True Hermaphroditism: Cytogenetic Analysis, Surgical Repair, and Social Implications

True hermaphroditism is rarely encountered in man. Whenever this condition exists the contradiction between genotype and phenotype stimulates an extensive investigation of such an affected individual.

The chromosomal findings of true hermaphroditism were first reported by Hungerford et al (1959) who demonstrated a 46,XX chromosomal complement in the leukocytes of peripheral blood. An attempt to simplify the nomenclature and assign a specific term to this anomaly (gonadal intersexuality) was made by Russell (1954). Overzier (1964) reviewed the findings of 171 authenticated cases of true hermaphroditism reported in the literature and of these cases only 14 had the benefit of cytogenetic analysis. However, with the progress in cytogenetic techniques and the incorporation of gonadal biopsies more comprehensive analyses have been reported. From this it has become apparent a normal female 46,XX karyotype is the usual finding in true hermaphroditism with the exception of a limited few who demonstrate a 46,XY chromosomal complement or a variant due to mosaicism.

The diagnosis of true hermaphroditism requires the demonstration of both ovarian and testicular tissue in the same individual. These patients usually have varying degrees of ambisexual development. The testicular tissue is generally located in the scrotum or outside the abdomen, while the ovarian tissue is usually found in an intra-abdominal position.

Hinman (1935) classified true hermaphroditism into four categories. 1) Bilateral with testis and ovary or ovotestis on each side and usually demonstrating a uterus and tubes. 2) Unilateral with ovotestis on one side and an ovary or testis on the other side (these appear to be the most frequent). 3) Lateral with testis on one side and an ovary on the other side. 4) Indeterminates with no conformity as to location or type of gonadal tissue.

Case Report

Clinical History and Details of Surgical Repair. The patient was a well developed, well nourished, alert, cooperative 3-year-old Tunisian child with no visible anatomic abnormalities other than ambiguous genitalia. He was the 3rd sib of a normal healthy young mother aged 26 at the birth of the propositus. There was no history of hormonal therapy or other medication taken prenatally. The pregnancy was normal and delivery in a local Tunisian hospital was without incident with a sage-femme (midwife) in attendance. There was no history of consanguinity nor was there a history of any similar defect in the family. The child progressed normally, walked and talked at approximately one year. This child was being reared as a male despite the fact that the ambiguous genitalia were noted at birth.

Physical examination of the external genitalia revealed a small phallus which lacked a penile aperture. A slit-like mucosal lined aperture resembling a urogenital sinus was located on the ventral side at the base of the phallus. Urine was voided through this slit-like aperture and caused the child no discomfort. The scrotum was not fused and gave the appearance of labia. Palpable masses in both inguinal areas could be expressed downward into the labia like structures. A chordee was present.

Laboratory examinations were not remarkable; creatinine, urea, total protein, and electrolytes were all within normal range. Urinary excretion of 17-ketosteroids (2-8 mg/24 hr) was within normal limits for age of the patient. No tests for 17-hydroxycorticoids or gonadotropins were available. Retrograde cystography and voiding urethrography indicated a normal male-type urethra with no unusual bladder neck obstructions. There was no evidence of urethral reflux. Intravenous pyelograms showed bilateral reduplication of the renal
collection systems. This is a normal variant and was not thought to be relevant, apart from this the urinary tract appeared functionally and anatomically normal. Radiology showed a normal bone age and no abnormalities in the thorax.

Laparotomy revealed bilateral cryptorchid ovotestes; there was no evidence of a uterus. A right and left vas deferens were present along with a male type bladder and prostate. Bilateral gonadal biopsies were taken. The gonads, both grossly ovotestis, were then delivered through an incision in the tunica vaginalis and placed in the under developed scrotal sack and fixed. The chordee deformity was corrected.

Biopsy material showed: On the right side a 0.7 cm irregular nodule of tissue with a generally roughened surface showing areas of a smooth shiny white membrane or capsule. Histological sections showed a typical infantile ovarian pattern with many ova and a few small follicles in the cortex, as well as infantile testicular tissue. The left side showed 4 pieces of tissue ranging from 0.3 to 0.8 cm. Histological sections showed infantile ovarian tissue, Fallopian tube type tissue, and a small portion of infantile testicular tissue. These are usual findings when ovotestes are present (Fig. 1).

A second surgical procedure for removal of the ovarian tissue was performed. On the right a 1 x 0.5 cm mass of gritty yellow ovarian tissue was removed in toto from the newly fixed testis. On the left the ovarian portion of the ovotestis was not well demarcated and appeared fused with the testicular tissue, however the ovarian tissue was removed as completely as possible from the newly fixed testis. Following an uneventful recovery the child was discharged in good condition.

