Surgical exploration of the pelvis confirmed that there were no Mullerian structures, as had been indicated by a sinogram. The left testis was found high in the inguinal canal and was brought down to the scrotum by orchidopexy. Further exploration of the right side of the pelvis failed to detect a gonad. The post-operative appearance of the external genitalia is shown in Fig. 48.

The karyotype (Fig. 49) was that of a normal male and there was no sex chromatin. Blood chemistry was normal. The dermatoglyphic patterns were normal (Table XV).

DISCUSSION

It has been shown that the male intersexes form a very heterogeneous group in which genetic males show every grade of somatic sex from nearly normal male to almost perfect female, with a large intermediate body of epicene phenotypes The subjects fall into three broad subdivisions: the masculine group, who never develop breasts; the intermediate group where features of both sexes

occur together, and thirdly, the femininized individuals. In the first two of the subdivisions the final somatic appearance is dependent upon the state of the testes and so it follows that there is great inter-individual variation, a fact which creates some difficulty in classifying patients.

Because male intersexes show an almost continuous range of phenotypes it is, at times, difficult to decide on the category into which a particular patient should be placed. The most acceptable solution to this dilemma is to classify awkward patients as nearly as possible within the existing system: the alternative to this is to create new syndromes, thereby increasing the complexity of the taxonomy. This is a regression from modern trends and so no new syndrome should be proposed unless there is a large number of subjects; large enough to warrant a separate group. For this reason the proposal by PHILIP and TROLLE (1965) was rejected.

A further complication to the classification of male intersexes is the uncertainty regarding pubertal changes. However, when investigating young patients it should be reasonably obvious from the phallic architecture which direction further sex specialization will take.

One of the more remarkable facts to emerge during the course of this work was the paucity of information on ancillary studies such as intellectual development, radiographic findings, dermatoglyphic patterns, etc. Apart from the testicular feminization syndrome none of the other syndromes have attracted the interest of psychiatrists, radiographers or other workers. This is the more remarkable in respect of the group with asymmetrical gonadal differentiation because they are known to have frequent Turner stigmata which lend themselves to radiographic and dermatoglyphic investigation. As support for this, it should be noted that the patient reported here (Case 24) as having only a single testis had dermatoglyphic profiles similar to those seen in

Turner's syndrome. Another point which is conspicious by its absence is the lack of data concerning incidence of the different syndromes other than that of testicular feminization. This omission seems strange because they are not rare.

The aetiology of male intersexuality is still somewhat obscure although the pathogenesis has, in most cases, been elucidated. Individuals of the first group, andro- and gynae-morphic types, have no obvious chromosomal anomaly and no hereditary mechanism has been established in humans. In pigs, which frequently produce male intersexes of a comparable type, the sire has no influence on transmission and the female is a heterozygote carrier (ASHLEY, 1962). If the human female is a carrier it is strange that so few reports have appeared of siblings being affected: this would be expected to occur quite often, especially in the large sibships that are so common amongst the Indian and Bantu communities.

Asymmetrical gonadal differentiation and the partial testicular feminization syndromes form an intermediate group with epicene characteristics. In the former chromosomal mosaicism is found in the majority of patients, which is accepted as the cause of the anomalies. No definite cause has been found for the other syndrome, although its familial occurence does suggest a gene controlled mechanism (MORRIS and MAHESH, 1963).

In the syndrome of testicular feminization there appears to be complete insensitivity in the target organs to androgen stimulation, the cause of which is not known but is assumed to be a mutant gene. The karyotype is invariably normal in this and the syndrome of pure gonadal dysgenesis. FERGUSON-SMITH (1965) included the XY gonadal dysgeneses in his theory which postulated a submicroscopic deletion from one of the gonosomes: this mechanism was examined in Chapter VII.

A very noticeable feature of the cases reported here was the low maternal age at the time of the patients' births. In the first group (Cases 20, 21 22), all Indians, this was 22 years in two cases and 23 years in the other; the mother of the patient with testicular feminization was aged 17 years. No details were available for the patient with asymmetrical gonadal differentiation. From these cases it would appear that maternal age has no significance in the aetiology of male intersexuality.

In general the patients reported here were typical and demonstrated the expected features of the syndromes. Of the patient with asymmetrical gonadal differentiation, the failure to locate any internal Mullerian structures was possibly due to an oversight by an unsuspecting surgeon: some Mullerian development is said to be present in all patients of this sort (ZOURLAS & JONES 1965). The absence of any testicular remnants was not surprizing: 5 of 22 patients listed by Zourlas and Jones shared this deficiency. It is interesting to speculate on the association of congenital lymphoedema and testicular failure: was the gonadal defect due to a similar, or perhaps the same, mechanism which obstructed drainage from the leg, or were both linked to a similar genetic defect, in this case probable X/XY mosaicism?

CHAPTER XII

IDIOPATHIC FEMALE INTERSEX

Introduction
Classification
Pathology
Aetiology
Case Reports
Discussion

INTRODUCTION

Masculinization of the genitalia in genetic females, without any obvious

cause for the deformity, is a rare event. These individuals are the idio-

pathic female intersexes and are defined as being genetic females with ov-

arian gonads and genitalia which show unexplained masculinization.   This

definition excludes the Klinefelter and testicular feminization syndromes,

which were included by some of the older classifications, from the group.

The taxonomic position of those females with defective, but not virilized,

genitalia must be considered. Such anomalies as vaginal atresia and fe-

male hypospadias are analogous to simple male hypospadias and so, unless

accompanied by virilization or contrasexual somatic features, they must

be relegated to the 'pseudo' intersexual conditions (Chapter XIV).

CLASSIFICATION

The spectrum of signs seen in idiopathic female intersexes is not as wide

as those in the male counterpart but there are three distinct types. The

simple form of the disorder involves only the genitalia, particularly the

phallus; in severe cases masculinization is taken to the extent that a

penile type of urethra is formed. In many instances a number of extra-

genital anomalies occur: these affect, particularly, the upper urinary

and lower intestinal tracts. Frequently these complications occur when

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a phallic urethra is present. From this brief outline it is apparent that there are 3 subdivisions into which an idiopathic female intersex may be placed:

i.   simple; in which there is no phallic urethra or extragenital anomaly.
ii.   severe; in which there is a phallic urethra, with or without a perineal urethra.
iii. complicated; when there are extragenital abnormalities.

These subdivisions should only be used as a guide to the description of any particular patient and not as rigid groups. As OVERZIER (1963) commented, the range of pathology shown by these individuals indicates a graded series. This is a valid assessment of the situation and so it seems superfluous to attempt subdivision into defined categories because that introduces a decision effect: where does one group end and another begin? It is preferable to refer simply to idiopathic female intersexes and qualify the term with one of the abovementioned adjectives. Many names have been given the 3 subgroups: of the simple form, for example, non-adrenal female pseudohermaphroditism (GROSS and MEEKER, 1955); specific group without associated malformations (CARPENTIER and POTTER, 1959); idiopathic group (WILKINS, 1965) and non-specific female pseudohermaphrodites (BARTALOS and BARAMKI, 1967). The majority of authors were content with two sections, a simple group and another which included all subjects with phallic urethrae, with and without extragenital malformations.

PATHOLOGY

In its simplest form the disease presents as clitoral hypertrophy; the organ may be erectile and penile in appearance, frequently with a glans and distinct prepuce. The glans in such cases, which correspond to urogenital types II and III, is dimpled. Closure of the vestibule gives rise to a urogenital sinus. In the more severely affected individual with type IV genitalia there is a predominantly male appearance and the urogenital sinus

is incorporated into the shaft of the phallus. However, the sinus is hypo-spadic and opens near the base of the organ. Such a patient was described by GLEN (1957) and may be interpreted as being transitional between the simple and the severe forms. Another feature of this group is that in some patients the terminal section of the urethra is formed as a blind invagin-ation of the glans (OVERZIER, 1963).

Severe masculinization, shown by patients with a phallic urethra, is a very rare event. The phallic urethra traverses the length of the phallus and in structure resembles the male urethra. It may (WILLIAMS, 1952; PERLOFF et al, 1953; SIEBER and KLEIN, 1958) or may not (PAQUIN et al; JONES, 1957; GRACE and SCHONLAND, 1970) be patent. It is usually associated with a second, perineal urthra which is functional and joins the vagina to form a vertical urogenital sinus (HOWARD and HINMAN, 1951; PAQUIN et al, 1957; REILLY et al, 1958; GRACE and SCHONLAND, 1970). Rarely the urogenital sinus is transmitted to the tip of the phallus, there being no second urethra (WILLIAMS, 1952).

The complicated form is seen almost as frequently as the severe form. In this usually inviable syndrome there are concomitant defects of the urin-ary and alimentary canals: renal hypo- or aplasia, anal atresia and the formation of a cloaca are the most frequent anomalies (ATKINSON and MASSON 1934; BROSTER, 1956; SIEBER and KLEIN; REILLY et al, 1958; CARPENTIER and POTTER, 1959; ASHLEY, 1962).

The internal genitalia retain their female identity: the ovaries are hist-ologically normal and the Mullerian tract is present. Occasionally the uterus is bicornuate or the vagina is divided by a septum (HOWARD and HIN-MAN, 1951; GRACE and SCHONLAND, 1970).

Most patients with type III or IV urogenital architecture were assigned to the male sex, an error which might only become apparent at puberty when no masculine changes occur but breast development and menstruation appear. In these patients menstruation is dependent more on the degree of uterine development than on hormonal activity, which is usually adequate. Secondary hair growth occurs in the female pattern. Several reports have been made of these patients being reared and marrying as males (HAYNES et al, 1941; CHANIS, 1942; ARMSTRONG, 1955; GLEN, 1957) and of others, as females (OVERZIER, 1963; WILKINS, 1965). Since they do not suffer progressive virilization and hormone production is essentially normal, they may be fertile, as were patients reported by COTTE (1947) and MORRIS (1957).

AETIOLOGY

The pathogenesis of idiopathic female intersexuality, in all of its forms, is surrounded by complete obscurity. The great similarity of the simple and severe forms to females with adrenogenital or drug-induced masculinization does suggest that some similar cause might be found in this syndrome. Perhaps extreme sensitivity to androgens produced by the mother during pregnancy (FRIEDMAN et al, 1955; JONES, 1957) or to small amounts of androgenic drugs not normally sufficient to be teratogenic but which might have been taken by the mother at a critical stage of pregnancy could be responsible (LEIBOW and GARDNER, 1960). There is, however, nothing to support any of these hypotheses.

The very close relationship of the embryonic genital and urinary tracts does suggest that concurrent defects of both cannot be always due to chance. Why some should have only masculinized genitalia and others gross, and usually lethal, anomalies of other organs is perplexing. Genetic control with variable penetrance might be postulated to explain the gradation from simple to severe masculinization, but it is hard to imagine that the same mechanism

could be influential in, say, renal development. Another alternative suggested by ASHLEY (1962) was focal teratogenesis by any of a number of agents that can induce embryonic damage.

It is difficult to ascertain the incidence of idiopathic female intersexuality because the number of cases reported is small; the severe form is especially rare (OVERZIER, 1963).

CASE   REPORTS

Case 25   (Severe idiopathic female intersex)

A 19 year old Bantu woman was delivered of her second baby by normal delivery after an uneventful pregnancy. There was no family or medical history of any consequence. The first infant, a male, had died aged 1 year, from an unknown cause.

At birth the baby weighed 1645 G and was noted to have very abnormal genitalia (Fig. 50). Head and chest circumferences were 28 cm and 23.5 cm, respectively Crown to rump length was 40 cm. The ears were slightly low-set; the abdomen was greatly distended (Fig. 51) and the baby was dyspnoeic.

The genitalia appeared to consist of a phimotic, swollen penis, 21 mm long and 11 mm in diameter. The glans was enclosed in preputial skin and had a terminal indentation at the probable site of the urethral meatus. Two firm swellings surrounded the base of the phallus and were presumed to be scrotal folds, although no gonads could be palpated within them or the adjacent inguinal and perineal areas. There was no median raphe. There was a tiny meatus about 1 mm anterior to the anus: on several occasions urine was seen to pass freely from this meatus. The anus was normal and mecomium was passed shortly after birth.

The clinical course was unsatisfactory and the baby died 46 hours after birth. Prior to death blood had been taken for cytogenetic analysis, but because of the patient's moribund condition no other investigations were felt to be justified.

Analysis of karyotypes prepared from lymphocyte chromosomes revealed the surprizing fact that the gonosomes were those of the normal female. This was confirmed by the sex chromatin frequency of 47 percent. The main palmar flexion creases were normal.

Post mortem investigation revealed a patent foramen ovale in the heart. Coils of the small bowel were loosely bound together by fibrinous exudates. There were no other somatic abnormalities: specifically, the adrenal glands were not enlarged. The genitalia consisted of a short urogenital sinus which led from the meatus anterior to the anus, to a well developed vagina. A sagital septum divided the vagina. The uterus was bilocular with a thin fallopian tube arising from each side. A small ovoid gonad was associated with each tube   at

PLATE XIII

Case 25

Fig. 50: Epicene external genitalia.

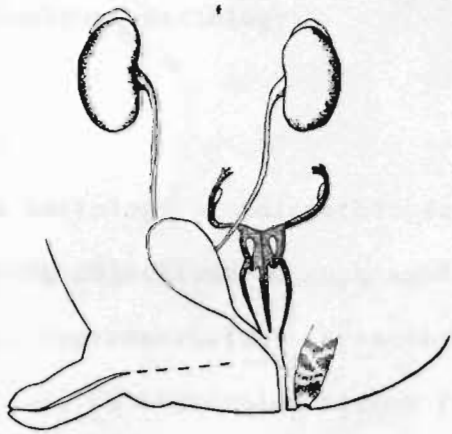Fig. 51: The patient. Note
distended abdomen.

Fig. 52: Diagram showing location
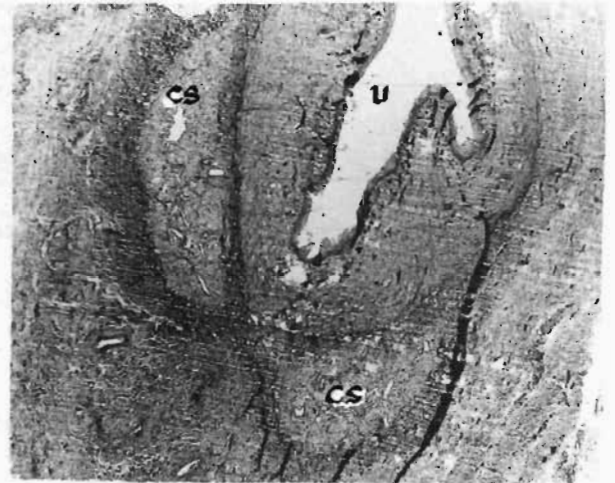of urogenital structures.

Fig. 54: Cross-section of phallus.
(see legend below).
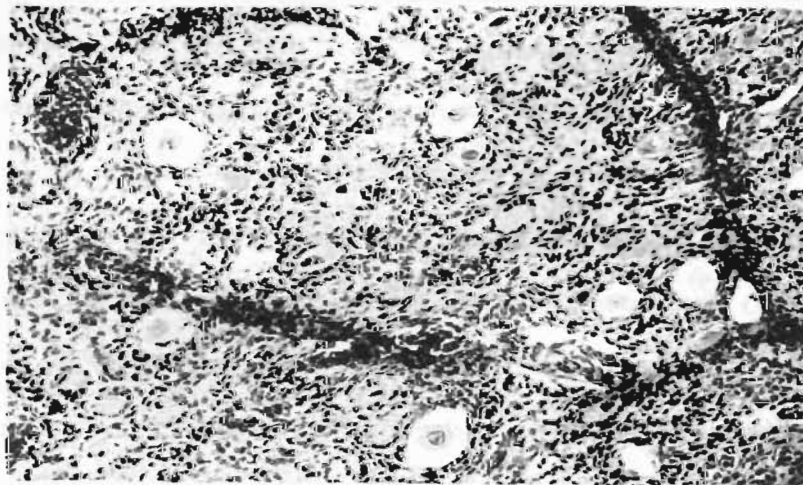
Fig. 53: Section of ovary showing normal neonatal
structure with numerous follicles and ova.

(Fig. 54: The central urethra (U) is shown surrounded on the antero-
lateral aspects by erectile tissue (CS)).

the normal ovarian position. The bladder was located anterior to, and slight-
ly above, the vagina into which it opened through a short urethra. There was
some resistance at the urethrovesical junctions to the introduction of a fine
probe but there was no evidence of hydroureter or hydronephrosis. A urethra
was found to traverse the length of the phallus; it was stenosed at the dis-
tal end and the proximal origin was not found during dissection. No gonadal
or other structures were found in the swellings at the base of the phallus.
The disposition of the urogenital organs is shown in Fig. 52.

