XX True Hermaphroditism in Southern African Blacks: An Enigma of Primary Sexual Differentiation

Michele Ramsay,* Renee Bernstein,* Esther Zwane,* David C. Page,† and Trefor Jenkins*

*MRC Human Ecogenetics Research Unit, Department of Human Genetics, School of Pathology, South African Institute for Medical Research and University of the Witwatersrand, Johannesburg; and †Whitehead Institute for Biomedical Research, Cambridge, MA

Summary

A high incidence of 46,XX true hermaphroditism exists among southern African blacks. The gonadal distribution and clinical presentation of 38 patients are described. The aim of our study on 11 families with histologically proven XX true hermaphroditism was to determine whether a common genetic or environmental etiology could be identified. Pedigree analysis excluded the presence of a simple inheritance pattern, and no constant environmental factors could be implicated. Hybridization studies with Y chromosome–specific probes (pDP132, pDP61, pDP105, pDP31, pDP97, and pY431-HinfA) excluded the presence of a large portion of Yp in these patients. It is possible that smaller portions of the Y chromosome or one or more X-linked or autosomal mutations, either interacting and/or with incomplete penetrance, are present.

Introduction

A true hermaphrodite is an individual in whom both testicular and ovarian tissue are present. External genitalia are often ambiguous. More than half of the reported cases have a 46,XX karyotype (Van Niekerk 1974, 1976; Donahoe et al. 1978); the remainder have a 46,XY karyotype or sex-chromosome mosaicism.

In southern Africa numerous patients with both ovarian and testicular differentiation and ambiguous genitalia have been observed. With the exception of three caucasoids (referred to as whites in the present paper) and two individuals of mixed caucasoid-negroid ancestry (Grace and Edge 1973; Roux et al. 1974; Van Nierkerk 1974), all cases documented from southern Africa have been Bantu-speaking negroids (referred to as blacks in the present paper) of two main ethnic subdivisions, the Nguni and Sotho speakers (Klempman 1964; Dinner 1969; Wilton

1969; Grace 1970; Roux et al. 1974; Van Niekerk 1974, 1976; Van Niekerk and Retief 1981a, 1981b; de Souza et al. 1984). The vast majority of these patients have shown a 46,XX karyotype.

Neither the etiology of XX true hermaphroditism nor the reason for its relatively high frequency among southern African blacks is known. The present study was initiated with three objectives in mind: (1) to determine the incidence of XX true hermaphroditism among black and white patients referred for cytogenetic investigation of sexual ambiguity and to review their clinical features; (2) to establish, on the basis of pedigree analysis, whether the condition has a straightforward genetic basis; and (3) to determine whether these patients' genomes contain detectable Y-specific DNA sequences, as is true of most XX males (Guellaen et al. 1984; Page et al. 1985; Affara et al. 1986; Müller et al. 1986; Vergnaud et al. 1986; Buckle et al. 1987).

Material and Methods

From 1976 to 1985, we ascertained 152 black and 31 white patients with ambiguous genitalia and a 46,XX karyotype. Sources of referral were diverse and included distant rural hospitals, peripheral urban
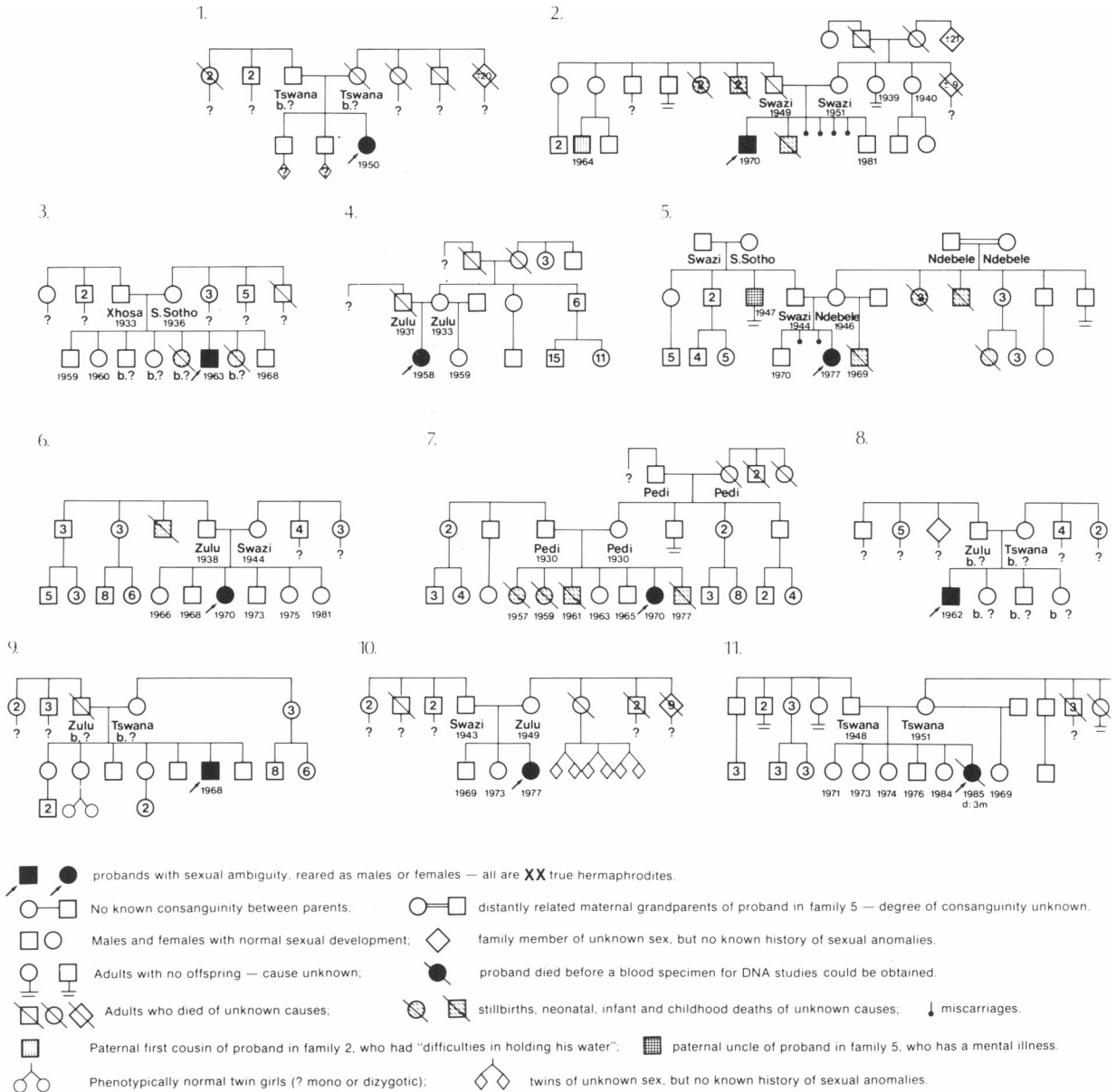
Figure 1   Pedigrees of 11 families with XX true hermaphroditism