**Cytogenetics**

Buccal smears were taken from all members of the immediate family and showed the 2 normal female sibs as well as the mother to be sex chromatin positive. The father was sex chromatin negative. Repeated buccal smears from the propositus were sex chromatin positive. A known sex chromatin positive control was used to confirm all buccal smears results (Table I). The laboratory which did this study took a count of 15% to be sex chromatin positive.

Peripheral blood smears from the propositus showed 2% of the neutrophils to have sex chromatin appendages (drumsticks).

Analysis of 200 cells from three peripheral blood leucocyte cultures from the propositus showed only a normal female 46,XX chromosome complement (Table II and Fig. 2).

Fibroblast cultures were not available in Tunisia so that neither the biopsied gonadal tissue nor skin could be used to exclude the possibility of a Y chromosome being present in other tissues.

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**Fig. 1.** Photomicrographs of ovotestis. (x 150.)
Left: Testicular portion showing immature seminiferous tubules containing sertoli cells.
Right: Ovarian portion showing infantile ovarian tissue with a few primordial follicles.
### Table I

**SEX CHROMATIN DETERMINATIONS**

<table>
<thead>
<tr>
<th>Number of Buccal Smears</th>
<th>Number of Cells Counted</th>
<th>Number of Cells with a Barr Body Present</th>
<th>Percentage of Barr Bodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propositus</td>
<td>5</td>
<td>5000</td>
<td>773</td>
</tr>
<tr>
<td>Mother</td>
<td>2</td>
<td>500</td>
<td>109</td>
</tr>
<tr>
<td>Sib 1</td>
<td>2</td>
<td>500</td>
<td>148</td>
</tr>
<tr>
<td>Sib 2</td>
<td>2</td>
<td>500</td>
<td>163</td>
</tr>
<tr>
<td>Father</td>
<td>3</td>
<td>1000</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>2</td>
<td>200</td>
<td>56</td>
</tr>
</tbody>
</table>

*Thought to be random loss.*

### Table II

**CHROMOSOME COUNTS OF CELLS FROM CULTURED PERIPHERAL BLOOD**

<table>
<thead>
<tr>
<th>Chromosome No.</th>
<th>Number of Cells Analysed in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture 1</td>
</tr>
<tr>
<td>45</td>
<td>1*</td>
</tr>
<tr>
<td>46</td>
<td>66</td>
</tr>
</tbody>
</table>

### Fig. 2

Karyotype from peripheral blood 46,XX.

### Discussion

The exact mechanism causing true hermaphroditism has yet to be fully understood. Pedigree studies have not shown conclusive evidence for a familial heritable factor, although a report of 3 affected brothers (Rosenberg, 1963) suggests such a mechanism. All 3 brothers were sex chromatin positive and had a 46,XX karyotype. This case has been listed by McKusick (1968) as an autosomal recessive. One autosomal recessive in each parent would produce one quarter affected genetic female sibs. Other explanations for such a heritable factor might be: a dominant mutant, X-linked or autosomal. The X-linked dominant mutant would produce one half affected genetic female sibs, while an autosomal or a maternal X-linked dominant mutant would produce one half affected genetic female sibs. A sex-linked recessive depressor gene in both parents would result in an expected one half affected genetic female sibs and all normal male sibs. This mode of inheritance would suggest a heterozygous female carrier, as well as an unaffected hemizygous male carrier which would result in more frequent appearance of affected genetic females (on a population basis) than would be expected with an autosomal recessive gene.

Approximately 80% of all true hermaphrodites have a 46,XX karyotype. Ferguson-Smith (1966) suggested that one of the X chromosomes contains the testicular determining gene, normally found on the Y chromosome, due to a DNA exchange during the development of the embryo.
meiosis thus providing a genetic make up of XX'v.
If the Lyon hypothesis is correct then variations in
gonadal tissue could be accounted for by random
inactivation of the X or X'v chromosome.

Still another possible explanation, as suggested by
McFeely, Hare, and Biggers (1967), is the presence of
a mutant male derepressor gene present on one of
the X chromosomes which would function in a
manner similar to that of an active Y chromosome.
Additional supportive evidence for a male
deressor gene has been given by Hamerton et al
(1969) in their work on genetic intersexuality in
goats. Evidence was presented for a male dere-
sessor gene tightly linked with the autosomal
dominant 'P' (polled = lack of horns) gene. Phen-
typic variability could be due to incomplete pene-
 trance and degree of expressivity of a derepressor
gene.

Sex chromosome mosaicism has been demon-
strated in true hermaphroditism by Mentz (1968),
Mosaicism may result from the fusion of 2 blasto-
meres, each resulting from an individual fertili-
 zation of 2 ova or an ova and a polar body. Sub-
sequent genetic competition between cell lines would
determine which would predominate as suggested by
Herschler and Fechheimer (1967). There is
also the possibility of cells from a second embryo
passing the placental barrier into the first embryo
thus producing an organism genetically and chro-
mosomally chimeric. Death and reabsorption of
this second embryo would result in its loss account-
ing for a single chimeric offspring.