Histological examination of post mortem tissues confirmed the earlier obser-
vation: no hyperplasia of the adrenal cortices was present; there was pro-
visional and actual cortex. The uterus, tubes and gonads were histologically
normal: numerous primordial follicles were seen (Fig. 53). The vagina had
double canals; each was histologically normal. Sections of the uterus had
normal neonatal endometrium and cervical structure. There was no gonadal
tissue in the labioscrotal swellings. On section the phallus was penile and
had a central urethral canal with two antero-lateral areas of erectile tissue
(Fig. 54).

The cause of death was attributed to prematurity and fibrinous peritonitis
of unknown aetiology.

DISCUSSION

The aetiology of idiopathic female intersexuality is obscure and there are

strong objections to such explanatory hypotheses as transient adrenal cort-

ical hypersecretion; hypersecretion of maternal androgens during pregnancy

or loss of testicular tissue from a potential hermaphrodite during develop-

ment (OVERZIER, 1963).

The formation of a phallic urethra in a genetic female is a rare event. The

frequent concomitant finding of septate or duplicated genital structures in-

dicates a failure of the embryonic transverse Mullerian ducts to fuse, but

the mechanism which prevents them from doing so and at the same time induces

the formation of a phallic urethra remains undiscovered. That such phallic

urethrae occur in subjects with only a dimple phallus suggests that the cause

is not hormonal; virilization that occurs early enough to form a phallic

urethra would also be expected to cause elongation of the genital tubercle

to form a penile or hypospadic phallus. From a study of the cases recorded

in the literature it seems probable that whatever the cause, it has variable

penetration, or expression. For example, patients have been reported to

have a cloaca and a second, phallic urethra in a tiny phallus (BROSTER, 1956; SIEBER and KLEIN, 1958); more frequently the ancillary urethra traverses a penile phallus whilst a urogenital sinus opens in the perineal midline (HOWARD and HINMAN, 1951; PAQUIN et al, 1957; REILLY et al, 1958) or, in its extreme form, the urogenital sinus is transmitted to the tip of the phallus (WILLIAMS, 1952). The patient reported by GLEN (1957) had penoscrotal hypospadias and might be regarded as transitional between those with functional phallic urethrae and those with perineal urogenital openings.

The classification of all female intersexes in one syndrome is justified as the range of pathology indicates a graded series. These may be described as either simple, severe or complicated depending upon the extent of the abnormality but no rigid limits can be set: for instance, the patient reported above had mild macrogyria but such a minor defect (and of an extra-genital structure) surely does not mean that this should be classified as 'complicated', together with patients such as those reported by CARPENTIER and POTTER (1959).

Idiopathic female intersexuality is a relatively uncommon problem and in its severe form, rare. WILTON (1969) reported only 6 patients amongst 238 intersexes seen over a 6 year period. Similarly, DINNER (1969) described 15 patients from a six year period. However, because both workers' subjects were selected the figures are of very little use in gauging the incidence of the condition; also, there is the possibility that the two authors mentioned common patients since both cover the same area.

There is little doubt that the patient reported here was an idiopathic intersex: apart from the unique case of adrenogenital syndrome reported in this series (Case 19), the disorder is unknown in the Bantu; there was no evidence of masculinization by any other agent. The case is therefore of considerable

interest because it demonstrates that the Bantu are not immune to this disorder in its severest form. The patient reported here is believed to be the first example of severe idiopathic female intersexuality in a South African.

CHAPTER XIII

HERMAPHRODITISM

                    Introduction
                    Classification
                    Pathology
                    Cytogenetics
                    Aetiology
                    Case reports
                    Discussion

            'For Spirits, when they please
            Can either sex assume, or both;

                 Milton, 'Paradise Lost'
                      Bk. I; line 423.

INTRODUCTION

The combination of both sexes within a single individual is one of the most
exotic abnormalities of man. Such bisexuality, or hermaphroditism, is char-
acterized by the presence of both ovarian and testicular tissue in a person
whose habitus may be masculine, feminine or ambiguous.   A feature of herm-
aphroditism is its multifarious nature and it is correspondingly difficult
to give a 'typical' description of the syndrome. During the past few years
the volume of literature pertaining to this type of intersexuality has in-
creased enormously but fortunately there are several excellent reviews and
summaries (MERRILL and RAMSAY; OVERZIER, 1963; JONES et al; GUINET, 1965).

The coexistence of male and female structures and physical characteristics
has been known for many centuries (cf Chapter III) by various names. More
recently there has been a tendency to refer simply to 'hermaphroditism'
instead of using the adjective 'true'.   This is acceptable because those
previously known as pseudohermaphrodites are now called male or female in-
tersexes and so the word, hermaphrodite, is left for use in describing the
more appropriate individuals.

CLASSIFICATION

There are no distinct syndromes within the hermaphrodite group and the only means of separating them is according to the gonadal disposition. The combinations in which the gonads may occur are known as:

lateral, when an ovary and a contralateral testis are present;
unilateral,when an ovary or testis is subtended by an ovotestis;
bilateral, when both types of gonads are present on both sides.

The term 'ovotestis' is used loosely in the above definitions and it should be remembered that an ovary and a testis may occur separately on the same side or conjoined in an ovotestis. The possible arrangements were detailed by JONES et al; and GUINET (1965).

PATHOLOGY

Hermaphroditism has no absolute or typical appearance because genital structure, habitus and secondary sex features range from almost-male to almost - female. Also, the cytogenetic status of patients is ambiguous; hormonal and biochemical values range between the normal values of both sexes and there are no diagnostic characteristics in the dermatoglyphic, radiographic or other tests. Diagnosis depends on the histological demonstration of both gonadal tissues. This may well be done at birth, although many clinicians are reluctant to submit an infant to surgery and usually postpone gonadal biopsy for a year or longer. In the past it was considered exceptional to diagnose the condition before puberty (YOUNG, 1937*; OVERZIER, 1963) but increased awareness and improved diagnostic methods have begun to reverse this situation (BARREIRO et al, 1969).

Mature patients show clinical signs of hormone activity: some two-thirds of the reported patients had female breasts and in most there was pronounced pubic hair; this was reminiscent of that seen in virilescent females. Less

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* see reference to Young, p34.

commonly, male hair distribution was found. If androgenic stimulation is strong enough, beard growth is also possible. Menstruation has been seen in many cases and in some was the presenting sign (OVERZIER, 1963; GRACE et al, 1970). The appearance of approximately one-third of the patients is feminine; of an equal number, masculine: the remainder were difficult to classify because an otherwise masculine physique was offset by well developed feminine breasts (OVERZIER, 1963).

Gonadal anatomy

When both gonads occur ipsilaterally they may do so in combination, as an ovotestis, or separately as ovary and testis. They usually occupy the normal positions of an ovary or testis, but an ovotestis may occur at any position. There is a single report which provides the exception to the rule that an ovary never descends: a 10 year old Bantu hermaphrodite had a left scrotal ovotestis and a right scrotal ovary (DINNER, 1969; case 'Frans'). Gonads are often ectopic in inguinal herniae and less frequently in the labioscrotal folds.

Ovarian development is said to be more complete in chromatin positive than in chromatin negative individuals because the former group have more numerous primordial follicles, Graafian follicles and corpora lutea (OVERZIER, 1963). The ovary retains its function throughout life, in comparison to the testis which usually atrophies after puberty.

The testis has normal histological appearance only during the early years of life and with the approach of puberty the germinal elements dissappear and the tubules are obliterated. Thus, the few Sertoli cells and spermatogonia which may have been present become lost (OVERZIER, 1963; JONES et al, 1965). In cases with complete testicular maturation spermatogenesis may be complete but there is always severe oligospermia and no hermaphrodite is known to have

fathered a child. Leydig cells, which appear during the third decade of life, gradually increases in number and eventually appear to be hyperplastic. It is interesting that the karyotypic pattern has no influence on testicular structure.

Combined gonads show several peculiarities. The testicular and ovarian zones are generally separated by a fibrous membrane but some show more or less gradual blending of the one into the other; functional follicles and seminiferous tubules have been found side by side (BREWER et al, 1952). In the majority of ovotestes there is a superficial constriction which marks the separation of the two tissues. The close apposition of these conflicting tissues produces interesting changes in their influence on the development of the Mullerian and Wolffian ducts. In a few ovotestes the histological arrangement is so disorgansized that the change to malignacy is but a small one. An unusual case was reported by CHARLEWOOD and FRIEDBERG (1955): a unilateral hermaphrodite had the ovarian and testicular portions of the right gonad arranged longitudinally, with the ovarian zone medially. Normally these zones are polar.

Mullerian and Wolffian ducts

Some 75 percent of hermaphrodites' testes are capable of suppressing Mullerian duct differentiation (JONES et al, 1965) but when the embryonic testis is in combination with ovarian tissue this power is lost: an ovotestis has the same effect as an ovary. Usually both ducts subtend an ovotestis and, exceptionally, a fallopian tube may be adjacent the testis of a unilateral hermaphrodite (SCHWEIBINGER and HODGES; ARMSTRONG, 1955). The specific absence of any Wolffian derivatives was noted in 2 patients (BROMWICH, 1955). In most a vas deferens and epididymis accompany a testis, but only about a third of the ovotestes have these anlage (ASHLEY, 1962).

Uterine differentiation occurs in most hermaphrodites, varying from a small, unspecialized knob of tissue to a normally sized, functional organ which with its associated structures occupies the same position as in the normal female. Very few patients have been reported to lack a uterus and of these, Overzier postulated that the Mullerian tract must be defective. Aberrant forms of uterine development are rare. BALDACHIN and WHITE (1965) reported an infant who had fused fallopian tubes but no uterus. Lateral hypoplasia of the uterus results if the homolateral fallopian tube was suppressed by testicular activity. The uterus, alone or accompanied by the gonad of one side, has occasionally been found in an inguinal hernia. The cause of this movement is unexplained. Normal endometrial activity is proved by the number of hermaphrodites who menstruated regularly (ASHLEY, 1962; OVERZIER, 1963).

Vaginal development ranges from the merest slit in otherwise solid tissue to a normal, functional canal which is adequate for coitus (YOUNG, 1937; LAYCOCK and DAVIES, 1953). Vaginal atresia is uncommon and is probably caused by a failure of the Mullerian tubercle to fuse with the embryonic urogenital sinus.

External genitalia

Embryonic differentiation of the external genitalia is controlled by the prevailing hormones and it is therefore reasonable that hermaphrodites should show such wide variety. Androgens have a much more profound effect on the conformation of the genitalia than do oestrogens and so there is a preponderance of patients with masculinized external genitalia. This is supported by the fact that the patients with the least amount of testicular, and so androgen producing tissue, the unilateral hermaphrodites with ovary and ovotestis, are more frequently interpreted to be females. JONES (1968) found that of 16 such patients, half were reared as females; by contrast, the other groups in which there was more testicular tissue showed a marked predominance of 'males'.

Although all 5 urogenital types are found in hermaphrodites, the majority are of types III and IV. Very infrequent subjects with separate perineal openings for the urethra and vagina (type I) are known (FRIEDBERG and ROSENBERG, 1965; HEFELFINGER et al, 1969). Commonly the pudenda consist of a large, erectile, penile phallus with glans and prepuce, and bound down by chordae. On closer inspection a single meatus is found at some station at or below the base of the phallus, which is invariably hypospadic in all except the rare type V arrangement. Enlarged labioscrotal folds, with more or less midline fusion, create the impression of an empty, bifid scrotum: this is enhanced if there should be a single descended gonad. From the subjects for whom cytogenetic data were obtained it is evident that the genital appearance is independent of karyotype. Patients reported by, amongst others, GUINET et al, (1965) illustrate this point.

Endocrine patterns

The patterns shown by hormone assays are equivocal. In part this may be due to the incomparability of laboratory techniques (ZANDER and HENNING, 1963) but nevertheless, the frequent finding of normal amounts of androgens and oestrogens in hermaphrodites suggests that this is a true reflection of the situation (DE ASSIS et al, 1960). Obviously the hormone levels vary according to the gonadal disposition. Urinary excretion of 17-oxosteroids in a number of patients was within, or just below, the normal range of males and females (ZANDER and HENNING, 1963; HIRSCHOWITZ, 1969). In the prepubertal hermaphrodite, as in normal children, the total output of 17-oxosteroids is from the adrenal cortices and so the levels are normal. It has been shown that postpubertal excretion may be normal (STROMME, 1948; MERRILL and RAMSEY 1963) and that at least some of the postpubertal production is in the gonads since a decrease followed castration (WEED et al, 1947). In others the gonads did not contribute 17-oxosteroids: a patient reported by HUNGERFORD et al (1959) had low levels both before and after castration.

The data concerning pituitary gonadotrophin metabolism is very limited. On the basis of 15 observations Overzier wrote that FSH excretion was normal or slightly raised. Other reports have confirmed this.

Generally the non-sex endocrine glands funtion normally (OVERZIER, 1963).

Psychosexual orientation

When seen at birth a small phallus is usually interpreted to be a small penis rather than a large clitoris. This probably explains the fact that the majority of hermaphrodites are reared as males. OVERZIER (1963) recorded that of 24 patients with urogenital types III or IV, and none with type V, had been raised as females, compared to 90 who were regarded as males. Of types I and II, only 5 of 23 patients were raised as males.

Subsequent agreement between assigned and psychological sex following this somewhat arbitrary method of sexing by genital appearance at birth was, in most cases, good. Overzier found that only 15 percent of the cases that he had researched were dissatisfied, being 5 patients reared as females who felt that they should have been males. In a few instance the legal sex was changed during childhood from female to male (CANTEY, 1953).

The social and sexual roles assumed by hermaphrodites are usually concordant with the assigned sex. Many have been reported to enjoy reasonable sexual relationships with normal partners, performing as males (ATAKAM, 1954; ZACH-ARIAE, 1955; GRACE et al, 1970) or females (MALASHAK, 1954; BEARZI et al, 1955). In some exotic cases it was said that the hermaphrodite excercised either role as the fancy took him; or her! Several such cases were recalled by YOUNG (1937). As some form of heterosexual relationship is possible, the hermaphrodites may marry and enjoy reasonably normal lives. Personality changes are not severe; reticence and introversion were mentioned, but

intelligence is of at least normal level (OVERZIER, 1963).

CYTOGENETICS

Cytogenetic observations have not been able to explain the cause of herma-
phroditism in more than a few cases. For an obscure reason the overwhelming
majority of patients who were investigated cytogenetically had an apparently
normal female karyotype. A much smaller group, probably not much more than
5 percent of the total, had mosaicism of XX and XY cell lines. Several other
karyotype variations have been reported in hermaphroditism but none in suffic-
ient numbers to even question the status of the 46,XX pattern as the 'usual'.
The 46,XY combination is rare in hermaphrodites (GRUMBACH et al; SANDBERG et
al, 1960). Apart from the mosaic which might be expected to occur in herm-
aphrodites, the XX/XY, a number of others such as XX/XXY (TURPIN et al 1962)
and XX/XXX (FERGUSON-SMITH et al, 1960b) are known to occur. Several with
three cell lines have been reported: X/XX/XY (SCHUSTER and MOTALSKY, 1962);
XX/XY/XXY (RIBAS-MUNDO and PRATS, 1965); and XX/XXY/XXYYY (FRACCARO et al,
1962b), as examples. The correspondence of karyotypes with variations of
phenotype was reviewed by GUINET et al, (1965).

The origin of mosaics is intriguing. A few were proved to be due to super-
fecundation, in which the 2 post-meiotic (and thus genetically identical)
nuclei of an ovum were each fertilized, one by an X- and one by a Y-bearing
sperm, to form an XX/XY mosaic zygote (GIBLETT et al, 1963; JOSSO et al,
1965). Such double fertilization might be expected to occur more frequently
because binucleate ova are known to occur, albeit infrequently, in normal
women. They were found 'with great regularity' in neonatal and infantile
ovaries (BACSICH, 1949) but were rare in adult ovaries (HARTMAN, 1926). In
a search of 900 oocytes taken from several normal women, 2 binucleate ones
were found (KENNEDY and DONAHUE, 1969): the authors suggested that these
ova could be ovulated in the normal way. Binucleated ova are said to occur

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more frequently following gonadotrophic therapy (G.S. JONES, 1968).

FORD (1963) was dubious of the theory of double fertilization and favoured somatic non-disjunction as the cause of mosaicism. That he was not entirely correct was shown by JOSSO et al, (1965), although somatic non-disjunction is certainly a factor in the origin of some mosaics.

<u>AETIOLOGY</u>

There are many unexplained factors in the aetiology of hermaphroditism; perhaps more so than in any other syndrome, and a number of theories have been proposed to explain some of these mechanisms. Undetected mosaicism is always a possibility but this seems unlikely to be the case in so many patients with the XX karyotype: extensive searches by many investigators have met with but little success. BROGGER and AAGENAES (1964) found XY cells only in their patient's right gonad, all other tissues being XX. A patient reported by MANUEL et al, (1965) had XX skin cells and XX/XY mixture in the lymphocytes. Chimaerism might account for similar mixtures; this is known to occur frequently in cattle (see pp16 -17).