hospitals, and academic referral hospitals. These 183 cases were reviewed so as to identify histologically proven true hermaphrodites. Only those cases in which both testicular tissue (with distinct tubules) and ovarian tissue (containing follicles) were histologically demonstrable were classed as true hermaphrodites. Gonadal distribution in the proven cases was classified according to the criteria established in 1935 by Hinman (quoted in Van Niekerk 1974).

Pedigrees of 11 black families with proven cases

were compiled (fig. 1), and a structured interview posed questions designed to establish a possible genetic or environmental etiology.

Chromosome Studies

Metaphases were derived from 72-h phytohemagglutinin-stimulated and methotrexate-synchronized peripheral blood cultures (Yunis 1976). Fibroblast cultures were established from skin and/or gonadal biopsies in six of the patients. Giemsa (GTG) and

Table I

Y Chromosome–specific Probes

Probe	Y-Chromosome Deletion Interval[a]	Restriction Enzyme	Y-specific Fragment Size (kb)	Reference
pDP132 (DXYS23)	1	TaqI	4.4	D. C. Page, unpublished results
pDP61 (DXYS8)	2	TaqI	2.1 or 2.6	Geldwerth et al. 1985;[b] D. C. Page, unpublished results
pDP105 (DYZ4)				D. C. Page, unpublished results
pDP105/A	3	TaqI	2.3	
pDP105/B	6	TaqI	5.1	
pDP31 (DXYS1)	4A	TaqI	15	Page et al. 1984
pDP97 (DYZ3)	4B	EcoRI	5.5	Wolfe et al. 1985;[c] D. C. Page, unpublished results
pY431-HinfA (DYZ2)	7	EcoRI	Several	K. Smith, personal communication

[a] Source: Page (1986) and Vergnaud et al. (1986).
[b] Probe derived from plasmid 115.
[c] Probe derived from cosmid Y 97.

quinacrine (QFQ) banding of the chromosomes was performed. In some cases, buccal smears were examined for X and Y chromatin.

Molecular Hybridization Studies

Peripheral blood samples were obtained from 10 histologically proven black XX hermaphrodites and from the majority of their mothers and fathers. DNA was extracted according to the method of Sykes (1983). DNA from the probands and parents was digested with either EcoRI or TaqI, electrophoresed in 0.8% agarose, transferred to nitrocellulose or nylon membranes (Southern 1975), and hybridized with the six Y chromosome–specific DNA probes described in table 1. Hybridization studies using probes that detect X-linked RFLPs were performed on five complete families (father, mother, and proband) in order to test paternal and maternal inheritance of the two X chromosomes in the proband (Page and de la Chapelle 1984). Probes L1.28, RC8 (Davies et al. 1983), pDP31 (Page et al. 1984), and St 14 (Oberle et al. 1985) were used for this purpose.

