

The Origin of 45,XO Males

Maleness in association with a 45,XO karyotype is a very rare and hitherto unexplained condition, previously described in fewer than ten patients. Most individuals with this karyotype develop as phenotypic females with Turner's syndrome. How maleness arises in the XO males, who have invariably been sterile, has been unclear until the study of De la Chapelle et al.¹

Two 45,XO males were studied. Both had third-degree hypospadias and cryptorchidism, but two testes were found in each. One testis, which was examined in the first patient at 6 to 7 years of age, was "normal." In the second patient, both testes were on the left side and shared a common vas deferens. Both patients were below the second percentile in height; there was no significant mental retardation. There were characteristics suggestive of Turner's syndrome in the first patient, including a mild pterygium colli, highly arched palate, shield-shaped chest, laterally located mamillae, clinodactyly of the fifth fingers, deep-set nails, and coarctation of the aorta.

Both parents of both patients were cytogenetically normal. Four blood cultures and one fibroblast

culture from the first patient had only 45,XO mitotic cells. However, a buccal smear revealed 15 of 1,000 cells had fluorescent spots that were believed to reflect the presence of a Y chromosome or a Y chromatin body. A repeat buccal smear several years later showed that 5% of the cells had a fluorescein-staining body. A repeat skin fibroblast culture showed five of 186 cells with a 46,XY karyotype. Another repeat culture yielded similar findings, and these cultures were used for studies to identify Y-DNA sequences. Repeat cultures in the second patient were negative and repeat buccal smears were negative for fluorescein-staining material.

By using restriction digestion, agarose electrophoresis, gel transfer, and hybridization with radiolabeled, cloned DNA probes, it was possible to demonstrate a small amount of Y-DNA material (3%) from the cells of the first patient. There was no demonstrable Y-DNA material from the cultures of the second patient. Using refined techniques, it was possible to show that the X chromosomes of both patients originated from their mothers.

A 45,XO male might be a 45,X/46,XY mosaic, in whom the XY line is rare or has been eliminated altogether, at least in some tissues. The first patient appears to

fall into this category. The Y chromosome present in 3% of fibroblasts was structurally normal. Extensive cytogenetic and DNA studies in the second patient produced no evidence of Y chromosomal material, even in a minority of cells. Current techniques used in this study permit identification of a normal Y chromosome in as few as one in 10,000 cells. Therefore, mosaicism of a normally structured Y chromosome is unlikely in this patient. However, some of the identifiable fragments of the Y are located principally in the distal Yq and, thus, would be of little use in detecting mosaicism involving an abnormal Y chromosome lacking that region. The DNA hybridization studies alone, then, cannot argue against low-grade mosaicism for a structurally abnormal Y chromosome in the second patient. There is also the possibility that a Y-bearing cell line existed in tissues other than those that were sampled or existed in the fetal stage, but later eliminated.

Maleness in 46,XX males may be explained by the X-Y interchange hypothesis, which states that the Xq-bearing position of the father's X chromosome can be replaced by a testicular-determining portion of his Y chromosome, which hypothetically might occur as a result of interchange of genetic material between the X and Y

chromosomes at paternal meiosis. Consistent with this hypothesis is the identification of certain single-copy, Y-specific DNA sequences that were detected in 12 of 19 XX males who were tested by Page et al.² Thus, it appears that X-Y interchange can account for many cases of XX maleness. In both cases of XO maleness reported here, however, there is no evidence for genetic transfer of Y material. The X chromosome in both patients was of maternal origin. Mosaicism may have accounted for the differentiation of the genitalia along male lines in the first patient. In the second patient, the absence of a certain single-copy Y-DNA sequence argues against, but cannot exclude, the presence of the testis-determining portion of the Y chromosome.

1. De la Chapelle A, Page C, Brown L, et al. *Am J Hum Genet* 1986;38:330-340.
2. Page C et al. *Am J Hum Genet* 1986;38:109.

Editor's comment—*These patients, although extremely rare, remind us how much we do not know about normal sexual differentiation. For several years, attention focused on the presence of H-Y antigen to explain differentiation of the normal male fetus along male lines. We now have learned that H-Y antigen is probably of no consequence, even if it exists. The concept that Y chromosomal material is necessary for differentiation of the gonad along male lines has been defied by the second patient, although mosaicism may have been present at*

some time early in his life.

Of importance to clinicians and investigators is the concept that cultures of fibroblasts from the gonads are exceedingly important when karyotypes from lymphocytes or skin fibroblasts confuse our interpretation of what has taken place. Several years ago, Goldstein et al (J Pediatr 1977;90:604) described a short female with stigmata suggestive of Turner's syndrome and gonadal agenesis. Cultures of skin fibroblasts and lymphocytes revealed a 46,XX karyotype; when grown from biopsies of the gonadal streaks, fibroblasts had a karyotype of 45,XO. Possibly, if fibroblasts had been grown from the testes of the two 45,XO males, Y chromosomal material would have been more readily identifiable.