To explain the XX karyotype another theory hypothesized the translocation of a small paracentric fragment of the Y chromosome on to the X (FERGUSON-SMITH 1966). This theory is very attractive and a similar event might be involved in the origin of the XX males (see Chapter VIII). There is little doubt that the male determinants are located on the Y chromosome, probably near the centromere (JACOBS, 1969; GRACE and HARRIS, 1970), which is demonstrated by the fact that masculinization occurs even when only a small centric fragment of the Y chromosome remains (VAHARU et al, 1961; FRACCARO et al, 1962). But, attractive as this theory of a submicroscopic translocation may be, there is the report by ROSENBERG et al, (1963) of 3 hermaphroditic siblings with the XX karyotype. To invoke such a translocation in each case is presuming too

much, unless the father himself was t(Y-X+). The father, however, had an apparently normal chromosome complement.

Another perplexing fact is that not all subjects with the XX/XY karyotype are hermaphrodites. The phenotypic diversity shown by such mosaic individuals was very well demonstrated in an article by JACKSON and MARINE (1970).

CASE   REPORTS

Case 26   (Bilateral hermaphrodite)

A Zulu male aged 18 years presented at hospital complaining of haematuria and pain in the lower abdomen, both of 2 days' duration.

The patient, M.M., was of slender build with feminine features and soft voice. There was bilateral gynaecomastia (Fig. 55); breast development was good and the nipples were large. The external genitalia were ambiguous (Fig. 56). The phallus measured 6.5 cm in length and 2.5 cm in diameter; it was penile with a prominent prepuce and glans. There was extensive chordee which caused ventral curvature of the organ and also caused it to obscure the hypospadic urogenital meatus located near the base. The scrotolabial folds were flat, empty and rugose. No gonads could be palpated in the perineal, inguinal or abdominal areas. Anterior to the anus the perineum was pliant and did not resist pressure: this was thought to be suggestive of a hidden vagina. Rectal palpation detected a cervix but no prostatic tissue was felt. There was a tender cystic mass in the right iliac fossa. Secondary sex characteristics were feminine: no beard growth had occurred; axillary and pubic hair was sparse, pelvic contours were feminine and mammary development was prominent.

The presenting symptoms resolved spontaneously after 3 days but recurred 4 weeks later. This suggested that the haematuric incidents were actually the menarche and second menstrual periods.

Psychiatric evaluation confirmed that the patient was, and always had been, male orientated. He was raised as a boy and worked as a man; he had attempted sexual intercourse with his girlfriend. The patient's single complaint regarding his odd habitus was that his erections were inadequate.

Karyotype analysis revealed a mixed lymphocyte population, of 46,XX and 46,XY cell lines, equally represented (Fig. 57a,b). Sex chromatin was seen in 20 percent of buccal mucosal nuclei. Intravenous pyelography showed kidneys and ureters to be normal but the bladder shadow had a superior indentation which suggested a uterus. This was confirmed on a sinogram: a shallow urogenital sinus, vagina, uterus and tubes were outlined (Fig. 58). An imperforate hymen was seen by cystoscopy.

Urinary excretion of 17-oxo- and 17-oxy-steroids was 3.6 mg and 2.5 mg per

day, respectively. These values were lower than the normal male range. FSH excretion was 12 mu per day. Haematological and extensive serological investigations failed to detect any unusual patterns which might have indicated double fertilization.

One week after the second menstrual episode surgical removal of a uterus, vagina and adnexae with both gonads was done. The excised tissues (Fig. 59) consisted of the upper portion of vagina, hypoplastic cervix; a large uterus with bilateral fallopian tubes; bilateral gonads, each at the site of the normal ovary, and each with an equatorial constriction.

Histological examination of the tissues revealed that the vagina was normal; the cervix was hypoplastic and had bilateral Gartner's ducts; the uterine corpus was normal and the endometrium, which was autolytic, appeared to be proliferative. The fallopian tubes were normal and had fimbriated ostia. A thick, fibrous tunic enclosed each gonad; both were ovotestes with atrophic testicular poles and, in the left, fibrosis. A number of Graafian follicles, corpora albicantes and an ovarian cyst were seen. There was a single corpus luteum in the left ovary. All tissues were heavily infected with calcified bilharzia (Schistosomum sp) ova. Sections of ovary and testis are shown in Fig. 60.

It was concluded that this patient, a bilateral hermaphrodite, was normally orientated as a male and in spite of his abnormal habitus he was only motivated to seek medical advice when 'haematuria' commenced. There was no doubt that the haematuria was in fact menstrual bleeding: the presence of bilharzia ova was of no significance because all were calcified and the patient was asymptomatic.

Case 27   (? hermaphrodite)

A newborn Bantu, Baby M, was seen to have ambiguous genitalia at birth. The infant was delivered of a 26 year old mother who had had two previous pregnancies which produced dizygous twins and a normal female. The twins had died during the neonatal period from an unknown cause. There was no relevant history.

At birth the patient weighed 2260 G and measured 29.2 cm from crown to rump. The Apgar score was 10/10. Armspan was 38 cm and chest circumference, 24.4 cm; head circumference was not recorded. The genitalia consisted of a penile phallus 2.5 cm long and 1.5 cm thick. It was held down by chordae and obscured a single meatus which opened at its base. Swollen labioscrotal folds surrounded the base of the phallus (Fig. 61); they were rugose and resembled an empty bifid scrotum. No gonads could be palpated but on Day 8 the right gonad descended into the scrotal sac.

Lymphocyte karyotypes were all 46,XX and the sex chromatin count was 17 per centum. The main palmar flexion creases were normal. Urinary excretion of 17-oxosteroids was normal, at 0.2 mg per day. A sinogram outlined a normal bladder and a structure which was thought to be a uterus (Fig. 62) but there was no obvious connection between them.

The possible diagnoses were hermaphroditism, idiopathic female intersex or induced masculinization. Adrenal hyperplasia was excluded by the low excretion of 17-steroids. That a gonad descended to the scrotal sac indicated the presence of testicular tissue: there was no evidence that there had been any exogenous cause of masculinization, and in any event, that would

not have induced descensus of an ovary. Thus hermaphroditism was the diagnosis of choice. The baby was discharged and was seen again at the age of 8 months but medical opinion was then still against doing a gonadal biopsy and the infant remains undiagnosed.

Case 28   (? hermaphrodite)

An 8 month old Bantu, Baby N, was seen in hospital for elucidation of its sex. No details of the family history were available, other than that the parents regarded the infant as a girl and had expressed their desire to rear it accordingly.

On admission the infant was healthy, well nourished and active. There were no abnormalities other than the epicene genitalia (Fig. 63). The genitalia consisted of a large, penile phallus 2 cm in length and 1.5 cm in diameter. There was a well developed glans and prepuce; chordee was severe. A single hypospadic meatus was located at the base of the phallus (Fig. 64). Raised labial folds surrounded the phallus, and both labial structures could be identified. There was no perineal raphe and no gonads could be palpated.

The genetic sex was female: all karyotypes were 46,XX (Fig. 65) and the sex chromatin count was 48 percent. Both palms had normal flexion creases. Urinary excretion of 17-oxosteroids was normal at 1.2 mg per day. Contrast radiographs showed a normal urinary tract and uterus but failed to outline any connection between these systems.

In keeping with the parents' wishes, the phallus was amputated and the infant was discharged. The final diagnosis remains obscure because surgeons were not prepared to do gonadal biopsy. The possible results of this will depend upon whether or not the infant is a hermaphrodite or idiopathic female intersex.

Case 29   (? hermaphrodite)

A newborn white, Baby E, was seen to have epicene genitalia at birth. The patient was the second child born to a 30 year old mother; the parents were unrelated and there was no contributory family history.

On examination the baby weighed 2640 G and measured 31.5 cm from crown to rump. Except for the anomalous genitalia there were no other abnormalities. The phallus was penile with marked ventral curvature. It was approximately 1.2 cm long and 1 cm thick (Fig. 66), with glans and prepuce. There was a single opening at the base of the phallus (Fig. 67). Bilateral labioscrotal folds were present; they were rugose but there was no perineal raphe. No gonad could be palpated on the right; the left gonad was high in the inguinal canal.

There was mosaicism of XX and XY cell lines in equal proportions. The sex chromatin count was 8 percent. The main palmar flexion creases were normal.

Further investigations were postponed until the infant was 18 months old and consequently no diagnosis can be made. In view of the equivocal karyotype, a number of possible syndromes have to be considered: hermaphroditism; male intersex; asymmetrical gonadal differentiation, to mention a few.

PLATE   XIV

Case   26

Fig. 55: Breast development in a
hermaphrodite.

Fig. 56: Ambiguous external genitalia
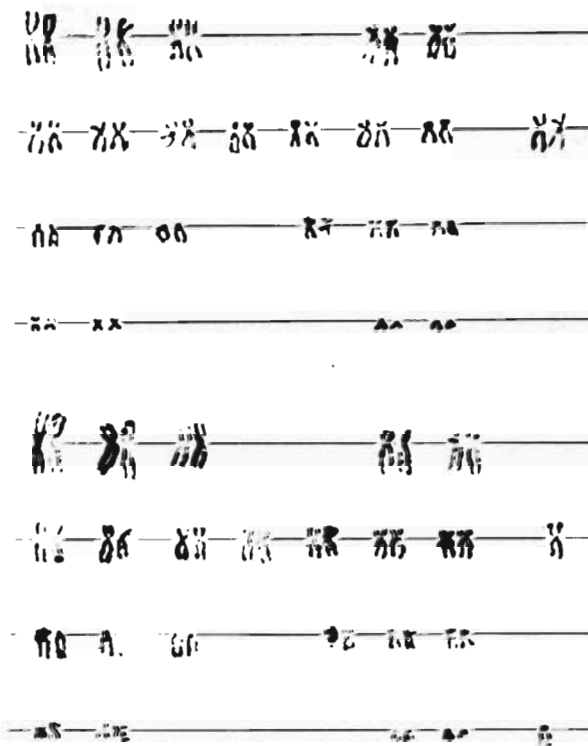
Fig. 57: Mosaic karyotype of (a) 46,XX and
(b) 46,XY cell lines.

PLATE   XV

Case 26
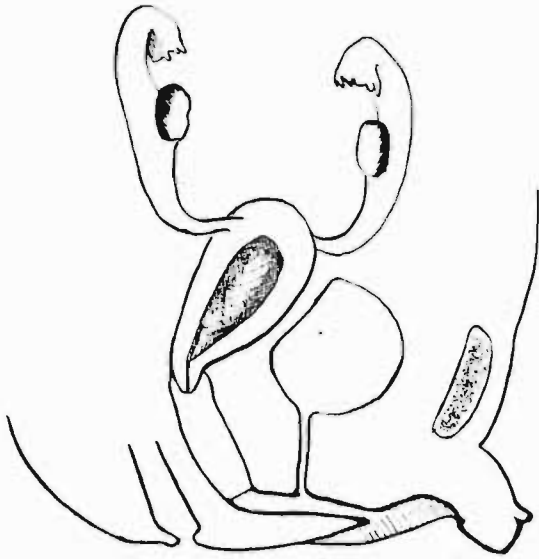
Fig. 58: Disposition of urogenital
structures.
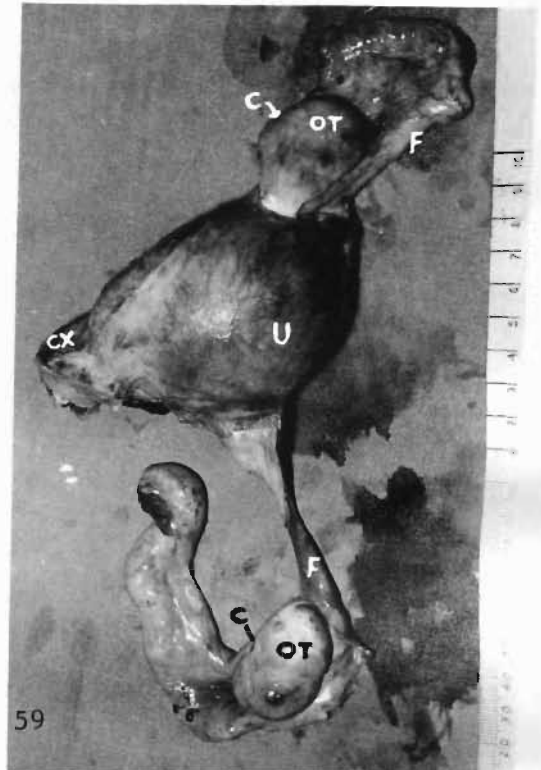
Fig. 60

Fig. 59: Organs removed at laparotomy: large uterus (U), cervix (CX), tubes (F)
and bilateral ovotestes (OT) with equatorial constrictions (C).

Fig. 60: Histology of (a) ovarian zone, showing corpus luteum (CL); and (b)
testicular zone with atrophic tubules (T) showing gross hyalinization
of the basement membranes (M); also interstitial cell hypoplasia.
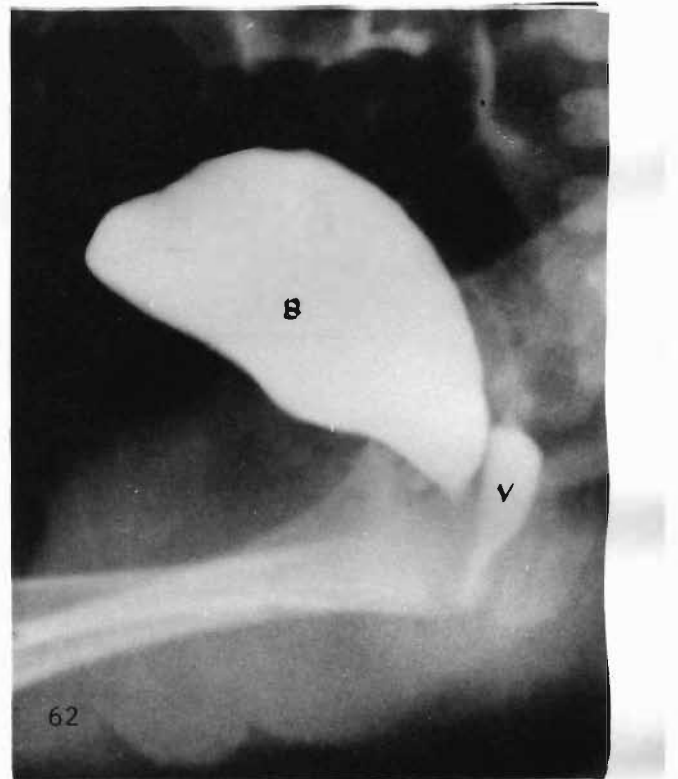
PLATE XVI

Fig. 61: Case 27, epicene genitalia. Note right scrotal gonad.

Fig. 62: Case 27, cystogram with bladder (B) and vagina (V) shadowed.

Fig. 63: Case 28, ambiguous genitalia with well-defined labial structures.

Fig. 64: Case 28, showing hypospadic urogenital meatus.

PLATE XVI

Fig. 61: Case 27, epicene genitalia. Note right scrotal gonad.

Fig, 62: Case 27, cystogram with bladder (B) and vagina (V) shadowed.

Fig. 63: Case 28, ambiguous genitalia with well-defined labial structures.

Fig, 64: Case 28, showing hypospadic urogenital meatus.