Results

Of 152 blacks with ambiguous genitalia and a 46,XX karyotype, the diagnosis of true hermaphroditism was proved in all 38 who were histologically investigated. Of 31 whites with ambiguous genitalia and a 46,XX karyotype, none were shown to be true hermaphrodites on histological examination.

The gonadal distribution of ovarian and testicular tissue in the 38 proven black hermaphrodites is shown in table 2. Testicular tissue was identified on the right side (32 cases) far more frequently than on the left side (15 cases).

Clinical Data

Clinical data are summarized in table 3. Of 38 patients studied, 16 were <5 years of age and 12 were postpubertal when the diagnosis was made. As most patients were not personally seen, their gender identity is uncertain, but the majority of probands diagnosed after 5 years of age were confused about their sexual identity, and several had distressing psychological problems.

The cardinal presenting feature in all 38 patients was a phallus of abnormal size, termed an "enlarged clitoris" in patients reared as females or termed a "small penis" in patients reared as males. A separate vaginal opening was noted in 14 of 24 cases, but the vagina was rudimentary in most such cases. In no case were gonads palpable bilaterally. A gonad was palpable unilaterally in 13 of 29 patients, but in six of these the gonad was situated in the inguinal canal. The gonad was more frequently palpable on the right side. In one individual two ovotestes were found in a right hemiscrotum. Information on labial/scrotal differentiation was available on 23 patients: 16 showed either labial/scrotal fusion or a bifid scrotum. A description of the internal genitalia at the time of gonadal biopsy was available for 22 patients, 20 of

Table 2

Gonadal Distribution in 37[a] Southern African Black XX True Hermaphrodites

GONAD DISTRIBUTION	SIDE		NO. OF PATIENTS
	Left	Right	
Individual:			
Lateral	Ovary	Testis	5 ⎱ 6 (16.2%)
	Testis	Ovary	1 ⎰
Bilateral	Ovotestis	Ovotestis	7 (18.9%)
Unilateral	Ovary	Ovotestis	15 ⎱ 19 (51.4%)
	Ovotestis	Ovary	4 ⎰
	Testis	Ovotestis	2 ⎱ 3 (8.1%)
	Ovotestis	Testis	1 ⎰
Other	?	Ovotestis	2 (5.4%)
Total			37
Total:			
Ovaries	20 (57.1%)	5 (13.5%)	25 (34.7%)
Testes	3 (8.6%)	6 (16.2%)	9 (12.5%)
Ovotestes	12 (34.3%)	26 (70.3%)	38 (52.8%)
Total	35	37	72

[a] The histological report on the 38th patient cannot be traced to determine the exact gonadal distribution.

Table 3

Clinical Data on 38 Southern African Black XX True Hermaphrodites

Parameter	No. of Patients	Total No. Assessed[a]
Assigned name	18 M; 17 F; 3 N	38
Sex of rearing	13 M; 17 F; 3 A	33
External genitalia:		
Enlarged clitoris (or small phallus)	38	38
Hypospadias with perineal urethral meatus	33	35
Urogenital sinus	12	28
Separate vaginal opening with formed vagina	14 (9 R)	24
Palpable gonads:		29
Left	5 (2 I)	
Right	8 (4 I)	
Anomalous labial/scrotal differentiation:		23
Labio-scrotal fusion	6	
Bifid scrotum	10	
Uterine and fallopian tube differentiation	20 (9 R, 2 H)	22
Anomalous secondary sexual differentiation in postpubertal patients (N = 12)[b]	8	10

NOTE.—Median age of the 38 patients at time of presentation was 8 years (range 1 day–39 years). M = Male; F = Female; N = Neutral; A = Ambivalent; R = Rudimentary; H = Hypoplastic; I = Inguinal.

[a] Number of individuals on whom the relevant information was available.

[b] Refer to text for details.

whom had recognizable (though often rudimentary or hypoplastic) uterus and fallopian tubes. One patient had a bicornuate uterus.

Secondary sexual characteristics are known in 10 of 12 postpubertal patients; eight showed secondary sexual characteristics contrary to their sex of rearing. All five "males" had anomalous secondary sexual characteristics. Gynecomastia was present in four of them and was associated with a gynecoid body contour in three of them. One lacked facial hair. One of these individuals claimed that he performed adequately as a male. Two males complained of hematuria, but it is not clear whether this was cyclic. Of the five "females" two had no secondary sexual anomalies; both menstruated and had well-developed breasts. A third woman who menstruated had an android build, whereas another had well-developed breasts, was amenorrheic, had severe acne, a deep voice, and led a bisexual sex life. One female with very small breasts complained of cyclic hematuria.

Pedigree Analysis Based on Interviews

None of the 11 sets of parents was known to be related. The only instance of consanguinity occurred in family 5, in which the proband's maternal grandparents were related; but their degree of relatedness is uncertain (fig. 1).