After a review of other studies done in both
human and animal true hermaphroditism, it is sug-
gested as a possible explanation for human familial
transmission of this anomaly that a sex-linked
deressor gene may be present in the population.

This case report and its ensuing surgical repair is
of interest for several reasons. A uterus is present
in the vast majority of such patients (Butler et al,
1969; Federman, 1969). This patient showed no
evidence of a uterus. The case study, counselling,
and surgery were done in Tunisia by American
medical personnel. The total management of this
patient necessitated an entirely different approach
due to the cultural, social, and economic differences.
The need for familial genetic studies, beyond buccal
smears, was not deemed necessary within the cul-
tural pattern of this child's family. Such thinking
of course ruled out a pedigree analysis or a more
complete study. The child had been reared as an
only son and the father felt strongly that this status
must be preserved no matter what the genetic sex
might be. Eventual sterility for this child would
have no grave social consequences as a male, while
as a female, sterility would result in severe social
problems. To be a nonfecundating woman, proven or otherwise, would be a well grounded
cause for the dissolution of her marriage. Which in
turn would necessitate the ability and the opportu-
nity for such a woman to be self supporting. Neither
of these two conditions prevail at the present time
for the vast majority of women in Tunisia. The
American point of view in the assignment of sex is
not necessarily that of, nor perhaps most efficacious
for, peoples reared within the structure of other
cultural patterns. The strong feelings of this de-
 voted, well meaning father were no different than
those of his fellow country men.

It was not an objective of the medical personnel
involved with this case to offer suggestions that
would be contrary to the normal concepts of this
family, thus the immediate surgical repair decided
upon was perhaps the most prudent for all con-
cerned.

Summary

A 3-year-old child with ambiguous genitalia was
found at laparotomy to have bilateral ovotestis,
Fallopian tube type tissue but no uterus. Histol-
ogical examination of the gonadal tissue revealed
both ovarian and testicular tissue. There were
15% chromatin positive cells found in buccal
smears. Cultured leucocytes consistently showed
a 46,XX chromosome complement. The possi-
bility of an X-linked derepressor gene for this
anomaly is suggested. Indigenous social patterns
were a contributing factor to the surgical course
taken.

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REFERENCES

Butler, L. J., Snodgrass, G. J. A. I., France, N. E., Russell, A.,
and Swain, V. A. J. (1969). True hermaphroditism or gonadal inter-
sexuality. Archives of Disease in Childhood, 44, 666-680.
Philadelphia and London.
Ferguson-Smith, M. A. (1966). X-Y Chromosomal interchange in
the aetiology of true hermaphroditism and of XX Klinefelter's
syndrome. Lancet, 2, 475-476.
Hamerton, J. L., Dickson, J., Pollard, C. E., Grieves, S. A., and
Two Cases of Trisomy D Associated with Adrenal Tumours*

It is becoming increasingly clear that congenital abnormalities due to chromosomal aberrations may be associated with a high incidence of neoplastic disease (Miller, 1966). In patients with Down’s syndrome, the prevalence of leukaemia is increased 20-fold compared with the general population (Wald et al, 1961) and recent reports indicate that other autosomal aberrations also may have a propensity for developing neoplastic disease (Schade, Schoeller, and Schultze, 1962; Zuelzer, Thompson, and Mastrangelo, 1968; Geiser and Schindler, 1969).

The present report describes two cases of trisomy D associated with adrenal tumours.

Case Reports

Case 1. The youngest of 6 sibs, this boy was born on 2 May 1965 to unrelated healthy parents aged 38 (mother) and 52 years (father). Birthweight was 2950 g; delivery was normal. There was no radiation exposure, viral infection during pregnancy, or previous fetal loss. The remaining sibs (3 sisters and 2 brothers) were normal.

Multiple abnormalities were present at birth. The head was small with several mid-line scalp defects. The face was moon-shaped with bilateral microphthalmia, corneal opacities, low-set abnormal ears, a left accessory auricle, a severe bilateral hare lip, and a wide cleft involving both hard and soft palate. There was an extra digit on the right hand and on the left foot. Fingers were tightly flexed and the elbows showed a flexion deformity. Testes were small and the penis showed a mild degree of hypospadias.

Skeletal radiology showed no abnormality other than a thin cranial vault. Chromosome analysis was done on preparations of peripheral blood. Of 30 metaphases studied, all but 2 cells, which had a normal diploid number, had 47 chromosomes with the additional chromosome in the D group (47,XY,D+). The chromosomes of both parents were normal.

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