PLATE   XVII
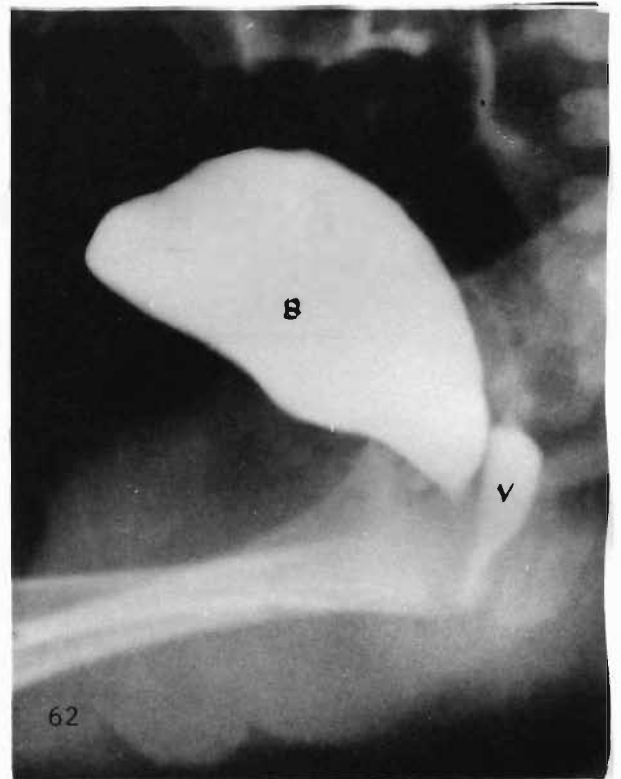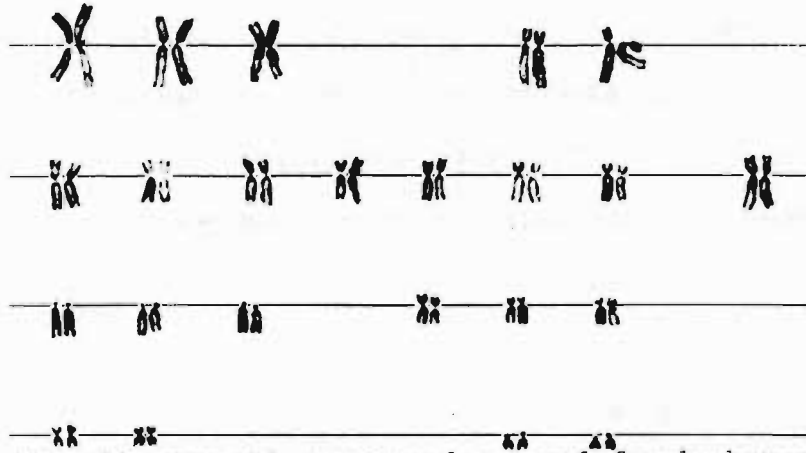
Fig. 66: Case 28, apparently normal female karyotype
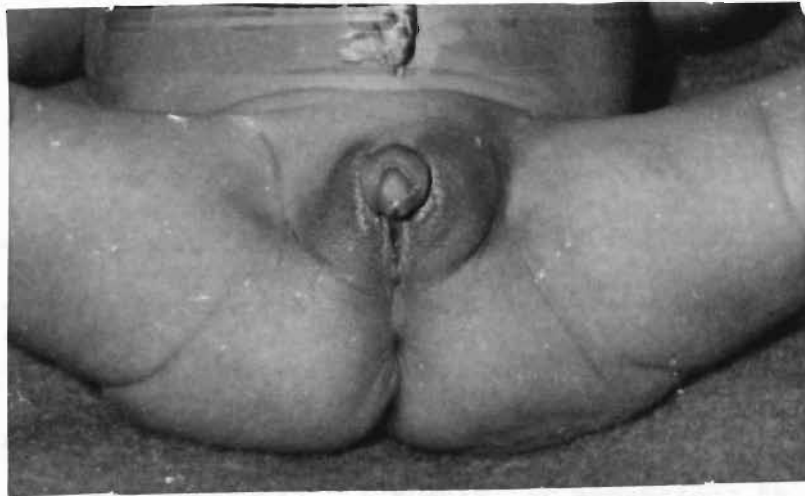
Fig. 66: Case 29, intersexual genitalia.
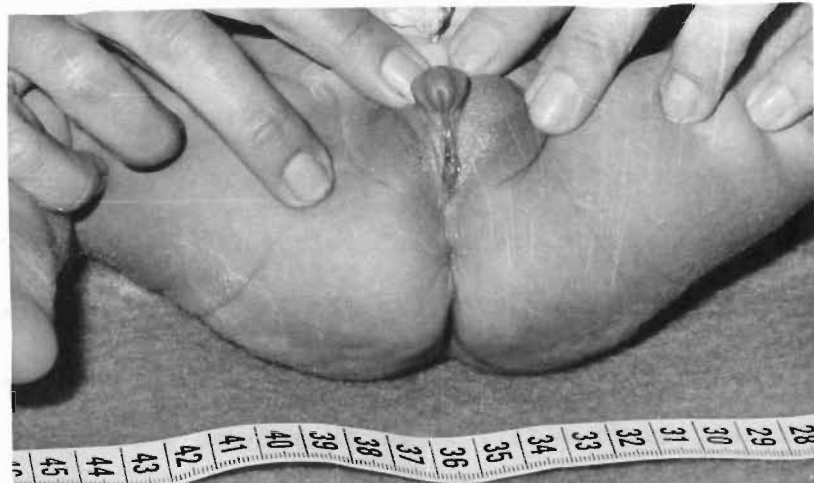
Fig. 67: Case 29, showing hypospadic urogenital
meatus. Left gonad is in the inguinal
hernia.

DISCUSSION

Since time immemorial the origin and significance of the 'hermaphrodite' has

taxed the minds and imagination of men. The ancients of classical Greek and

Roman times have left us their theories (see pp20-26) but as they did not

distinguish between real hermaphroditism and other forms of intersexuality,

those opinions must, unfortunately, be disregarded here!

Present understanding of the origin of the hermaphroditic state is more com-

plete but there remain several significant gaps in our knowledge. No proof

has yet explained the mechanism whereby an apparently normal female karyotype

causes hermaphroditism; this, and the apparent non-conformity between karyo-

type, phenotype and gonadal disposition, is an intriguing feature of the syn-

drome. It has been shown that any of the six possible combinations of gonads

(JONES et al, 1965) can occur with any karyotype (GUINET; GUINET et al, 1965).

Similarly the outward appearance of the genitalia has no apparent correlation

with either karyotype or gonadal pattern, except that those who have less

testicular tissue are more likely to be of urogenital type I and thus will be

reared as females (OVERZIER, 1963). A number of exceptions to that general

rule have, however, been recorded. It is also particularly interesting to

note that the sex chromatin pattern may or may not be positive in subjects

with similar karyotypes: even those with the XX/XY or XX patterns (presume-

ably determined from lymphocyte karyotypes) are not necessarily chromatin

positive (OVERZIER, 1963). Overzier laid great stress on the result of the

sex chromatin test and subdivided his patients accordingly. A number of

others have followed this practice (for example, KLEMPMAN, 1964; WILTON,

1969), which is surprizing because it is of little or no practical value. In

this and other syndromes individuals with similar karotypic and phenotypical

features can have different chromatin patterns (editorial, S. Afr. Med. J.,

1968). This contention, that the sex chromatin pattern is of little more

than academic value, is reflected in Overzier's own words: '..the results

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have been dissappointing'.

Because of these variables it was impractical to attempt subdivision of the hermaphrodites and so the classification is simple and uncontentious. Diagnosis too is relatively straightforward: having eliminated such possibilities as adrenal cortical hyperplasia, induced masculinization or idiopathic female intersexuality, then the diagnosis rests upon histological demonstration of both types of gonadal tissue. It must be emphasized that although a reasonable assumption may be made when an XX individual has ambiguous genitalia and a descended gonad, histological proof is still required. With a karyotype such as the highly suspicious XX/XY mosaic histological examination of the gonads is essential.

The predominance of psychological attitudes, induced by the sex of rearing, over the somatic sex features is again clearly demonstrated by the hermaphrodites. Despite such prominent contrasexual attributes as breasts and very imperfect genitalia, a hermaphrodite reared as a male will almost invariably behave and function as one. However, this does not imply that correction of genital anomalies is not warranted: on the contrary, it is extremely important that the individual should be given, by surgical or other means, as near normal habitus as possible. It has been emphasized on numerous occasions by many authorities that sex awareness and gender identification are established very early in life; certainly before the age of 3 years (WATSON and LOWREY, 1967), so it is imperative that any decisions relating to sex determination be taken before the subject becomes aware of his abnormalities. This point leads to two unfortunate features of the local situation.

There is a very poor follow-up response amongst all races: this is demonstrated adequately by some of the cases reported here (Cases 27, 28, 29) where in each instance the parents were instructed to return their infant when it

was 18 months old. Despite the fact that the necessity for gonadal biopsy was explained to them, none has yet returned. One wonders what will befall the patient when 'he' or 'she' reaches childhood and is exposed to the ridicule which only children are capable of;   and what distress the individual will suffer at puberty.

It is widely known that attendance for follow-up is poor but nevertheless, medical personnel are very reluctant to submit these infants to surgery. The common reason for this is that the consequences of the intersexual deformity are potentially less dangerous than those of operation.

A further example of the inherent dislike of hospitalization was shown by the patient reported as Case 26. This hermaphrodite submitted to surgery for removal of contrasexual organs and gonadectomy;   during the same operation surgical repair of the hypospadic phallus was undertaken. The patient was discharged after an uneventful recovery and was instructed to come back after 6 months for bilateral mastectomy. Nearly two years have passed and he has still not returned.

This series

Case 26 was in most respects a typical hermaphrodite;   the most outstanding feature was the unusual nature of the presenting symptoms. Comment has been made already on the fact that a person such as this patient, with such an unusual habitus, can go for so long without seeking medical advice. One wonders i this is due to the fear of ridicule, or painful treatment, or just the belief that there is nothing that can be done. A Bantu patient reported on by HAMMAR and FORBES (1965) believed himself to have been bewitched and so did not seek assistance until haemturia (menstrual origin) and urinary incontinence occurred.

The remaining 3 patients presented in this section could not be diagnosed accurately because no gonadal biopsies were done. They were nevertheless included here because th y illustrate the problems of differential diagnosis and also serve to emphasize the need for complete diagnosis to be made in infancy. It is very probable that unless this is done the patients will not return at the recommended time and that when they do eventually seek further attention it will be too late to correct the sexual ambiguity without causing serious psychological trauma to the individual.

The problems relating to the incidence and racial prevalence of hermaphroditism are discussed at length in Chapter XV.

CHAPTER XIV

'PSEUDO-INTERSEX' CONDITIONS

Introduction
Common defects
Case reports
Discussion

INTRODUCTION

The definition of intersexuality stipulates a discrepancy between any one or more of the parameters by which sex is assessed, with particular attention being given the genetic, gonadal, genital and somatic sex attributes. In a number of individuals a small defect occurs and it is therefore necessary to decide the extent of deformity required to qualify as intersexual. An argument was presented earlier (Chapter XI) in respect of male intersexes for regarding males with simple penile hypospadias as 'not intersexual'. There is more difficulty in delineating between intersexes and those females with simple developmental defects. As ASHLEY (1962) pointed out, Wolffian remnants in the female are so much smaller and correspondingly less prominent that they tend to be overlooked. Also, to search for such structure as the ducts of Gartner would entail major pelvic surgery, which is not justified. For the present, females with single defects, without evidence of masculinization, will be regarded as 'not intersexual' and are considered in this section. There are a number of possible causes for the defects which are described here; some of these are considered below.

METABOLIC DISTURBANCES

An intrinsic metabolic defect can occur in either sex and result in retarded sex differentiation or development. WILKINS (1965) presented an extensive discussion of metabolic defects, for instance, hypopituitarism, hypothalamic lesions, etc. In the male gynaecomastia may result from a failure of the

liver to conjugate circulating oestrogens for excretion in the urine; this may occur during infection, or if liver damage is caused by siderosis or cirrhosis, both common disorders in sections of the local population.

PENILE DEFECTS

Developmental defects of the penis are very common. Hypospadias is seen most frequently; epispadias is very infrequent (HASCHE-KLUNDER, 1963) and other defects such as congenital torsion (SCHWART and FARR, 1957) or absence of the penis (HALLER et al, 1957), or transposition of the penis and scrotum (MAJUMDAR et al, 1968) are all very rare.

TESTICULAR DEFECTS

Various defects of testicular development can occur. Of these cryptorchidism is the commonest problem (COUR-PALAIS, 1966). Secondary testicular atrophic conditions may be due to focal ischaemia or interference by mechanincal or chemical agents during foetal life; this may result in complete resorbtion of the gonad. In such patients the adnexae usually remain to indicate that a testis was, at one time, present. If both testes are involved the patient will not virilize at puberty and the extent of genital masculinization is dependent upon the time at which the testes were ablated (ABEYARATNE et al 1969).

VAGINAL DEFECTS

Atresia of the vagina is due to a failure of the Mullerian tubercle to fuse with the wall of the urogenital sinus. This is the commonest developmental defect of the female genitalia. Vaginal aplasia, due to failure of the uterovaginal cord to canalize, is less common. Female hypospadias, in which the urethra opens into the anterior vaginal wall is very uncommon, possibly because it usually is hardly noticeable (HASCHE-KLUNDER, 1963).

SOMATIC DEFECTS

A few otherwise normal individuals may lack one of the features regarded as evidence of secondary sex development; for example, beard growth in males and mammary enlargement in females.

CASE REPORTS

Case 30   (glandular hypospadias)

A newborn Bantu had simple glandular hypospadias but was normal in all other respects. The karyotype was apparently normal (46,XY).

Case 31   (Coronal hypospadias)

An Indian neonate had hypospadias at the level of the corona. The penis was small, 20 mm long and 8 mm in diameter, with severe chordee (Fig. 68). He was normal in all other respects. The karyotype was normal.

Case 32   (Penile hypospadias)

A Bantu neonate had microphallus and the urethra was hypospadic at the mid-shaft level (Fig.69). There were no extra-genital abnormalities and the karyotype was apparently normal.

Case 33   (Vaginal aplasia)

An Indian baby was admitted to hospital for examination 'because she had no anus'. The baby was born at home without medical assistance.

On admission to hospital she was aged one day. She was cold, cyanotic and unresponsive; she died aged 48 hours. Examination showed that the anus was in fact normal: the urethral meatus, clitoris and labia were present but no vaginal orifice was seen.

Post mortem examination showed that the infant was premature, weighing only 1700 G at birth, and was microcephalic: head circumference was 26.7 cm. The internal genitalia were seen to consist of normally appearing gonads and tubes and the uterus was present. There was no obvious vagina. Histological exam-ination showed the cervix uteri to communicate with a narrow slit in otherwise solid tissue; this was lined by pseudostratified epithelium and was thought to represent the upper pole of the vaginal cord (Fig. 70).

Case 34   (Imperforate vagina)

A 16 year old Bantu complained of amenorrhoea. Her build was normal, with good breast development. Rectal palpation detected a normally sized uterus and cervix. The external genitalia were normal (Fig. 71) but the vagina was closed by a persistent membrane.

PLATE XVIII

Fig. 68: Case 31, coronal hypospadias

Fig. 69: Case 32, penile hypospadias
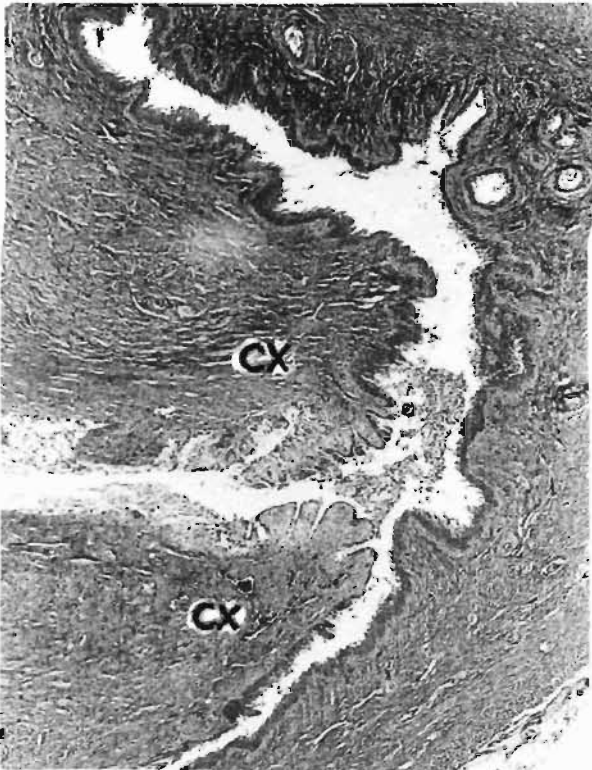
Fig. 70: Case 33, section through
        cervical (CX) area; vagina
        is atretic.

Fig. 71: Case 34, imperforate vaginal
        meatus is shown (M).

DISCUSSION

The causes of the minor abnormalities of genital development are largely matters of speculation. With some disorders, for example, hypospadias, there may be a family history but there is no indication that this is inherited in a Mendelian fashion (HASCHE-KLUNDER, 1963). None of the defects included in this group are known to have any chromosomal abnormality in their aetiology; teratogens or nutritional deficiencies in a localized area are more probable causative factors.

Although these disorders are, by definition, not truly intersexual, their occurrence must be acknowledged because every person with defective genitalia must be regarded as a potential intersex until investigations have shown otherwise.

THE   INCIDENCE   AND   PREVALENCE
OF   INTERSEXUALITY   IN   DURBAN

Introduction
The Durban Population
Vital Statistics
Sampling methods
Incidence
Prevalence
Discussion

INTRODUCTION

The purpose of the present study was to estimate the incidence and preval-
ence of intersexual disorders in four separate communities, determined by
race. Durban was considered to be an ideal area for such a study because
each of the races is represented and, with the exception of the Coloureds,
by substantial numbers.

No similar survey has been reported from South Africa and so this is the
first attempt to establish the actual figures: for many years there have
been a number of beliefs and opinions relating to the occurrence of inter-
sex in the diverse race groups, but none has yet been substantiated by a
direct investigation.

THE   DURBAN   POPULATION

The Durban metropolitan area is defined as extending from Amanzimtoti in
the south to Umhlanga in the north, and from the sea to Hillcrest in the
west; all areas inclusive. This is an area of some 400 square miles and
which, according to the mid-year projections for 1969, includes approxim-
ately 958,000 people of the four major race groups*. The four races make

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* kindly supplied by the City Planning Division of the Durban Corporation

up almost the entire population and so the minute percentage of Chinese

and other minority communities are not considered in the following pages.