The probands' parents originated from seven different negroid chiefdoms (fig. 1). The Zulu, Swazi, and Xhosa are ethnically related, Nguni-speaking peoples who do not approve of consanguineous marriages. The Ndebele are related to the Nguni-speakers but form an ethnically distinct group in which there is not such a strong taboo against cousin marriages. The second large group are the Sotho-speakers, consisting of Tswana, Sotho, and Pedi, among whom consanguineous marriages are relatively common (Nurse et al. 1985). Of the 11 families surveyed (fig. 1), five couples were from the same chiefdom (two were Nguni-speakers and three were Sotho-speakers), three were from related chiefdoms, and three were from ethnically unrelated chiefdoms. The 11 probands collectively had 42 siblings (excluding six miscarriages), whose sex ratio was 0.91male:1 female (fig. 1), which is not significantly different ($\chi^2_{[1]}$ = 0.24; $P > 0.5$) from the sex ratio of 1.06males:1 female in the general South African black population (South Africa [Republic] Department of Statistics 1982). The sex ratio (1.08males:1female), of all 145 male and 134 female relatives was again not significantly different ($\chi^2_{[1]}$ = 0.5 $P > 0.8$) from that in

the general population (South Africa [Republic] Department of Statistics 1982). There is no indication that the 51 individuals of unknown sex showed any features of sexual ambiguity.

Likewise, there was no indication in any of the pedigrees (fig. 1) that the probands had similarly affected siblings, nieces, nephews, aunts, uncles, or cousins (none of the siblings or other family members were, however, personally examined to confirm their phenotypic normality). Many of the probands' siblings had died of unknown causes before puberty, but this is perhaps not unusual in families from a socioeconomically deprived community, in which the infant mortality rate is high.

Four of 58 adult maternal siblings (two males and two females) had no children, and five of 52 paternal siblings (four males and one female) were childless (fig. 1). There is no indication that any of these individuals either was childless because of infertility or had any anomaly of sexual differentiation.

None of the probands was a twin or had twin siblings. The proband in family 9 (fig. 1) had twin nieces, and the maternal aunt of proband 10 had apparently given birth to three sets of twins whose sexes and zygosity are not known. DZ twinning is relatively common in South African blacks—12.5/1,000 births compared with 3.8/1,000 births for monozygotic twins (J. Kromberg, personal communication).

The parental ages are known in eight of the 11 families (fig. 1). The median age of eight mothers at the time of their affected child's birth was 26.5 years, with a range of 19–40 years. The median age of eight fathers was 32.5 years, with a range of 21–40 years. These median ages are not strikingly different from that estimated for the black community in general (W. P. Mostert, personal communication). The proband was the last born in four families and second last in three families. Only three of the 11 probands were first born (fig. 1).

No useful information was obtained about the use of conventional or traditional medications during pregnancies leading to the birth of probands.

Cytogenetic Studies

Sex-chromatin screening of buccal smears was performed in 13 of 38 patients. Their X-chromatin values ranged between 20% and 30% (>15% is accepted as the lower limit in our laboratory for nonmosaic XX individuals). None of them showed any Y chromatin–positive nuclei. A total of 2,132 meta-
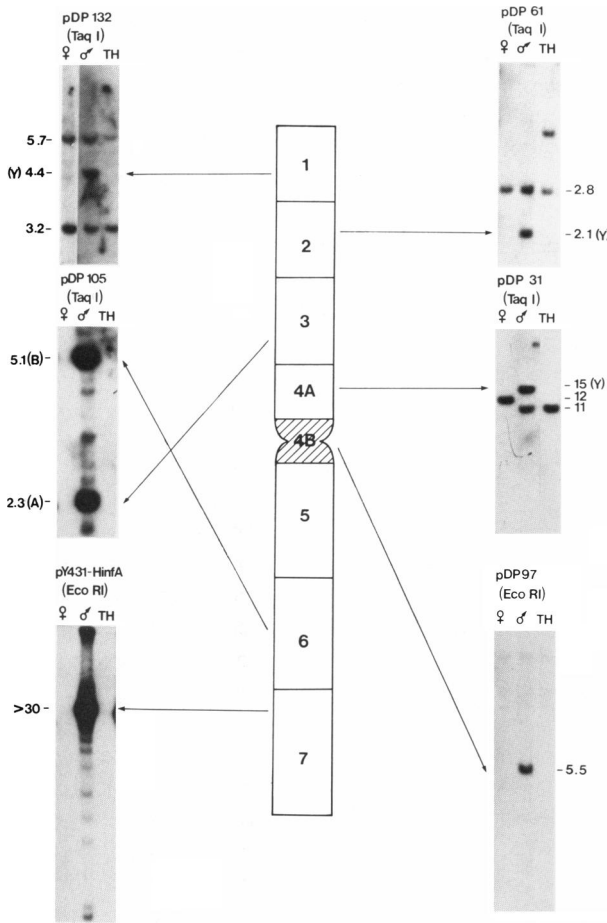
Figure 2   Hybridization patterns with 6 Y-specific probes (described in table 1), showing absence of a Y band in an XX true hermaphrodite (TH) (right lane) and a normal female control (♀) (left lane), in contrast to the Y-positive bands seen in a normal male control (♂) (middle lane). All 10 hermaphrodites had the same negative patterns as shown for one of them, in this figure.

phases were analyzed in 38 patients (a mean of 56 cells/patient). Giemsa banding revealed two morphologically normal X chromosomes, and no quinacrine fluorescence, indicative of the Yq12 region, was detected. In six patients, cultures of both ovarian and testicular portions of gonadal biopsies revealed a normal 46,XX karyotype.

