"Mixed" Gonadal Dysgenesis: A Variety of Hermaphroditism

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PERUSAL of the results of cytogenetic studies in individuals with sex anomalies (Sohval, 1961; 1963a) suggested the existence of a special type of intersex which has not yet been classified definitively. These individuals appear to have sufficient clinical and anatomic features in common to warrant their consideration as a distinct variety of hermaphroditism. They may present as phenotypic males or females but the nuclear sex in all cases studied to date is chromatin-negative. As in all intersexes, the reproductive system exhibits a mixture of male and female elements. These include an enlarged clitoris or phallus with urethral opening at its base, a vagina, uterus and Fallopian tubes as well as an intra-abdominal testis.

The nosologic difficulty stems from the state of the gonads. Situated intra-abdominally in the normal position of ovaries, these consist of a rudimentary or vestigial "streak" gonad on one side and a testis on the other. Since the former is identifiable as neither testis nor ovary, such cases cannot be properly categorized on the basis of gonadal histology as male pseudohermaphrodites (bilateral testes), female pseudohermaphrodites (bilateral ovaries) or true hermaphrodites (presence of both testicular and ovarian tissue).

Five such cases are now to be found in the recent literature. These are the patients of Ferguson-Smith and Johnston (1960), Bloise *et al.* (1960), Conen *et al.* (1961), Schuster and Motulsky (1962a; 1962b) and Willemse, van Brink and Los (1962). The latter three are phenotypic female adults and the first two are children raised as boys. Karyotype analysis disclosed the presence of cells with an XO sex-chromosome complement in each case. In the two male children these cells were the only type demonstrated (only bone marrow cells were cultured). However, XO/XY sex mosaicism was encountered in cultured leukocytes of peripheral blood in two of the females (Conen *et al.* 1961; Willemse *et al.* 1962) while a triple mosaic XO/XY/XX, was found in cultures of skin and peripheral blood of the third female (Schuster and Motulsky, 1962a; 1962b).

There are four other patients who seem to qualify for inclusion in this group although complete clinicopathologic data are not supplied. They are among nine individuals described as male pseudohermaphrodites by Alexander and Ferguson-Smith (1961). Each had an XY sex-chromosome complex in their cultured bone marrow cells.

The term "mixed" gonadal dysgenesis is offered as a tentative designation for these examples of intersexuality which are usually not classified decisively in the literature. The term "mixed" refers to the coexistence of different forms

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of defective gonadogenesis in the same individual. The gonadal dysgenetic process is more marked than that encountered in classical true or false hermaphroditism but is less severe than that which characterizes the bilateral "streak" gonads of "pure" gonadal dysgenesis and Turner's syndrome. The overall condition of the gonads in these cases apparently represents an intermediate form between "pure" gonadal dysgenesis on one hand and male pseudohermaphroditism or true hermaphroditism on the other.

The fact that this condition has been described in five cases and alluded to in four others within the past two years suggests that intersexes with a "streak" gonad on one side and an intra-abdominal testis on the other are not too rare. The general lack of such cases in the prior literature probably reflects a common unawareness of the inconspicuous "streak" gonad as a pathologic entity before its description by Wilkins and Fleischmann (1944).

The question may be raised as to whether or not an intersex patient with a rudimentary, undifferentiated gonad on one side and a testis on the other should be regarded as an instance of male pseudohermaphroditism, or possibly as a variant of it (Alexander and Ferguson-Smith, 1961). However, the accumulated results of chromosome analysis in persons with anomalous sex development strongly suggest the existence of a clear distinction between intersexes who have classical male pseudohermaphroditism (with bilateral testes) and those with "mixed" gonadal dysgenesis. Whereas an XY sex karyotype is almost invariable in the former, the XO complex seems to predominate in the latter, occurring alone or more probably as one component of a mosaic. In the instances where an XO constitution was not found (Alexander and Ferguson-Smith, 1961) the possibility of sex mosaicism with an undetected XO stem-line of cells cannot be excluded.

The demonstration of significant numbers of XO cells, existing alone or as part of a sex mosaic, suggests that chromosomal aberrations play a major role in the pathogenesis of "mixed" gonadal dysgenesis. The presence of two different kinds of gonads in the same individual is readily explainable on the basis of sex-chromosome mosaicism, a finding already documented in three of the patients. In the cases under discussion, the existence or predominance of the XO sex complement in one gonadal anlage with a different sex karyotype (*i.e.*, XY) dominant in the other would account for the markedly dissimilar gonadal anatomy ("streak" gonad on one side and testis on the other). An alternative, although less likely, explanation is the possibility that other teratogenic factors of a chance nature may be operative locally and unilaterally during very early gonadogenesis.

While the evidence suggests that this atypical form of hermaphroditism with "mixed" gonadal dysgenesis is due to sex-chromosome mosaicism, especially of the XO/XY type, the converse does not always hold. In other words, XO/XY mosaicism does not necessarily result in this variety of intersex. This is indicated by the fact that XO/XY mosaics have also been reported in nine other chromatin-negative individuals with various kinds of sex anomalies. With one exception all are phenotypic females.

Included in this miscellaneous group of persons with XO/XY mosaicism and aberrant sex development is the patient of Hirschhorn, Decker and Cooper

(1960a; 1960b) who may be a true hermaphrodite although the gonadal histology is not conclusive. Each of the two intersexes studied by Miller, Breg and Jailer (1960) had only one gonad. This was intra-abdominal in location and was composed predominantly of testicular tissue in which a seminoma had developed. The case of Judge *et al.* (1962) appears to be an instance of "pure" gonadal dysgenesis although histologic examination was performed in only one of the two very small gonads. The two individuals studied by Jacobs *et al.* (1961) have Turner's syndrome. A patient observed by Miller, Breg and Schmickel (unpublished) has a variant form of Turner's syndrome. The adult male reported by de la Chapelle and Hortling (1962) is a unilateral cryptorchid with hypospadias. Since abdominal exploration was not performed the character of the internal genitalia and other gonad, if any, is not known. In the patient studied by Blank, Bishop and Caley (1960) there was a small intra-abdominal gonad on one side but its histology was not determined. No gonad could be identified on the opposite side.*

From these observations it is evident that XO/XY mosaicism is indeed associated with diverse types of sex anomalies. As in most forms of defective gonadogenesis the associated clinical and anatomic features depend more upon the extent and nature of the fetal testicular secretory failure than upon the precise sex-chromosome constitution, a point recently stressed by Dewhurst (1962).

Recognition of intersexes with "mixed" gonadal dysgenesis as a distinct variety of hermaphroditism should help in the evaluation and classification of atypical forms of gonadal dysgenesis with anomalous sexual development. Moreover, insistence on rigid diagnostic criteria based on gonadal histology will serve to render more meaningful the interpretation of associated sex-chromosome findings.

A detailed discussion of this type of hermaphroditism, its variant forms and its relationship to gonadal neoplasm is presented elsewhere (Sohval, 1963b).

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*Three additional instances of XO/XY mosaicism have come to attention. Each is a chromatin-negative phenotypic male. One is apparently a male pseudohermaphrodite (Ferrier *et al.*, 1962). Another (Ferrier *et al.*, 1963) is a unilateral cryptorchid with an increased urinary level of pituitary gonadotropin. The third (Lewis *et al.*, 1963) is an intersex with a seminoma of an undescended testis. Because of inadequate clinicopathologic data the type of sex anomaly in the latter two instances is not classifiable.

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