A break-down of the population into the percentage in each decade by race

and sex is shown in Table IX. It is evident from this table that the birth

TABLE   IX

The Durban Population, analyzed by
Race,   Age   and   Sex

age in decades	Whites M	Whites F	sex ratios Indians M	Indians F	Coloureds M	Coloureds F	Bantu M	Bantu F
15 -	*34	32	45	45	45	47	41	42
25 -	51	49	67	67	64	66	60	61
35 -	65	63	80	81	77	79	75	76
45 -	78	76	89	90	86	88	86	87
55 -	89	88	96	95	94	95	93	94
65 -	96	96	99	98	98	99	97	98
Total	267,000		316,000		41,500		334,000	
%	27.85		32.96		4.32		34.84	

* cumulative percentages

rate of the three non-white groups is higher than the whites, there be-

ing at least 10 percent more children in the first age group of Indians,

Coloureds and Bantu. This is confirmed by the estimated growth rates of

3.0; 4.26; 3.67 and 4.97 percent for the four groups, respectively.

VITAL   STATISTICS

Vital statistics, for the present purposes, are concerned only with birth

data since morbidity and death rates have no effect on the inferences drawn

from this study. During the survey no abortuses or stillbirths were insp-

ected specifically for signs of intersexuality so that the overall figures

must be adjusted to account only for live births. Accordingly, the crude

and corrected birth data and the sex ratios are shown in Table X.

TABLE   X

Crude and Corrected Birth Statistics
from Four Maternity Departments
Surveyed during 1969

Race	Crude Total	Male	Female	*SB	Correct Total
Whites	2 546	1337	1209	29	2517
Indians	3 239	1606	1633	136	3103
Coloureds	1 344	680	664	34	1310
Bantu	14 469	7274	7195	712	13757
Totals	21,598	10897	10701	911	20687

*SB   stillbirths

Factors which influence these figures must be considered at this point.   An unknown number of births, particularly of Bantu and Indians, occur in areas which are remote from Registrars of Births and Deaths, and certainly never are seen in hospital. By contrast, it may be safely assumed that the few white births which do take place in outlying areas are registered. In order to try to avoid discrepancies in calculations, because these could easily result from using population statistics projected from a census taken ten years ago, it was decided that in this study incidence should be calculated only on the number of infants born in hospitals covered by this survey.

SAMPLING   METHODS

The machinery necessary for a controlled population study; establishing population limits, selecting random samples and also providing adequate controls, is not available in Durban. Assuming that it were, a vast number of subjects would have to be screened in order to obtain useful data because the prevalence of intersex appears to be very low. For this reason and that mentioned above, that the population figures currently available are open to doubt, it was decided to study a total population of neonates.

Four hospital maternity departments were chosen to supply the study population. At the outset some 13000 Bantu, 3000 Indian, 2000 white and 1000 Coloured births were anticipated during the year, and this expectation was realized (Table X). The maternity departments included in the survey were at the King Edward Hospital, which caters for most of the Bantu and Indian confinements in the Durban area; Addington Hospital, in which a large proportion of Coloured births and about 1000 white births are accomplished per year, and a private hospital which caters for approximately 1000 white confinements annually. This choice had no marked selective effect on the Bantu because their socio-economic stratification is not very great. There was no great selective pressure on the Coloureds either because their department is used by all social ranks and handles some 60 percent of Coloured confinements each year. However, in respect of the whites and Indians a certain amount of selection was inevitable because many of the wealthier classes are precluded, either from choice or by regulation, from using the facilities at the hospitals concerned. No attempt was made to correct for this discrepancy between the social and economic status of the groups because there is no evidence to suggest that these factors have any influence over the occurrence of intersexuality; irrespective of the sampling method, the numbers involved were large enough to offset any bias.

Prevalence of intersexual disorders in Durban was gauged from the numbers of new patients referred to the author during the year. It should be noted that patients drawn from outside of the Durban metropolitan area, or who were seen before 1969, were not included in the calculations.

INCIDENCE

During the year of study, 1969, a total of 20,687 live births were recorded at the four maternity departments. Of these only 7 were seen to have frank anomalies suggestive of intersex; these are detailed in Table XI and except

for one with simple penile hypospadias, all are reported in the text (see cases 25, 27, 29-32).

TABLE XI

Analysis of Infants with Disorders of Sex Development

Diagnosis	No.	W	B	I	K
? Hermaphrodite	2	1	1		
Idiopathic female intersex	1		1		
Hypospadias	4		3	1	
Totals	7	1	5	1	0

The numbers recorded were too low to permit any detailed statistical analysis.

PREVALENCE

The prevalence of intersexuality among the four race groups was assessed on the basis of 17 patients, all Durban residents, who were seen for the first time during 1969. This group is detailed in Table XII.

TABLE XII

Prevalence of Intersex in the Durban Population

Diagnosis	No.	W	B	I	K
Hermaphrodite	1		1		
? hermaphrodite	1		1		
Male intersex:					
andromorphic	1			1	
Primary hypogonadism	3	1	2		
Female intersex:					
induced virilization	2	1	1		
adrenogenital synd.	1		1		
gonadal dysgenesis	5	1	2	2	
Male hypospadias	2	1	1		
Vaginal defect	1			1	
Total	17	4	9	4	0

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DISCUSSION

Durban was considered to be an ideal area in which to conduct an investiga-
tion such as this because the four races are all represented and only the
Coloured community is numerically very much smaller than the others. Also
the major proportion of all births occurs in two easily accessible hospitals
which between them cater for all races, and so a large study population was
available. In the sample populations of whites and Indians there was some
degree of social and economic selection which favoured the lower-incomes:
this loading was not thought to have any possible aetiological significance.

Before discussing the results it is necessary to consider some factors that
might influence the conclusions.

The incidence at birth of certain types of intersex could not be calculated
here because there are, at present, no suitable techniques for their rapid
identification: universal screening even by the sex chromatin test would
have been impracticable. It was estimated that to have done so in this in-
vestigation, the examination of slides alon would have required the services
of two technicians. None were available.

None of the races are particularly eager to present themselves for investi-
gation of intersexual problems, but this is complicated by racial idiosyn-
chrasies: for instance, the Bantu male does not seem unduly perturbed by
gynaecomastia unless there is some concomitant pain. These racial charac-
teristics must have some influence on the apparent distribution of intersex
amongst the four communities.

The sampling method employed here for the determination of incidence was
thought to be reliable: a large number of live births was involved and all
races were, with the exception of the Coloureds, well represented in the

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total (see Table X). Numerical disparity between the races was unavoidable but because of the relatively large numbers involved this should not have a marked effect on the figures for incidence. The number of patients who appear in the prevalence study is thought to be a reliable indication of the situation because the author enjoys good colaboration from most of the private practitioners and hospital staff concerned with this type of patient in Durban. There was no reason to believe that staff at any of the maternity units was not competent to recognize babies with intersexual deformities or that they did not notify the author of any patients.

The incidence of genital anomalies suggestive of intersex was very low and amongst 20,690 live births recorded during the year, only 7 babies with obvious defects were found. Of these four had simple penile hypospadias. The remaining 3 included an idiopathic female intersex (Case 25) and 2 who were possibly hermaphrodites (Cases 27 and 29).

The only possible conclusion from these figures is that intersex recognizable at birth by physical deformity is much less common than was expected. This observation was probably accurate: a survey of 3500 male neonates in Britain did not detect any with physical intersex, but 9 had anomalous karyotypes (RATCLIFFE et al, 1970). No inferences regarding inter-racial distribution or predilection of any race group towards a particular type of intersex can be drawn from the very low figures obtained here. It is problematic whether or not any one year is 'typical' or sufficient to establish incidence patterns from and further observation is required to establish this. It may be found that there is annual variation, in which case the figures presented here can only be taken as an indication of incidence during a particular year.

In even the mildest epidemiological sense the results of a survey such as is reported here cannot be regarded dogmatically as an absolute indication of

prevalence amongst the different races. Some bias was unavoidable because any hospital or private practice provides a selected sample: selection is due to the patient's motivation to seek medical attention, and this itself is governed by certain geographic, economic and domestic conditions. Also, as was mentioned earlier, the population itself is not stable and particularly, the Bantu seen in Durban may prove to be a visitor to the city.

Several features of interest were noted in the study of prevalence. Of the 17 patients, 5 were females with gonadal dysgenesis and 3 were hypogonadal males; there was only a single hermaphrodite.

The distribution of gonadal dysgenesis amongst the whites, Indians and the Bantu indicated that prevalence in each race was approximately similar, and together with male hypogonadism is the most common intersexual disorder. This is controversial to opinions expressed by workers in the northern areas of southern Africa (FORBES and HAMMAR, 1966; WILTON, 1969) who maintained that hermaphroditism was the commonest intersexual state seen in the Bantu. Perhaps this indicates that there is inter-tribal variation, since the Bantu population of Rhodesia and Transvaal consists more of the northern Ndebele and Basotho tribes than of Zulu (Nguni) tribes.

Male hypogonadism occurred with similar frequency in whites and Bantu but has not been seen in Indians or Coloureds by the author. In Chapter VIII it was explained that no accurate diagnoses were established for these patients so that the prevalence of each clinical syndrome cannot be established here. It is interesting that no Klinefelter males were seen during the period.

Another interesting observation was that all 3 male intersexes seen were of Indian origin. This condition is not common in South Africa: WILTON (1969) mentioned only 11 subjects out of 238 intersexes, and DINNER (1969) reported

having seen 10 Bantu male intersexes during a 6 year period.

Other syndromes were represented by single patients only and so do not permit analysis of inter-racial trends.

When the series is examined as a whole, including the 11 patients who were disqualified from these calculations because they were seen outside of the Durban area, the pattern remains the same but is more pronounced. In addition to the patients with Turner's syndrome, a single woman had the Turner female phenotype: she and the the Bantu with Turner's syndrome were thought to be the first records of those syndromes in the Bantu (GRACE, 1970).

In conclusion it may be said that the incidence of those intersex syndromes which are recognizable by physical signs was dissappointingly low and it is impossible to make any comment on the inter-racial differences. Prevalence was also found to be low; only a single hermaphrodite, a Bantu, was found during the survey and it was shown that this is not the commonest form of intersexuality in that race. Certainly in the Bantu of Natal gonadal dysgenesis has that distinction.

Despite the uncontrolled variables the present study was justified because there was an absolute lack of comparable data. The conclusions drawn from this study are certain to be criticised; that, however, is often the fate of any new data which conflicts with prevailing opinion. Until future surveys contradict or confirm these findings they should be regarded as giving a reasonable indication of the situation.

DERMATOGLYPHICS

Introduction
Normal patterns
Dermatoglyphs in
    intersexes
Discussion

INTRODUCTION

Dermatoglyphic examination in clinical medicine is a relatively novel prac-
tice and is still not in widespread use; as evidenced by the large number
of cases reported without details of the hand and finger ridge patterns. Al-
though the study of dermatoglyphs was initiated some 80 years ago it was only
during the past 30 years that the association of constant patterns with some
specific disorders was noted. There are only a few conditions from which
sufficient data has been collected to permit correlation of the dermatoglyphs
with the nature of the intersexual state.

There is a virtual lack of data from the indigenous and immigrant populations
of South Africa. Recently, DE VILLIERS and CLARK (1969) reported briefly on
the northern Bantu and Indians, but their samples were small and measurements
were incomplete. The present situation is that there are no reliable, est-
ablished normal values for the South African races and for normal values it
is necessary to resort to population studies done overseas. It is impossible
to comment on the validity of such comparisons.

Because of the relative difficulty in making plantar prints these have not
been used in any part of the present work.

NORMAL PATTERNS

The terminology used in the study of dermatoglyphs is remarkably uniform, a fact that is certainly due to the limited number of workers in this field. During recent years there have been several publication which describe the basic techniques involved in making handprints (ALTER, 1966; PENROSE; HOLT; ACHS and HARPER, 1968) so that these will not be repeated here. The main features of manual dermatoglyphs will be discussed briefly, using the definitions given by PENROSE (1968).

Fingerprint patterns

The four basic ridge configurations found on the finger pads are, in order of complexity, arches, radial and ulnar loops, and whorls. The ulnar loop is the commonest pattern but the frequency of arches and whorls shows wide inter-racial variation (HOLT, 1968; ZAVALA et al, 1969, amongst others). The frequency distributions of the 4 patterns in the Bantu were comparable to other populations (DE VILLIERS and CLARK, 1969).

Total Ridge Count (TRC)

In most European and Asiatic races the normal TRC is in the range of 80 to 160 for females and 100 to 180 for males; the means are approximately 125 and 145, respectively (HOLT,1968). De Villiers and Clark found that the TRC in the Bantu was the lowest yet reported; mean for males was 131.4, and for females 111.4. A lower TRC is characteristic of negroid races.

The atd Angle

In the event of there being more than one palmar triradius then the most distal is used in measuring atd; this is the maximal angle between triradii a, d and distal t. The atd angle is generally controlled by the position of t, although this is one of the few points about which there is disagreement between different schools. However, the position of t is likewise influenced

by individual variation and so such arbitrary correlation is equivocal. The normal atd angle, expressed as the sum of both hands, is in the range of 70° to 100°, the means being 85° for both sexes (HOLT, 1968; ALTER, 1969).

Pattern Intensity Index

This is a useful guide to the complexity of palmar ridge patterns and is simply the total number of triradii located on the palm.

The a-b Count

This refers to the number of ridges transected by a line drawn between triradii a and b and is thus an indication of linear ridge density. It is usual to give the total a-b count, from both hands. The normal range for both sexes is between 47 and 122, with the mean, 83 ridges (HOLT, 1968). There are no data for the Bantu, and inter-racial variation is not mentioned in the literature.

Main Line Index

This gives an indication of the alignment of the ridges as they traverse the palm. The four main lines, termed A, B, C and D, arise from triradii a,b,c and d, and by tracing their course it can be established in which area of the palm each terminates. The palmar areas were given numerical scores (PENROSE, 1968) and the sum of the scores for the areas in which the lines end gives a guide to their slope.

Main Palmar Flexion Creases

There are three prominent flexion creases on the normal palm and unlike ridge patterns, they are distinguishable at birth. The commonest anomaly of flexion creases is that in which the distal and proximal transverse creases are fused to form a single transverse, or 'simian', line. Such simian lines are found characteristically in mongolism and frequently in intersexes and other con-

genital diseases; they occur in about 1 percent of the normal population
(ACHS et al, 1966). Recently, another abnormality was described, in which
the proximal transverse crease was exrended to the ulnar margin of the palm,
the so-called 'Sydney' line (PURVIS-SMITH and MENSER, 1968). The aetiologi-
cal relationship of this to the simian crease was also discussed (MENSER and
PURVIS-SMITH, 1969). A less specific anomaly is seen in some palms where
there are many short, dissecting creases and the main flexion lines are more
or less obliterated.

Thenar and Hypothenar Patterns

Ridge configurations may also occur in the thenar and hypothenar areas of
the palm. Generally they are simple patterns but compound arrangements do
sometimes appear (PENROSE, 1968). The frequency of patterns, especially in
the thenar area, is low: ALTER (1969) found the incidence of hypothenar
patterns in males and females to be 45% and 47%; of thenar patterns, only
7% and 4%, respectively. There is marked bimanual difference: in both sexes
there is a predilection for thenar patterns to occur on the left palm. There
is no information concerning inter-racial variation.

Interdigital patterns

Loops and occasional whorls are found in the interdigital areas. These con-
figurations are not very common but occur equally in both sexes and with a
higher frequency in the I_3 and I_4 regions. No racial variation has been re-
corded.

Apart from the above parameters, which may be regarded as the major features
of manual dermatoglyphics, there are a number of so-called minutiae; details
of such features as pore distributions, breaks, bifurcations, etc. (OKAJIMA,
1966; 1967). Minutiae are extremely useful in forensic work and determining
homo- or hetero-zygousity of twins.

The number of intersex patients whose dermatoglyphs have been reported in
the literature is small and as recently as 1968, HOLT was unable to discuss
the profiles of hermaphrodites or male and female intersexes. This remark-
able deficiency in one of the only English-language texts on the subject is
taken to indicate a lack of material suitable for discussion. Similarly no
author concerned with dermatoglyphs gave details for those syndromes (ACHS
and HARPER, 1968; ALTER, 1966; 1969). However, during the past few years
a gradually increasing number of case reports have included details of the
dermatoglyphic profile but at present only Turner's and Klinefelter's syn-
dromes are known to have recognizable patterns.

Gonadal Dysgenesis and "Turner's syndrome"

Several workers have noticed increased frequency of large loops (HOLT, 1968)
with consequently raised TRC in Turner's syndrome (PENROSE, 1963; ENGEL and
FORBES, 1965) but unfortunately none gave details of patients' karyotypes so
that much of the data cannot be used for detailed comparison. There is also
the problem of inaccurate diagnosis to be contended with, as was explained
in Chapter VII. HOLT (1968) for example referred to 'Turner syndrome with
45,X' and then 'with all other karyotypes'. In contrast GUINET et al (1968)
gave details of of the karyotype when presenting dermatoglyphs in patients
with gonadal dysgeneses; some of his findings are shown in the following
tables. The relevant details from patients of this series with gonadal dys-
genesis, Turner's syndrome and phenotype are presented in Table XIII.