Molecular Hybridization Studies

DNA from 10 probands (a blood sample was not obtained from proband 11) was tested, and the Y-specific fragments detected by probes pDP132, pDP61, pDP105, pDP31, pDP97, and pY431-*Hinf*A were absent (fig. 2). Hybridization studies for the X

chromosome–specific RFLPs were done to determine the parental origin of the X chromosomes in the probands. Probe St 14 was informative in three families, showing that one X was paternally inherited and the other maternally inherited. Probes pDP31, L1.28, and RC8 were not informative in showing the parental derivation of the X chromosomes of the proband in any of the five complete families.

Discussion

Incidence of XX True Hermaphroditism in Southern African Blacks

In southern Africa ambiguous genitalia seems to be much more common in blacks than in whites. Even though more than twice as many whites as blacks were referred to our laboratory for cytogenetic studies during the period 1976–1985, 152 black and only 31 white patients were referred because of ambiguous genitalia and found to have a 46,XX karyotype. Thirty-eight (20%) of the black patients were histologically proved to be true hermaphrodites; the remaining 114 had an XX karyotype but were not histologically examined. None of the white patients was a histologically confirmed true hermaphrodite (the majority were affected by congenital adrenal hyperplasia). Thus, this type of hermaphroditism is unusually prevalent in southern African blacks. This leads to the conclusion that there must be some unique factor(s) causing the high incidence of this sexual anomaly in blacks. Furthermore, it seems likely that the condition has a common etiological and pathogenetic basis in this population.

The results of cytogenetic studies argue against any of the 38 cases being a 46,XX/46,XY chimera. Similarly, DNA hybridization studies that used highly repeated sequences on the Y chromosome as probes provided no evidence of mosaicism in any of the 10 patients investigated. The proportion of 46,XX as opposed to 46,XY and mosaic true hermaphrodites in southern African blacks appears to be much higher than those reported from other areas of the world: among our cases only one other black hermaphrodite (who was a 46,XX/46,XY chimera and was not included in this study) was identified. Similarly, the great majority (26 of 27) of Van Niekerk's cases were black, and all 24 of his chromosomally investigated cases had an XX karyotype (Van Niekerk 1974, 1976), compared with a frequency of only 59% in true hermaphrodites worldwide (Van Niekerk and Retief 1981a).

Clinical Findings

The anomalies of the external genitalia were similar to those described by Van Niekerk (1974, 1976). The majority had a perineal urethral meatus, but a separate vagina (albeit rudimentary in most cases) was found in approximately half of the cases. The other patients had a common urogenital sinus. Whereas in Van Niekerk's (1976) survey 13 cases had bilaterally palpable gonads, this was not true in any of our patients. A unilateral gonad was more often palpable on the right side, a finding that conforms with the more frequent presence of right-sided testicular tissue.

Information on the internal genitalia is scanty. In common with patients reviewed by Van Niekerk (1976), the majority (91%) of our patients had a uterus, albeit rudimentary or hypoplastic in many. Three of the five postpubertal females had menstruated, compared with 30% in Van Niekerk's series. Two of the five postpubertal phenotypic males and one phenotypic female complained of hematuria, which was possibly cyclic: very few such cases are recorded in the literature (Van Niekerk 1974). In our postpubertal cases, seven of 10, exactly the percentage reported by Van Niekerk (1976), had well-developed breasts.

The distribution of ovarian and testicular gonadal tissue in this study is remarkably similar to that found by Van Niekerk (1974, 1976). The most common distribution is the unilateral type, with an ovary on one side and an ovotestis on the other; it was found in >50% of the southern African patients, compared with a frequency of only 29% in the cases from the rest of the world (reviewed in Van Niekerk and Retief 1981a). In the great majority ovaries were found in the left pelvis, whereas the converse was true for testes, which were far more frequently confined to the right side, a feature also noted by Van Niekerk (1974, 1976) and Van Niekerk and Retief (1981a). Asymmetry of gonadal development in true hermaphrodites (and during normal gonadal development) may be the result of differential growth rates on opposite sides of the body (Mittwoch 1986).

It was distressing to note that only 16 of the 38 patients were <5 years of age when first investigated. It is well recognized that an appropriate sex assignment and surgical correction should be undertaken before 5 years of age, by which time gender identity is firmly established (reviewed in Ehrhardt and Meyer-Bahlburg 1981). This was borne out by the 11 patients and their families who were personally interviewed by one of us (E.Z.); seven of these patients had been diagnosed after 5 years of age. The emotional problems due to confused gender identity in these individuals attests to the tragic consequences of late diagnosis. Of 10 postpubertal individuals, eight had to contend with anomalous secondary sexual characteristics, in addition to their ambiguous genitalia.

Approximately equal numbers of patients were assigned male or female names, but slightly more were reared as females, whereas 75% of reviewed cases were reared as males (Van Niekerk and Retief 1981a).

Pedigree Analysis: Possible Genetic or Environmental Etiology

Detailed family histories were obtained for 11 of the 38 patients. Close questioning failed to reveal relatedness between any of these families. Only within family 5 was consanguinity reported, and this between the proband's maternal grandparents. No similarly affected family members were reported. The sex ratios in siblings and other relatives were not significantly different from that found in the general population, and reduced fertility does not appear to be present. It seems unlikely, therefore, that mutation of a single gene, either autosomal or sex linked, is responsible for the occurrence of the hermaphroditism in this population. There was no clustering in any particular chiefdom. As twinning is common in blacks (J. Kromberg, personal communication), the possibility that true hermaphrodites may be chimeras from a resorbed twin was explored. No siblings of the true hermaphrodites were twins (though in families 9 and 10 there were four sets of twins among the nieces and nephews of the proband). It therefore seems unlikely that twinning is the etiology of true hermaphroditism in blacks. The rarity of cytogenetically detectable XX/XY chimerism among the black hermaphrodites (one of 39 cases) also argues against twinning being a significant factor. As the twinning rate is declining in this population (J. Kromberg, personal communication), it will be of interest to see whether the rate of true hermaphroditism also declines.

An environmental etiology is extremely difficult to exclude. Three of the 11 mothers had taken differing "traditional" remedies of unknown composition. The above findings do not point to any discrete genetic or environmental etiology, but the strikingly higher frequency of XX true hermaphroditism in

southern African blacks indicates that there is likely to be some form of predisposition in this population.

DNA Hybridization Studies

XX males, who have small testes and are invariably sterile, have been studied in much greater detail than have XX true hermaphrodites. Although most XX males are sporadic, a few instances of familial clustering have been reported (de la Chapelle 1981). Ferguson-Smith (1966) proposed that an X-Y chromosome interchange was involved in the etiology of both XX males and XX true hermaphroditism. Some XX males have been shown to have an extra band on Xp which seemed to originate from Yp (Magenis et al. 1982). Studies on the inheritance of the Xg(a) blood group antigen and of the 12E7 antigen indicated that X-Y interchange had occurred on the paternally inherited X in two families of XX males (de la Chapelle et al. 1984). Molecular studies demonstrated that Y-specific DNA sequences were present in most XX males (Guellaen et al. 1984; Page et al. 1985; Affara et al. 1986; Müller et al. 1986; Vergnaud et al. 1986; Buckle et al. 1987).

Using probes that contain highly repeated Y chromosome sequences, in situ hybridization to metaphase chromosomes of three XX males showed that in each case Y material was present on the short arm of one of the X chromosomes (Andersson et al. 1986; Magenis et al. 1987). This evidence supports the hypothesis that maleness in XX males is frequently the result of the transfer of Y material to the paternally inherited X chromosome. Recent studies of the inheritance of pseudoautosomal RFLPs have shown that most XX males are due to the exchange of terminal portions of the short arms of the X and Y chromosomes (Page et al. 1987a; Petit et al. 1987).

The Y-specific sequences present in XX males and deleted in some XY females demonstrate that a particular small portion of distal Yp is male determining (Page 1986). Some of these sequences were tested for in the present group of hermaphrodites; none was found to be present.

In the present study of 10 histologically confirmed hermaphrodites, there was no hybridization to the probes representative of deletion intervals 1 (pDP132), 2 (pDP61), 3 (pDP105/A), 4a (pDP31), 4b (pDP97), 6 (pDP105/B), and 7 (pY431-HinfA) (described in Page 1986) (table 1). Since the completion of the present study, Page et al. (1987b) have cloned a Y-specific probe (pDP1007) that is a putative candidate for the testis-determining factor (TDF) gene.

Hybridization of this probe to TaqI blots of several of the cases in the present study and of other XX true hermaphrodites yielded negative results (D. C. Page, unpublished data). Although these findings do not definitively exclude the presence of Y-chromosome material, it is very unlikely that these hermaphrodites have TDF, indicating an etiological difference between most XX males and XX true hermaphrodites. Mosaicism for a Y-bearing cell line is difficult to exclude cytogenetically but was convincingly excluded by the lack of hybridization to highly repeated sequences, represented by probes pDP105 and pY431-HinfA, on the Y chromosome.

The X-linked RFLP detected by St 14 showed that in three of the five complete families one X was paternally derived and the other maternally derived, as has been shown to be the case in XX males (Page and de la Chapelle 1984).

The relatively high incidence of this condition in southern African blacks remains a puzzling phenomenon. All our cases were sporadic, but a familial occurrence has been described. A family with three affected "brothers" has been described (Rosenberg et al. 1963), as has a family with XX males and XX true hermaphrodites (Skordis et al. 1987). In the latter family a paternal uncle with XX true hermaphroditism had a niece who was an XX true hermaphrodite and two nephews who were XX males; Skordis et al. (1987) suggest that the two conditions are alternative manifestations of the same genetic defect. This hypothesis seems unlikely in the case of southern African blacks, in whom XX hermaphroditism is common but XX maleness is rare.