From the details given in Table XIII it is obvious that the 45,X karyotype
is most often associated with high frequency of loops and the TRC is raised.
Cases 1 and 3 of GUINET et al, (1968) to not adhere to this rule and so show
that exceptions do occur. According to HOLT and LINDSTEN (1964) the T line
terminated in I_2, usually only on one hand; Cases 1 and 3 of this series

showed this bilaterally (Figs. 72a, b). Neither had displacement of t towards the centre of the palm but both had grossly abnormal flexion creases and vertical alignment of the palmar ridges.

TABLE XIII

Dermatoglyphic Patterns in Gonadal Dysgeneses and the Female Turner Phenotype.

Reference	Case No	Karyo-type	Finger prints *L V - I : I - V R		TRC	a-b	atd
Guinet et al,	1	XO	rl; 1 7; w 2		109	109	
(1968)	2	XO	1 7; w 3		167	105	
	3	XO	1 8; w 2		150	89	
	4	XO	1 5; w 5		120	190	
	5	XO	1 7; w 3		170	101	
	6	XO	1 10.		161	93	
This series	1	XO	11111 : 11111		189	91	148
	3	XO	111rl : wl111		180	107	83
Guinet et al,	1	X/XX	al; 1 7; w 2		117	82	
(1968)	2	X/XX	1 6; w 4		118	79	
	3	X/XX	r2; 1 7; w 1		149	79	
	4	X/XX	1 6; w 4		-	-	
	5	X/XX	rl; 1 8; w 1		100	89	
	6	X/XX	1 8; w 2		132	81	
	7	X/XX	1 7; w 3		125	95	
This series	4	X/XX	1wl11 : 11111		168	72	91
	6	X/XX	1wlww : 111wl		154	78	75
This series	7	XX	111aa : arall		49	74	93
Nora & Sinha (1969)	Family studies of Turner phenotype; noted decreased TRC; no details were given						
This series	8	XX	allaa : aaala		12	101	131

* a = arch; 1 = loop; r = radial loop; w = whorl

The dilution effect of mosaicism is evident in Cases 4 and 6 who both had an equal mixture of 45,X and 46,XX cell lines. Both had a TRC higher than any of the similar patients from Guinet's series, but this was not as high as the TRC in the 45,X subjects. In all patients of this group the a-b count was more normal. Case 4 (Fig. 72c) had vertical alignment of the palmar ridges, a feature which was noted by ENGEL and FORBES (1965) in both 45,X and X/XX
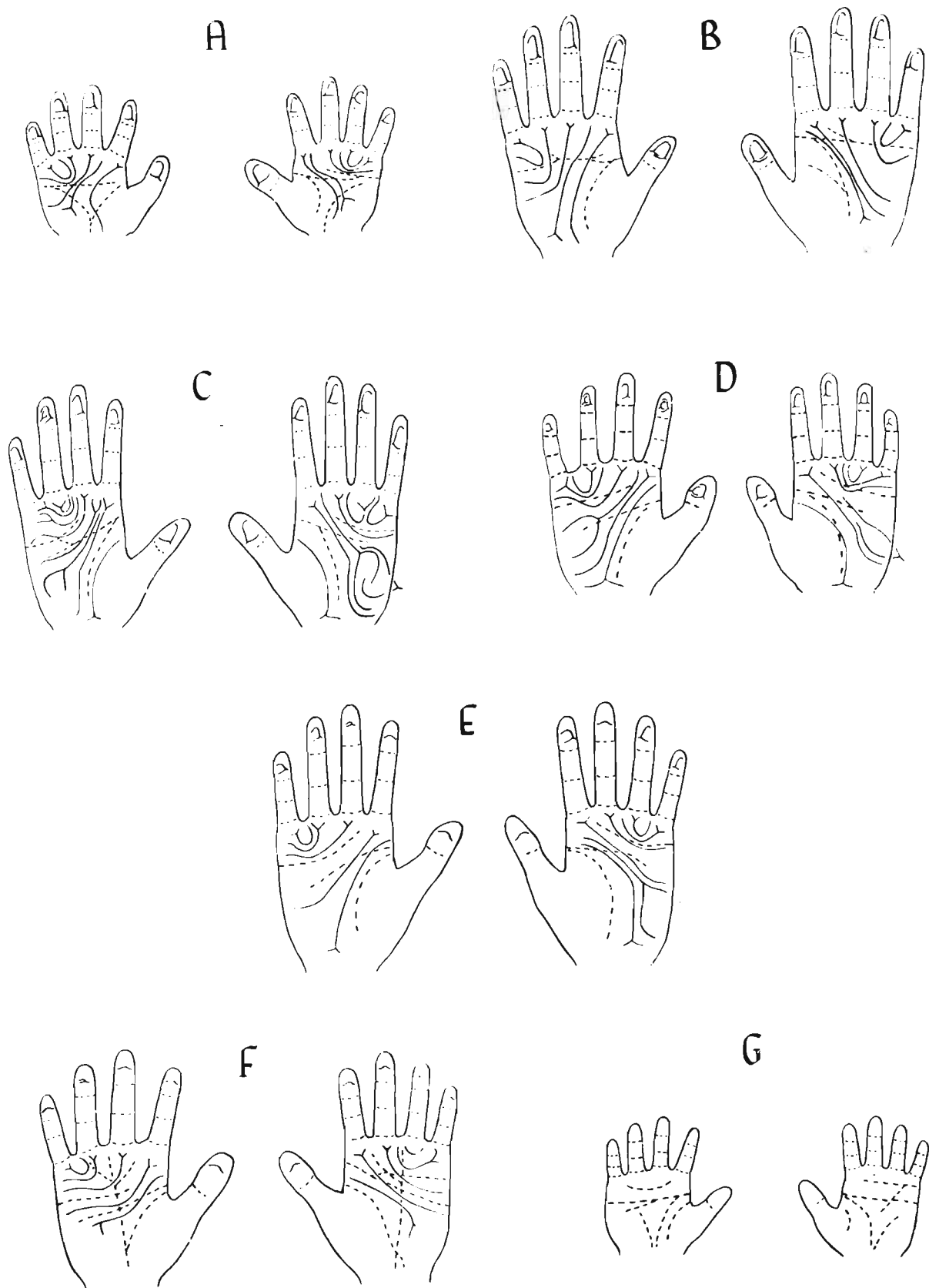
FIG. 72

Dermatoglyphic patterns in gonadal dysgeneses
and the female Turner phenotype.

patients. Both Cases 4 and 6 had hypothenar patterns, a trait which ALTER (1969) said might be frequent in the 'Turner syndrome'.

Neither the 45,X or mosaic patients reported here or by GUINET et al, (1968) support the claim that there is a raised incidence of whorls on the finger prints (ALTER, 1966) in all forms of X chromosome anomaly associated with Turner's syndrome. Also, several authors noted increased occurrence of a simian line in Turner's syndrome, but there was only a single example in this series (Case 3; Fig. 72b). It is obvious that the mosaic group have dermatoglyphs more nearly normal than do the subjects with 45,X karyotypes.

The dermatoglyphic profiles of pure gonadal dysgenesis have received little or no attention: GUINET et al, (1968) mentioned one patient whose patterns were 'not Turner-like', but gave no details. Only one of the 2 patients from this series (Case 7) with pure gonadal dysgenesis was hand-printed: the patterns were interesting. The TRC was very low because there were 4 arches (Fig. 72e); ridge alignment, a-b count and maximal atd angle were unremarkable but there was a Sydney line on the left.

Case 8 was very interesting. This patient had the female Turner phenotype and also had the most unusual dermatoglyphs of the whole series. The hands were short and broad; there was marked distal displacement of t, and atd was 131°. The palmar ridges were arranged almost parallel to the wrist creases (Fig. 72f) and most remarkable of all, she had 7 arches and only 3 small loops: the TRC was 12. The flexion creases were also anomalous and there were many finely dissecting lines. This patient's baby daughter (see Case 9) was assumed to have the same syndrome but no ridge details could be discerned. However, the flexion creases were quite bizarre and to some extent, resembled those of her mother's hands (cf Fig. 72g). In a single reference to the dermatoglyphs of this syndrome NORA and SINHA (1969) said

that 7 of 8 affected persons in 3 families had a high frequency of arches and a correspondingly low TRC; that there was distal displacement of t. In one photograph of a palm it appeared that there was a similar vertical crease and numerous small dissecting creases, as were seen in Case 8.

A single patient had the male Turner phenotype (Case 10). The fingerprint patterns on right and left hands were wlwwl:wrwll and the TRC was 181. The a-b count was normal, at 71; there was no displacement of t and the maximal atd angle was 82°. The palmar flexion creases were normal on the left, with a bridged simian crease on the right. FERRIER and FERRIER (1967) reported a series of 4 patients, with TRCs of 76, 160, 177 and 186. ACHS and HARPER (1968) interpreted these as showing elevation of the TRC: that is not correct since the first two were low and normal, and the last two were within the range of normal males. However, the number of cases thus far reported is small and no conclusions can yet be drawn.

Klinefeleter's syndrome and hypogonadal males

There is general agreement that the number of X chromosomes has a more pronounced effect on dermatoglyphic patterns than does the number of Y chromosomes; as the number of X chromosomes increases so the TRC is depressed (PENROSE, 1963; HUNTER, 1968) and chromatin positive males have significant reduction of the TRC. In 22 patients the mean was 115.9 (PENROSE, 1966) and HUNTER (1968) reported the mean to be 121.7. It has been said that the dermatoglyphic features offer a method of differentiating between XXY and the more exotic poly-X karyotypes: in the XXYY and XXXY syndromes the mean TRC is much lower (UCHIDA, 1966; PENROSE, 1967; ALTER, 1969).

The single XXY patient reported here (Case 11) had essentially normal dermatoglyphic configurations (Table XIV; Fig. 73a) and only the TRC, at 97, was low. That score was a lot lower than the means given above but is within the

range for XXY males (HUNTER, 1968).

A search of the literature failed to produce any reference to the dermal ridge patterns in the chromatin negative, hypogonadal male who has many clinical features of Klinefelter's syndrome but an apparently normal karyotype.

Five such patients were listed in Chapter VIII and another patient, who was not reported in detail (B.W.) had similar features. Dermatoglyphic details of these patients are shown in Table XIV and Fig. 73b-g.

TABLE XIV

Dermatoglyphs in Klinefelter's syndrome and in Male Hypogonadism

Case	Karyo-type	Finger prints *L R V - I : I - V	TRC	a-b	atd	Race	Build+
BW	XY	11111 : 1wlww	127	71	91	W	N
12	XY	wwllw : wlllw	152	86	80	B	N
13	XY	11111 : 11111	77	71	77	B	E
14	XY	lllal : rrlll	74	78	82	B	E
15	XY	wlllw : wllwl	134	79	80	W	N
16	XY	11111 : lllal	52	93	72	W	child
11	XXY	llrll : wllll	97	89	90	W	N

* a = arch   l = loop ulnar   + N = normal
  w = whorl   r = loop radial   E = eunuchoid

It is clearly evident from Table XIV that there are two distinct groups: one with TRC in lower range of normal, and those with drastically reduced scores. There was no correlation of TRC with either a-b count or atd angle but those with low TRC were noted to have long, narrow hands (see Fig. 73).

In all except Case 16, who was prepubertal, the presenting signs were either
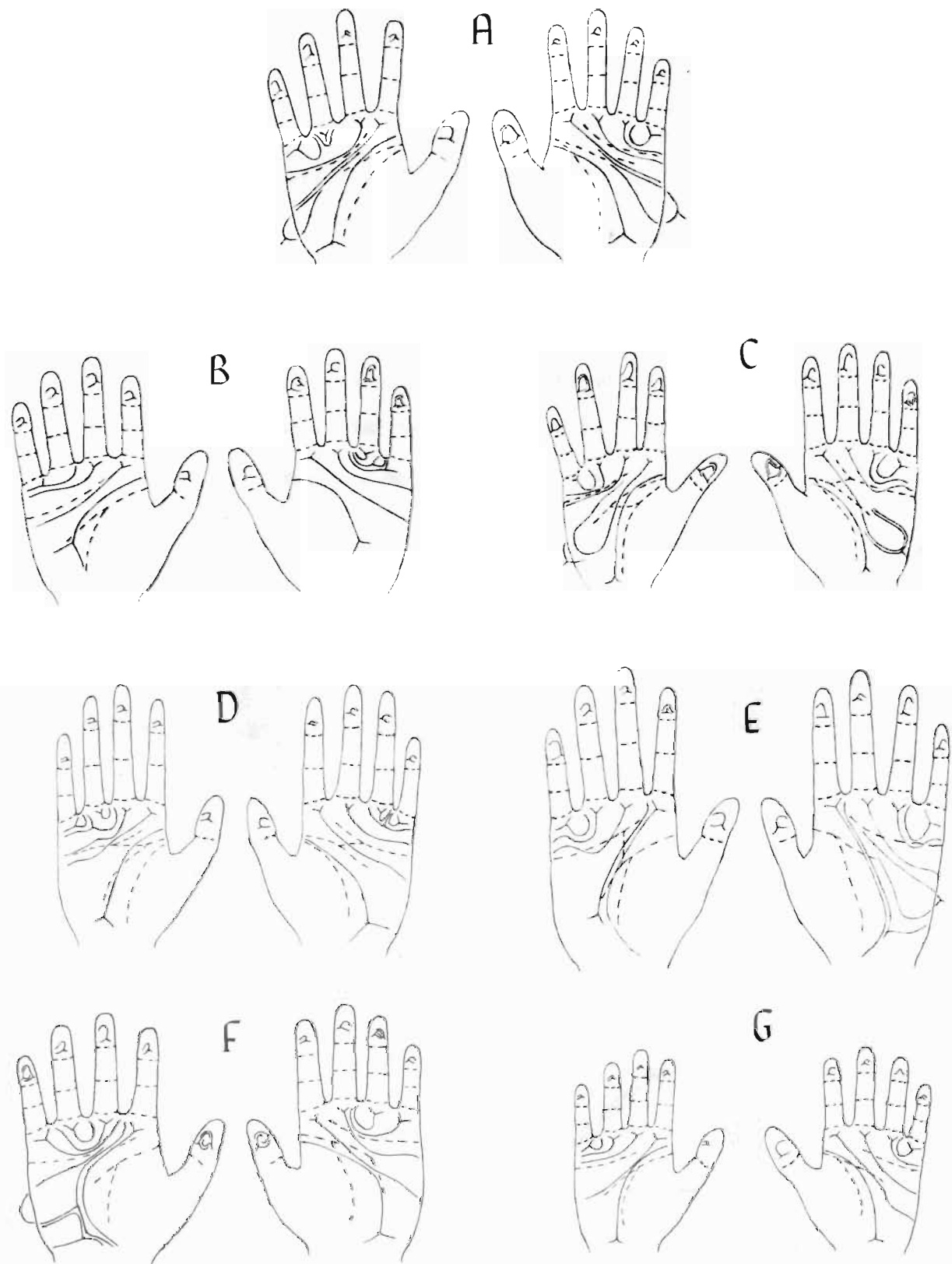
Fig. 73: Dermatoglyphs in (A) Klinefelter's syndrome, and B-G, other hypogonadal males. For explanation see Chapters VIII and XVI.

gynaecomastia or mental disturbance, or both. Clinically they were distinguishable into eunuchoid and non-eunuchoid (normal) groups, which grouping correlated well with their hand print patterns. But, on clinical investigation by hormone assay, karyotype analysis etc, the cause of hypogonadism could not be established. As only one patient had submitted for testicular biopsy (Case 14) it is at present not known whether gonadal histology will correlate with the dermatoglyphic disturbances.

A constant feature of the 6 hypogonadal patients reported here was the high proportion of small loops in those with low TRC and a normal frequency of whorls in those with more normal TRC.

Other Intersex Syndromes

The remainder of the patients from this study all either fell into syndromes represented by a single patient, or their dermatoglyphs were not recorded. The profiles of this miscellaneous group are shown in Table XV.

TABLE   XV

Dermatoglyphs in Miscellaneous Intersex Syndromes

Case	Karyo-type	Finger prints *L V - I : I - V R	TRC	a-b	atd	Race	Diagnosis
17	XX	llaal : lalll	82	47	90	B	Induced virilization ?
22	XY	lwlwl : lllwl	191	91	90	I	Andromorphic male intersex
24	XY	wwwww : wwwwl	181	84	89	B	Asymmetrical gonadal diffn.

* a = arch; l = loop ulnar; r = radial loop; w = whorl

Case 17, a young Bantu female, was held to be an example of induced virilization: she had a very low TRC and a-b score. The defective males of Cases 22 and 24 both had very high TRC and a-b counts. None of these syndromes is

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mentioned in the literature and so further discussion of these single pat-
ients is not warranted.

DISCUSSION

From experience with the Turner and Klinefelter syndromes, observed by many
workers, there is good indication that the dermatoglyphic arrangements of
other syndromes may also be characteristic. From the evidence presented in
the previous pages it seems that hand print patterns can be used to disting-
uish between at least two types of chromatin negative male hypogonadism on
the basis of the TRC.

Although the full significance of this observation is not appreciable at this
juncture because testicular histology was not studied and consequently there
were no accurate diagnoses, it is reasonable to assume that the odd patterns
are laid down at the same time as abnormal testicular differentiation occurs.
The testis is differentiated between the 7th and 9th weeks after fertiliza-
tion; the embryonic dermal mounds between the 8th and 12th weeks, so that the
obvious extrapolation from the observation made here is that those patients
with very low TRC have a gentically determined anomaly which was present, or
made its influence felt, very early in foetal life. The other individuals,
with slightly lowered TRC, have hypogonadism which is the result of some later
defect, perhaps not a genetic mechanism but an environmental or secondary in-
sult by some teratogen.

Perhaps when more data has been gathered on such hypogonadal males and family
studies have been done to ensure that the low TRC is not a familial attribute,
it may be possible to use the dermatoglyphic profile as a diagnostic aid in
differentiating between congenital and induced, or acquired, testicular les-
ions.

The general dearth of literature, both in textbook and article form, shows how little work has been done on this topic, especially in its application to clinical medicine. Although the numbers of case reports which are now accompanied by details of the hand and finger prints is increasing, there is still the need for an intensive study into the patterns of intersexes and hermaphrodites and for these to be correlated with other clinical parameters in order that the use of this test as an aid to diagnosis may be assessed.

In respect of the local medical practice there is the urgent need for normal values for the dermatoglyphs in each of the races to be established and for local workers to interest themselves more in this test: to date no publication in a South African medical journal has been accompanied by details of the hand prints.

CHAPTER XVII

DISCUSSION AND CONCLUSIONS

Anomalous sex development is a problem which has affected man and the lower animals alike for many thousands of years, certainly for the period covered by recorded history. Intersexuality as it occurs in vertebrates, with the exception of some fish families, is a fascinating problem that is still not fully understood and modern customs continue to regard the intersex with as much curiosity as did the ancients of 2000 years ago. Since the inception of Roman law no legal definition of 'sex' has yet appeared.

Fossil records indicate that the vertebrate phyla were certainly dioecious at the time when they colonized the land. However, sex is determined by extremely sensitive mechanisms and accidents of sex determination, differentiation and development have occurred frequently and affect individuals of many diverse species. During the past fifty years cytological techniques improved rapidly and culminated in the modern discipline which specializes in demonstration of chromosome composition and morphology; cytogenetics. Recently other forms of sex dimorphism were discovered, and during the past few years dermatoglyphic studies have also become incorporated into the regimen for identification and classification of intersexes.

Since the early days of investigation into the nature of the human chromosomes much has been learned and the discipline of cytogenetics is noe firmly established, with its own terminology and laws. The phase of describing new karyotypes and chromosomal anomalies is drawing to a close and the present period is one of consolidation, with fewer additions to the nomenclature and attention being given more to the 'normal' behaviour and functions of the chromosomes and sex determining mechanisms.

There is ample evidence that when intersexuality affects individuals of almost all phyla, this follows a very similar pattern. This refutes the claim (KOCH, 1963) that intersexuality in the lower animals is of no concern to the study of human ambisexuality; on the contrary, those same lower animals may afford excellent material for the study of the basic faults of sex determination.

South Africa has four well-defined population groups, caucasoids, negroids, Asiatics, and a mixed race of all three, the Coloureds, and is therefore an ideal area for studies of inter-racial variation; even more so than the west indies where miscegnation has obscured the true racial identity of the individual. Durban particularly well suited to such studies because three of the races are represented by substantial numbers and the minority, the Coloureds, are to a large extent cocentrated in a well-defined community so that in each case 'captive' populations for epidemiological study can easily be had.

The present investigation was designed to collect data on the prevalence of intersexuality among the races and to determine if there were any racial predilections towards particular syndromes; also, to observe patients in order to collect information regarding the clinical, physiological and genetical features of the separate syndromes. One of the more serious deprivations to such a study was the lack of facilities for conducting a random population study because the necessary organization was not available. For that reason the present work was limited to a total population study of all births accomplished at four maternity departments. The number of births recorded was, it is felt, large enough to offset bias through socio-economic selection although there is no suggestion in the literature that such material factors have any bearing on incidence.

A more pertinent factor in assessing the accuracy of this survey of incidence and prevalence of intersexuality in Durban was the competence and extent of

co-operation shown by local medical personnel and midwives in recognizing and notifying the author of possible intersex patients. In two of the three hospitals involved there was little doubt that all births were checked by medical staff; in the case of the third hospital it is difficult to be dogmatic since the department was under-staffed and it is conceivable that a number of babies would only have been seen by an attendant midwife. It is impossible to assess the efficiency of such staff, but it is not thought to be likely that they would not have recognized an infant with epicene genitalia. Collaboration with hospital and private doctors was good. The numbers of private paediatricians and gynaecologists, the practitioners most likely to encounter intersex patients, are small and as there are no local alternative facilities for cytogenetic studies all should have come to the attention of this laboratory so that the numbers reported here are thought to be very close to the real figure. As far as can be determined from the literature this is the first attempt to establish the incidence and prevalence of intersexual conditions in any South African community.

One of the primary aims of this work was to find out whether or not hermaphroditism was the commonest form of intersex to affect the Bantu, and if intersexuality generally affected the Bantu more frequently than any other race. There were several interesting observations: babies with frankly abnormal genitalia were very uncommon and of 7 affected (among 20,687 seen) only 3 were intersexual, an incidence of approximately 1 in 7000. It was said by OVERZIER (1963) in conclusion of his textboook that the overall incidence of all types of intersexuality was between 0.2% and 0.3%. In order to approach that figure in the population studied here it would have to be assumed that those syndromes not evident from physical deformity (e.g. Klinefelter's, gonadal dysgenesis and testicular feminization) would have to occur with a frequency of 3:1000 but clinical experience here does not support such an interpretation. Speaking of the Durban population, Klinefelter's and the testicular feminization

syndromes are quite uncommon and the XXX and XYY syndromes are virtually unknown.

The reason for the apparent deficiency of intersexes in this survey could be due to several causes. Assuming that the figures presented here are in fact close to reality then it may be that the preconception of intersexuality being rampant in South Africa was incorrect. Because there are only four laboratories in South Africa where cytogenetic facilities are offered, the very highly selected population seen at them could have been interpreted as indication of a very high prevalence in the population at large; in other words, a false impression of prevalence. Alternatively, 1969 might have been a lean year for the production of intersexes, although there was nothing to suggest that such was the case. However, a longer period of time will have to be monitored in order to elucidate the question of annual variation.

One of the primary motives of the investigation was to determine whether or not hermaphroditism was the commonest form of intersex in the Bantu: in the Bantu of Durban it is not, as is shown in Tables IV and XII. The overall impression gained from this work is that there is little difference between the frequency of intersex in whites and Bantu when it is considered that the Bantu community in Durban is nearly 10 percent larger than the whites'. What is clearly evident is that the prevalence and incidence of intersexual anomalies amongst Indians is extremely low. This is remarkable because the Indian community tolerates first-degree (cousin) relative marriages with the consequence that recessive congenital disorders occur frequently. This may indicate that intersexual conditions which have no obvious chromosomal disturbance are also not due to recessive gene action: was it so, then those types of intersex (masculine male intersex and testicular feminization are suspected of being recessive) should occur much more frequently in inbred families. Selective pressure against seeking medical advice, and thereby bringing attention to,

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for intersexuality was not thought to have been the reason for so few Indians having been seen: in outlook they are very similar to the whites. It can only be concluded that this is a real racial characteristic. Because the Coloured community of Durban is so much smaller than the other races, any conclusions drawn from the negative results here would be unreliable: papers from workers in the Cape have shown that a wide range of intersexual defects may affect the Coloureds (JACKSON et al, 1967; FRY et al, 1968; JACKSON and MARINE, 1970).

An inescapable fact is that all of the hermaphrodites thus far described from South Africa have been Bantu; it is assumed that DINNER (1969) had only Bantu in his series of 25 patients and that the patient (Case 1) of FRY et al, (1968) was a Bantu: neither of those authors stated the racial origin of their patients. What is surely one of the largest single series of hermaphrodites in the world was that of WILTON (1969): 46 patients were mentioned, although no details were given apart from the fact that one was an XX/XY mosaic and the remainder were all 46,XX. No data concerning genital, gonadal, hormonal or dermatoglyphic features were given. Twenty-five patients were reported in some detail by DINNER (1969) but it is not known whether or not any of these were included in the total recorded by Wilton. Another series of more than 20 patients (ROUX, 1970; personal communication) consisted entirely of Bantu. In addition to these large series, a number of other reports have appeared during the years; most of these were tabulated by GRACE et al, (1970) and subsequent reports have come from HIRSCHOWITZ (1969) of 2 cases, and JACKSON and MARINE (1970) of one patient. Altogether the number of hermaphrodites reported from South Africa must total between 85 and 100, depending on the number common to Wilton and Dinner. This is a phenomenal figure when one considers that the total number of cases reported in detail over the past 70 years is approximately 310 (POLANI, 1970). It is unfortuante that local workers have not conducted more research into this syndrome when such a volume a patient-material

is available. The relative rarity of hermaphrodites in the Durban area remains unexplained, although real. It is incredible that a people with such a rich folklore as the Zulus should have no explanation for the origin and the destinies of ambisexual individuals; this is especially true if hermaphrodites are as common as apparently they are in other areas of the country, and also because the Zulus attach great importance to a man's phallic prowess.

A more definite pattern was seen in respect of hypogonadal males, where both whites and Bantu were equally represented but, significantly, no Indian males were found. Klinefelter's syndrome was uncommon and only a single patient, a white, was included in this series; he was not included in the prevalence study. Only 2 Klinefelter males have been found amongst the Indian population, and one Bantu, during the past five years.

It was very interesting to see that the whole spectrum of gonadal dysgeneses occurred in the Bantu, and that these disorders are the commonest intersexual defects of that race in Durban. The same conditions are rare in Transvaal Bantu, and Turner's syndrome was said to be unknown (WILTON, 1969). The lack of Bantu male intersexes from this series was probably due to the small sample size.

The variety of intersexual syndromes seen during the course of this survey was quite comprehensive and most of the major syndromes were investigated. Since the survey ended a single patient with the XXX syndrome has been identified. She was a 23-year old Indian who gave the typical history: she had poor secondary sex development and had become amenorrhoeic after 7 years of irregular menstruation which had begun when she was 14 years old. Karyotypically she was an X/XXX mosaic.

Three babies, two Bantu and a white, were suspected of being hermaphrodites:

each was epicene and had an equivocal karyotype. In no instance were the attendant doctors prepared to submit the infant to laparotomy for gonadal biopsy until it was at least 18 months old, and each was discharged after the parents had been instructed to return the infant at the appointed time for further investigation and treatment. In each case there has been no further response and all 3 patients, now aged between 14 and 20 months, will presumably be reared in whichever gender the parents choose. But it can be expected that at some stage of life these individuals are going to be faced with the realization that either their genital anatomy or their pubertal experiences are contrasexual and they will then almost certainly suffer some degree of psychological shock.

Because of this poor response by patients; or in cases such as these, their parents, to return for further treatment it is essential that the subject, if he is to receive the treatment which his unfortunate intersexual habitus deserves, be retained in hospital until all procedures have been completed. Also, the necessary corrections should be undertaken as soon as possible: this view has been stated by many authorities in many texts and papers and so it is not necessary to provide further justification here. To discharge a patient when there is the very real probability that he will not return for further treatment is, it seems, a serious disservice to the patient, to those who bear the responsibility for rearing him, or, at a later date, for treating him.

The discovery that the dermatoglyphs of chromatin negative hypogonadal males indicate two distinct groups was interpreted in terms of the embryological sequence: the epidermal ridges and flexion creases are established under strong polygenic control (ALTER, 1969) during the 8th and 12th weeks of gestation (ACHS and HARPER, 1968). Concurrent with this, differentiation of the gonads from the unspecialized state to functional endocrine organs

occurs (at about 8 weeks). Since all patients had normally formed genitalia the testes must have been functional during the intra-uterine period until possibly during childhood or early puberty the production of androgens necessary at puberty failed. WITSCHI et al, (1957) theorized that only a few germ cells reached the genital ridges and were sufficient only to induce testicular development; that, in turn, stimulated the genital tract to masculinize. Until about the 10th year there is no further change but thereafter the few remaining tubules are destroyed by hyaline sclerosis (FERGUSON-SMITH, 1958) and so precludes virilization at puberty. Whether or not these events are due to a common, genetically induced mechanism or to an environmental factor is unknown.

That this feature has for so long gone undetected indicates how little interest has been taken in the hypoginadal male, particularly insofar as the hand print patterns are concerned. Many reports of the palmar and finger print patterns in XXY males have been made but no author has yet described them in the hypogonadal XY male.

There is the urgent need for an intensive study to establish the normal patterns of the dermatoglyphic profiles in all of the South African races. In a single reference (DE VILLIERS and CLARK, 1969) the information from Bantu and Indians of South Africa was, unfortunately, incomplete, and also no details were given of the tribal or caste origins of the 100 subjects of each race. As more data from abnormal individuals becomes available it is essential for interpretation of clinical material that the 'normal' values are established.

Similarly, of the sex chromatin test; the procedure is widely known and is used in many laboratories throughout the country but it does not seem to be appreciated that results may be meaningless unless standard, normal values

have been established for each observer: when this test is used as a rapid

indication of sex then it is imperative that it be done by an experienced

person. The study done at this laboratory on normal females failed to show

any inter-racial variation but there was a surprizingly high number of sub-

jects with frequencies of less than 20 percent, which was previously regard-

ed as the lower limit of normal, and so the lower limit for normal females

is now accepted as 10 percent.

An excercise which would be of great value in establishing whether or not

the apparent rarity of XXY males amongst the Bantu and Indians is real or

not would be a population survey using the sex chromatin test. This has

never been done on a large random sample in South Africa, although several

such investigations have been carried out at overseas centres with very

encouraging results. In a survey of mental institution patients ANDERSON

et al, (1964) discovered several XXX and XXY males: such work could be

extended to cover pupils at schools for the subnormal and patients incar-

cerated in hospitals for dangerous retardates.

Like the sex chromatin test, some hormone assays are difficult to evaluate

and apart from the estimation of 17-steroids, which is of great practical

value in the identification of adrenogenital syndrome in females, the other

sex hormone excretion patterns are so frequently equivocal that dogmatism

in their interpretation is dangerous. There is also the opinion in certain

quarters that the results from various centres are hardly comparable because

of technical variation, and more recently the disturbing suggestion has been

made that some of the methods used in the past, particularly for FSH determ-

ination, may not have been reliable (VINIK, 1969b). Regretably, therefore,

hormone assay cannot be regarded with more than academic interest. There

are no local facilities for estimation of androgen and oestrogen fractions

urine.

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The classification of intersexes within the limits of present knowledge is more or less uniformly accepted around the world, with major subdivisions for hermaphrodites, male and female intersexes and psychosexual intersexes. There is however, individual preference as to whether syndromes with endocrine disturbance or other extra-genetic factor in the aetiology should be included in a separate group or, as was done here, according to the basic sex. In the classification presented earlier sex was given prime importance because that is, in fact, what distinguishes 'intersex'. The parameters by which the assessment of sex was made were, in order of prominence, genetic, gonadal, genital and somatic features. Nuclear sex, as was pointed out in an earlier chapter, has no place in the classification because it is known to vary; even within a single syndrome. It is well known that the karyotype and phenotype do not always correspond and for this reason too, the karyotypic constitution is not considered in the classification. Generally the trend is towards reduction of the number of subgroups, or syndromes, and accordingly the classification was limited to the four major subdivisions with syndromes grouped by their prevailing genetic sex, or gonadal type. In all cases biochemical and somatic features were regarded with secondary importance. Thus, in the gonadal dysgeneses the number of syndromes was reduced to two; in the male intersexes the masculinized types with recognizably male external genitalia were termed 'andromorphic' irrespective of the internal genital architecture and those with ambiguous external genitalia were 'gynaemorphic'. These succinct terms are preferable to those such as 'male intersexes with predominantly masculine external genitalia' (JONES, 1968). Idiopathic female intersexes were classed as a single entity with three degrees of severity. Similarly, all chromatin positive males were placed in Klinefelter's syndrome, qualified according to karyotype. Hypogonadal males were, in this work, placed in a single group because there was insufficient information relating to their accurate clinical diagnosis and there is also no detailed description of the various syndromes in the modern literature.