There was no uniform chiefdom affiliation, and the sex ratio of relatives was not significantly different from that of the general black population. Twinning was not common in these families, though it is in the general black population, a discordance indicating that chimerism caused by a resorbed twin is not likely to be the cause of the condition. Only one of the 39 black hermaphrodites in our 10-year study was an XX/XY chimera, a proportion considerably lower than has been found elsewhere in the world (reviewed in Van Niekerk and Retief 1981a).

There are many theories explaining the genetic basis of primary sexual differentiation, and some remain compatible with our results. The translocation of a substantial portion of the Y-chromosome short arm seems highly unlikely in true hermaphrodites, and the transposition of a Y-located TDF gene to either the X or an autosome can be reasonably ex-

cluded in view of the unpublished data of D. C. Page. A mutation in an autosomal or X-linked gene functioning in sex differentiation remains a possibility, although pedigree studies do not support this.

Y-specific DNA sequences have now been shown to be present in ~90% of XX males (D. C. Page, unpublished results). In contrast, there is no convincing evidence for the presence of Y-specific DNA sequences in 46,XX true hermaphrodites in whom mosaicism for a Y-bearing cell line has been excluded.

Although our results have not elucidated the etiology of XX true hermaphroditism, the Y-DNA hybridization studies show that XX true hermaphroditism encountered in southern Africa is fundamentally different from XX maleness.

Acknowledgments

References

Affara, N. A., M. A. Ferguson-Smith, J. Tolmie, K. Kwok, M. Mitchell, D. Jamieson, A. Cooke, and L. Florentin. 1986. Variable transfer of Y-specific sequences in XX males. Nucleic Acids Res. 14:5375–5387.

Andersson, M., D. C. Page, and A. de la Chapelle. 1986. Chromosome Y–specific DNA is transferred to the short arm of X chromosome in human XX males. Science 233:786–788.

Buckle, V. J., Y. Boyd, N. Fraser, P. N. Goodfellow, P. J. Goodfellow, J. Wolfe, and I. W. Craig. 1987. Localisation of Y chromosome sequences in normal 'XX' males. J. Med. Genet. 24:197–203.

Davies, K. E., P. L. Pearson, P. S. Harper, J. M. Murray, T. O'Brien, M. Sarfarazi, and R. Williamson. 1983. Linkage analysis of two cloned DNA sequences flanking the Duchenne muscular dystrophy locus on the short arm of the human X chromosome. Nucleic Acids Res. 11:2303–2312.

de la Chapelle, A. 1981. The etiology of maleness in XX men. Hum. Genet. 58:105–116.

de la Chapelle, A., P. A. Tippett, G. Wetterstrand, and D. Page. 1984. Genetic evidence of X-Y interchange in a human XX male. Nature 307:170–171.

De Souza, J. J. L., P. Barnett, C. D. Kisner, and J. P. Mur-

ray. 1984. True hermaphroditism: a case report with observations on its bizarre presentation. S. Afr. Med. J. 66:855–858.

Dinner, M. 1969. Intersex: a review and report of experience at Baragwanath Hospital. S. Afr. Med. J. 7:49–60.

Donahoe, P. K., J. D. Crawford, and W. H. Hendren. 1978. True hermaphroditism: a clinical description and a proposed function for the long arm of the Y chromosome. J. Pediatr. Surg. 13:293–301.

Ehrhardt, A. A., and F. L. Meyer-Bahlburg. 1981. Effects of prenatal sex hormones on gender-related behavior. Science 211:1312–1324.

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.

Geldwerth, D., C. Bishop, G. Guellaen, M. Koenig, G. Vergnaud, J.-L. Mandel, and J. Weissenbach. 1985. Extensive DNA sequence homologies between the human Y and the long arm of the X chromosome. EMBO J. 4:1739–1743.

Grace, H. J. 1970. Penile urethra in a Bantu female intersex. S. Afr. Med. J. 44:1112–1115.

Grace, H. J., and W. E. Edge. 1973. A white hermaphrodite in South Africa. S. Afr. Med. J. 47:1553–1554.

Guellaen, G., M. Casanova, C. Bishop, D. Geldwerth, G. Andre, M. Fellous, and J. Weissenbach. 1984. Human XX males with Y single-copy DNA fragments. Nature 307:172–173.

Klempman, S. 1964. The investigation of developmental sexual abnormalities. S. Afr. Med. J. 38:234–236.

Magenis, R. E., M. Casanova, M. Fellous, S. Olson, and R. Sheehy. 1987. Further cytologic evidence for Xp-Yp translocation in XX males using in situ hybridization with Y-derived probe. Hum. Genet. 75:228–233.