The law, in its wisdom, recognizes only two sexes and at present seems un-
likely to compromise on this point.   In the biological world there is an
almost complete range of 'sex'; anatomically, physiologically and psycho-
logically, from perfectly formed, masculine men, through intersexes and
hermaphrodites, to perfectly formed, feminine females and so the problem
is one of deciding the most appropriate gender in which to rear an inter-
sex. Technically this is quite straightforward, although the subsequent
legal status and rights of the individual remain at the mercy of the law.

Until the public and its legislators are educated to appreciate that there
is a wide variety of 'sex', and that the intersex does not deserve to be
regarded as a freak, then there is little hope of the legal and social stat-
us being improved. Parents must be encouraged to bring their affected off-
spring as early as possible for treatment and adults must be reassured that
they will not be the subject of ridicule when they present themselves for
medical assistance.

The patients investigated in this study were in most respects typical of the
syndromes and generally exhibited the expected cytogenetic features.   There
is the growing realization that, to account for karyotype-phenotype variabil-
ity, there must be factors other than the number and identity of gonosomes in
an individual'skaryotype which control the nature of his abnormalities.

Current thought accepts that in the human the Y chromosome carries the genes
responsible for masculine development (FORD, 1963) and that male gonads will
not develop in its absence.   Also, the presence of a single Y is apparently
sufficient to induce masculine, rather than feminine or hermaphroditic, diff-

erentiation even when it is in competition with as many as four X chromosomes (RERRICK, 1969) or when only one cell line has a Y (for instance, the patient reported by FEDERMAN et al, (1965)). It appears that feminine development can only occur when there is no Y chromosome present. Exceptions to this generalization do occur: the syndromes of testicular feminization and pure gonadal dysgenesis have the female phenotype with an apparently normal male karyotype. The former is known to be due to a defect of androgen catabolism and therefore does not contradict the theory of sex determination proposed here. Phenotypic femininity in pure gonadal dysgenesis is the result of the gonads failing to differentiate. The converse is seen in males with the XX genotype and in the majority of hermaphrodites; in these subjects testicular tissue is formed although there is no obvious Y.

Various hypotheses have been proposed to explain these phenomena. Principally they invoke either undetected gonosome mosaicism or translocation of some of the sex determinants from either the X or the Y to its homologue (FORD, 1963 FERGUSON-SMITH, 1965; 1966). In the first case it has been suggested that a series of mitotic events result in the separation of male and female genotypes to produce, for instance, XX/XY mosaicism, or that such a mixture was formed through chimaerism or double fertilization. There is little evidence to support these theories because in spite of intensive searches for such cryptic mosaicism, very few patients have been discovered to have a small, localized area of heterosexual tissue (BRØGGER and AAGENAES, 1964). Chimaeras also are rare.

The second, and more popular theory, is that a submicroscopic translocation occurs between the gonosomes during synapsis. During the meiotic prophase the X and Y chromosomes form a bivalent with end-to-end synapsis between the short arm of the X and the long arm of the Y and so it is thought that they must have a common pairing segment in those regions. If true, it indicates

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that the X chromosome must carry 'male' genes in its common segment (FORD, 1963). Ford's thesis was that the determination of sex then rested on the ratio between paired segments and differential portions of X chromosomes, the assumption being that the differential-X segment carried 'anti-male' genes: when two or more Xs were present the anti-male genes of the differential segments countered the same number of male genes on the pairing segments and thus left the way clear for ovarian, and so, feminine development. If, on the other hand, there was an X and a Y, there would be a double dose of male determinants and only a single set of anti-male factors, thus acceding to testicular differentiation and consequent masculinization. This arithmetical theory was extended to account for other karyotypes such as XO, XXY etc.. Since Ford published that hypothesis it has been shown that the male determinants are located on the Y chromosome near the centromere (JACOBS, 1969) and are therefore far removed from the pairing segment. Also, deductions made by FERGUSON-SMITH (1965) from a study of the karyotypes in gonadal dysgenesis showed that the responsible genes for controlling the dysplastic features of Turner's syndrome were located on the short arms of the X chromosome, presumably on the homologous (pairing) segment because similar defects are seen in males with the Turner phenotype. To overcome this impedient fact FERGUSON-SMITH (1966) further postulated that in fact the homologous areas of the Y might be scattered at several points along its length so that on some occasions the X-Y bivalent might be formed with synapsis between the <u>short</u> arm of the Y and the short arm of the X: in this way a translocation of the short arm of the Y on to the short arm of the X could be accomplished. If the X thus added to (designated X^y) was combined at fertilization with a normal X, the resultant zygote would be XX^y. According to the Lyon hypothesis X chromosome inactivation occurs randomly so that in the embryo there would in effect be two cell lines and the proportion of each might account for the range of phenotypes; from persons with ovaries, hermaphrodites, and those XX males with testes.

An extention of this theory can be used to explain several other intersexual syndromes. Presumably the Y chromosome could also receive a donation from an X, in which case it would be effectively XY^X and result in the Klinefelter-like male with apparently normal karyotype. A corollary to this is the subject who inherits the donor X (X^-) and the combination of XX^- would result in gonadal dysgenesis with apparently normal gonosomes. The syndrome of pure gonadal dysgenesis in XY individuals might indicate that the Y had previously donated a submicroscopic segment carrying its male determinants (Y^-); in the male Turner phenotype either X or Y might have been a donor, thus creating a monosomic state for the genes concerned with Turner stigmata but not necessarily those for testicular differentiation.

The idea of a small segment of X and Y gonosomes being homologous is very feasible since it concurs with the basic principle that the sex chromosomes evolved by selective expulsion of non-sex genes from a previously homologous pair (see p66). It would seem that the homologous segment of the X has not yet been divested of its somatic genes. The variability of phenotype in the gonadal dysgeneses led to the suggestion that there are three genes (or sets of genes) which control the basic groups of signs (see p94 et seq.) although it was originally thought that there were deleterious mutants (HOFFENBERG & JACKSON, 1957). It is now obvious that deletion, not mutation, underlies the pathogenesis. However, these three loci must be lost independently to account for the variety of phenotypes (NORA and SINHA, 1969), a very acceptable hypothesis, and so the whole modern concept can be seen to fit the idea first outlined by Hoffenberg and Jackson (GRACE, 1970).

Mosaicism frequently gives rise to quite dissimilar phenotypes, as was shown very clearly, particularly in respect of the X/XX (FERGUSON-SMITH, 1965) and XX/XY mixtures (editorial, S. Afr. Med. J. 1968; JACKSON and MARINE, 1970). What causes such variation between patients with apparently similar chromosome

complement is unknown and since there is no obvious parallel between the
proportion of normal (or abnormal) cells and normality (or abnormality)
it does not appear to be a simple ratio. A similar phenomenon was seen
in bovine freemartins where the extent of masculinization was not always
proportionate to the volume of male cells. Possibly this is an expression
of variable penetrance, or otherwise it may be dependent upon which tissues
of the body are affected.

In connection with the phenomenon observed in foetuses with the 45,X karyo-
type (SINGH and CARR, 1968) that ova are present in the gonads but become
atretic during the latter part of the intra-uterine period so that at birth
there are few, if any, remaining, there is still no explanation. Equally
there is no explanation for ova in normal females atrophying (POLANI, 1970).

Very few cases have been proved to have mosaicism as the result of either
double fertilization or somatic nondisjunction and there is growing support
for the theory that postmaturity of the gametes is responsible for many of
the odd karyotypes. Postmaturity may be the result of maternal age, delayed
ovulation, late fertilization, dysmature spermatozoa and other causes; most
of these were discussed in an excellent review by WITSCHI (1970). From this
it is interesting to speculate that in older mothers, who produce a signifi-
cantly higher proportion of abnormal babies, the cause of anomalous concept-
uses is postmaturity, and that this might be related to decreased frequency
of coitus; contraceptive methods or a similar 'social' events. This does not
correspond very well with the maternal ages recorded for patients of this ser-
ies: in all syndromes except for the 'possible hermaphrodites' the mother was
invariably in her early twenties; in two of the patients who may prove to be
hermaphroditic (Cases 27 & 29) the mothers were 26 and 30 years old, respect-
ively.

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No definite causes have yet been found for the errors of hormone metabolism which cause adrenal cortical insufficiency or the androgen-insensitivity of the testicular feminization syndrome, and at present only debilitating gene mutations can be hypothesized. Similarly, there is no proven cause of the idiopathic intersexes: in these the deformities are such that they might have been caused by contrasexual hormones, or in the males, by lack of androgens, but despite intensive seraches by some workers to prove such a hormonal disturbance, none has yet been found. There is also no support for an alternative possibility that they are caused by gene translocation such as those envisaged by Ferguson-Smith.

From the study of all forms of intersexuality it can be seen that there are a number of potential causes: anomalous genotype; faulty gonadal differentiation; hormonal and metabolic disturbances, and, in the psychological field, incorrect assignation of gender and consequent disparity between biological and social sex. These pathogenic mechanisms lead to a state in which there is an almost continuous spectrum of phenotypes, from the perfect male to the perfect female, with every gradation in between: perhaps the older theories, that sex was a graded, continuous characteristic, were not so unreasonable after all (KNIGHT et al, 1921). Nonetheless, in terms of current thought, sex is a specialization; the evolution of the monoecious state can be traced in both the botanical and zoological worlds and so intersexuality of any sort in species which are normally distinctly male, or female, must be regarded as an abnormality.

Our knowledge of intersexuality has reached the stage where gross, crude errors of the sex determining mechanisms can be evaluated but there remain many, many more unexplained features in the aetiology of anomalous sex development.

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CONCLUSION

'Oh, that my words were now written!
Oh that they were printed in a book!
Chronicles xix: 20.

The methods employed here for the determination of sex were reliable, except in the few instances where surgical intervention was required to establish the nature of the gonads, and was not done. Solid-tissue culture facilities were not available and so mosaicism, when this was suspected, could not be searched for. A pilot study determined that there was no inter-racial difference in sex chromatin frequency and that the normal range for females was between 10 and 65 percent; males were almost invariably chromatin negative, but never more than 4 percent positive.

An improved and simplified system for classifying intersexes was presented and some changes in the nomenclature were proposed. A number of older names were rejected and, in some cases, syndromes were 'fused' because the distinctions between them were small.

Mechanisms by which intersexuality might be caused were demonstrated by many of the patients recorded in this series and the absence of the two major syndromes, XXX and XYY, was probably due to the small sample size. Generally, patients exhibited the typical features of their syndromes. Particular attention was given the dermatoglyphic profiles and the information derived from this series indicated that this field of study has great potential as a diagnostic aid.

The incidence of intersexuality characterized by physical deformity at birth was surprizingly low in all four race groups of the Durban community. Because of the small numbers detected, no inter-racial distribution patterns could be

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determined. Certain patterns were discerned in regard to prevalence and it was found that gonadal dysgenesis and not hermaphroditism was the commonest form of intersex in the Bantu, and that the Bantu had only a slightly higher frequency of intersexes than did the white population. Several original observations were made; the full spectrum of gonadal dysgeneses were seen in the Bantu; a female idiopathic intersex with phallic urethra was described and the first report of adrenal hyperplasia in a Bantu was made. A useful dermatoglyphic dimorphism was discovered in chromatin negative hypogonadal males.

More extensive studies of the normal population, using the sex chromatin screening technique, were recommended; further investigation of the normal dermatoglyphic parameters is needed and there is the urgent need for more information concerning the differential diagnosis of hypogonadism in males. The importance of making an early diagnosis and instituting treatment as soon as possible was demonstrated.

The present study was rewarding but the indications are that a longer period will have to be surveyed in order to establish unequivocally that the inci- dence of intersexuality in Durban is as it has been reported here. It is also hoped that this thesis will stimulate further investigation into the epidemiology of intersexuality in South Africa.

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SUMMARY

Chapter I

The ontogeny of sex development is introduced and a definition of the inter-
sexual state is given. A resume of intersexes recorded in South Africa is
presented together with figures showing the increased demand for cytogenetic
services in the country. The motivation for this study is discussed.

Chapter II

The biological concept of sex is outlined together with notes on the evolution
of the dioecious state in animals. Thereafter a brief account of the normal
and abnormal intersex states in invertebrates and vertebrates is given.

Chapter III

Examples of some of the abundant references to ambisexual individuals found
in the classical literature, history and mythology are listed and the status
of intersexes in modern society is discussed: it does not vary much from the
times of ancient Greece and Rome.

Chapter IV

A summary of the events which led to the establishment of cytogenetics as an
independent discipline is given. The discovery of nuclear sex dimorphism is
noted and methods of investigation of intersexual patients are described. A
detailed description is given of cytogenetic technical methods, and leads to
a diagrammatic explanation of the differential diagnosis of intersexes. This
is used as a basis for the classification and accordingly a simplified, un-
ambiguous system is proposed and defended. The sources and numbers of pat-
ients recorded in this thesis are explained.

Chapter V

The sex chromatin is described in detail, with a description of the methods
used for its demonstration and evaluation. A pilot study of normal women of
the four races established taht there is no inter-racial variation in chrom-
atin frequency. Reasons are given for disregarding nuclear appendages as an
accurate indication of 'sex'.

Chapter VI

Embryological stages in the development of the human urogenital tracts are
recounted after considering the mechanisms of sex determination. Pathogenesis
of intersexuality is considered briefly,

Chapter VII

Gonadal dysgenesis of the female, including Turner's syndrome and phenotypes
of both male and female are presented. The classification, pathology, aetiol-
ogical and cytogenetic factors are described. Illustrative case reports and
extensive discussion of the syndrome are presented.

Chapter VIII

The Klinefelter syndrome occurs in males with supernumerary X chromosomes; a
number of chromatin negative, hypogonadal conditions mimic the syndrome: they
are described, with notes on the classification, pathology, aetiology and the
cytogenetic features. A series of case reports demonstrate both chromatin
positive and negative types. Special reference is made to the dermatoglyphic
profiles which were discovered to differentiate the XY males into two groups.

Chapter IX

Three syndromes, the XXX, XYY and agonadism, were not encountered in this
study and are consequently not discussed.

Chapter X

The adrenogenital syndrome has several distinctive signs which are mimicked
by induced virilization; these are described and a number of case reports
are presented to illustrate the syndromes.

Chapter XI

Male intersexes occur in several different forms: the classification of the
group is explained and a distinction is made between intersexes and those with
simple, or 'pseudo-intersexual', defects. The signs of the different syndromes
are detailed, together with data concerning the aetiology and cytogenetics. A
series of patients' case histories is used to illustrate the various syndromes.

Chapter XII

Idiopathic female intersexuality is defined and a short explanation of the
classification is given. The signs found in this syndrome are detailed and
a single case report, which is of exceptional interest because of severe
masculinization and the formation of a phallic urethra, is presented.

Chapter XIII

Hermaphroditism is defined and the subgroups are explained. The variability
of signs is discussed and details of anatomy and histology of the genital tract

are given. A single hermaphrodite was encountered during the survey and the
case is described. Three other patients, all infants, were suspected of be-
ing hermaphroditic but because gonadal biopsy was not undertaken they were
discharged from hospital without a diagnosis having been made. Discussion
of the aetiological mechanisms is presented and the need for early diagnosis
and treatment is emphasized.

Chapter XIV
Some of the simple genital anomalies and somatic defects which resemble inter-
sex are mentioned and are illustrated by attenuated case reports.

Chapter XV
The incidence of those intersexual conditions recognizable at birth by anat-
omical deformity is calculated from a total population of 21,000 live births
recorded during the calendar year, 1969. The incidence was very low (1:7000)
and does not permit analysis of inter-racial distribution. Prevalence is
calculated from the number of new patients seen by the author during 1969 in
Durban. Some interesting observations were made but the primary objective,
to determine whether or not intersexuality is more prevalent in the Bantu
than any other race, could not be answered with certainty because of the
small number of patients. Hermaphroditism was shown not to be the most
common type of intersex syndrome in the Bantu.

Chapter XVI
An outline is given of the normal dermatoglyphic features of the finger prints
and palms. Some references of the patterns in Turner's and Klinefelter's syn-
dromes are available from the literature and are compared with the profiles of
patients from this series. A distinct dimorphism was found in chromatin neg-
ative hypogonadal males and was thought to distinguish between those with con-
genital or acquired pathology. Normal values for South Africans have not been
established satisfactorily and the urgent need for this information is stressed.

Chapter XVII
A general discussion of the highlights of this study of the epidemiology, clin-
ical presentation and cytogenetics of intersexuality is given and a number of
conclusions are drawn.

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APPENDICES

Appendix I   Aceto-orcein stain

Orcein, synthetic (Gurr's)   1.0 G
Lactic acid   35 ml
Acetic acid, glacial   50 ml
Distilled water   15 ml

Infuse for 7 days before use.

Appendix II   Biebrich's scarlet stain

Biebrich scarlet, soluble   1.0 G
Phosphotungstic acid   0.3 G
Acetic acid, glacial   5 ml
Ethanol 50% aq.   100 ml

Appendix III Fast Green stain

Fast green f.c.f   0.5 G
Phosphotungstic acid   0.3 G
Phosphomolybdic acid   0.3 G
Acetic acid, glacial   5 ml
Ethanol 50% aq.   100 ml