Magenis, R. E., M. J. Webb, R. S. McKean, D. Tomar, L. J. Allen, and H. Kammer. 1982. Translocation (X;Y) (p22.33; p11.2) in XX males: etiology of male phenotype. Hum. Genet. 62:271–276.

Mittwoch, U. 1986. Males, females and hermaphrodites. Ann. Hum. Genet. 50:103–121.

Müller, U., T. Donlon, M. Schmid, N. Fitch, C. L. Richer, M. Lalande, and S. A. Latt. 1986. Deletion mapping of the testis determining locus with DNA probes in 46,XX males and in 46,XY and 46,X, dic(Y) females. Nucleic Acids Res. 14:6489–6505.

Nurse, G. T., J. S. Weiner, and T. Jenkins. 1985. The peoples of Southern Africa and their affinities. Research Monographs on Human Population Biology. Clarendon Press, Oxford.

Oberle, I., G. Camerino, R. Heilig, L. Grunebaum, J.-P. Cazenave, C. Crapanzano, P. M. Mannucci, and J.-L. Mandel. 1985. Genetic screening of hemophilia A (classic hemophilia) with a polymorphic DNA probe. N. Engl. J. Med. 312:682–686.

Page, D. C. 1986. Sex reversal: deletion mapping the male-

determining function of the human Y chromosome. Pp. 229–235 *in* Molecular biology of *Homo sapiens.* Cold Spring Harbor Symposium on Quantitative Biology. Vol. 51. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Page, D. C., L. G. Brown, and A. de la Chapelle. 1987*a*. Exchange of terminal portions of X- and Y-chromosomal short arms in human XX males. Nature 328: 437–440.

Page, D. C., and A. de la Chapelle. 1984. The parental origin of X chromosomes in XX males determined using restriction fragment length polymorphisms. Am. J. Hum. Genet. 36:565–575.

Page, D. C., A. de la Chapelle, and J. Weissenbach. 1985. Chromosome Y–specific DNA in related human XX males. Nature 315:224–226.

Page, D. C., M. E. Harper, J. Love, and D. Botstein. 1984. Occurrence of a transposition from the X-chromosome long arm to the Y-chromosome short arm during human evolution. Nature 311:119–123.

Page, D. C., R. Mosher, E. M. Simpson, E. M. C. Fisher, G. Mardon, J. Pollack, B. McGillivray, A. de la Chapelle, and L. G. Brown. 1987*b*. The sex-determining region of the human Y chromosome encodes a finger protein. Cell 51:1091–1104.

Petit, C., A. de la Chapelle, J. Levilliers, S. Castillo, B. Noel, and J. Weissenbach. 1987. An abnormal terminal X-Y interchange accounts for most but not all cases of human XX maleness. Cell 49:595–602.

Rosenberg, H. S., G. W. Clayton, and T. C. Hsu. 1963. Familial true hermaphroditism. J. Clin. Endocrinol. Metab. 23:203–206.

Roux, J. P., D. Kowen, and P. J. M. Retief. 1974. The management of paediatric hermaphroditism. S. Afr. Med. J. 48:2088–2096.

Skordis, N. A., D. G. Stetka, M. H. MacGillivray, and S. P. Greenfield. 1987. Familial 46,XX males coexisting with familial 46,XX true hermaphrodites in same pedigree. J. Pediatr. 100:244–248.

South Africa (Republic), Department of Statistics. 1982. Population census 1980, Sect. 1. Government Printer, Pretoria.

Southern, E. M. 1975. Detection of specific sequences among DNA fragments separated by gel electrophoresis. J. Mol. Biol. 98:503–517.

Sykes, B. C. 1983. DNA in heritable disease. Lancet 2:787–788.

Van Niekerk, W. A. 1974. True hermaphroditism: clinical, morphologic and cytogenetic aspects. Harper & Row, New York.

———. 1976. True hermaphroditism: an analytic review with a report of 3 new cases. Am. J. Obstet. Gynecol. 7:890–907.

Van Niekerk, W. A., and A. E. Retief. 1981*a*. The gonads of human true hermaphrodites. Hum. Genet. 58:117–122.

———. 1981*b*. Nuwe kennis met betrekking tot die etiologie en patogenese van ware hermafrodiete. S. Afr. Med. J. 60:195–198.

Vergnaud, G., D. C. Page, M.-C. Simmler, L. Brown, F. Rouyer, B. Noel, D. Botstein, A. de la Chapelle, and J. Weissenbach. 1986. A deletion map of the human Y chromosome based on DNA hybridization. Am. J. Hum. Genet. 38:109–124.

Wilton, E. 1969. A cytogenetic study of patients with anomalous sexual development. S. Afr. Med. J. 7:45–48.

Wolfe, J., S. M. Darling, R. P. Erickson, I. W. Craig, V. J. Buckle, P. W. J. Rigby, H. F. Willard, and P. N. Goodfellow. 1985. Isolation and characterization of an alphoid centromeric repeat family from the human Y chromosome. J. Mol. Biol. 182:477–485.

Yunis, J. J. 1976. High resolution of human chromosomes. Science 191:1268–1270.