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THE CHROMOSOMES OF A TRUE HERMAPHRODITE

BY

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The recent work on the chromosomes of human intersexual conditions — for example, Klinefelter's syndrome (Jacobs and Strong, 1959) and Turner's syndrome (Ford *et al.*, 1959)—has led to a re-examination of known cases of other types of intersexuality. The case considered here is of a true hermaphrodite, and, though we can obtain no evidence of chromosomal imbalance, the findings are nevertheless of great interest from the developmental point of view.

The full clinical and pathological details of this case have already been published (Armstrong, 1955; Armstrong *et al.*, 1957), but a few of the most important features are worth repeating here.

The patient, aged 70, has lived as a female, but the general appearance is rather masculine. The hair distribution is male, there is no breast development, and the external genitalia are partially masculinized. The right gonad was found to be predominantly a testis but showed at least one atretic ovarian follicle. The left gonad is an ovary. The skin, the oral mucosa, and the internal genitalia (ovary, ovotestis, uterus, and vas deferens) are chromatin-positive, though in the latter "the typical chromatin mass is smaller and less frequent than usual." Two to three neutrophils in every 500 counted were found to have a typical female "drumstick."

Results

Chromosome examinations were carried out by the method described by Harnden (1959). Two skin-biopsy specimens, one from the left arm and one from the right arm, were sent from Newcastle to Harwell, and set up in culture about 24 hours after biopsy. Two separate cultures were established from each biopsy, so that there were four cultures in all. A slight yeast infection which appeared in all the cultures was eliminated by adding 100 units of nystatin per ml. of culture medium. The

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cultures varied somewhat in their rates of growth, but all were slow to start proliferating, and a period of about four weeks elapsed before cytological preparations could be made. The results of the examination of these preparations are shown in the Table.

Results of Chromosome Examinations

Tissue	Chromosome Counts (No. of Cells)						Sex Chromosomes
	<45	45	46	47	48	>48	
Left skin Biopsy { L1	—	—	32	—	—	—	XX
{ L2	2	1	30	1	—	1	XX
Right skin Biopsy { R1	1	1	31	—	1	—	XX
{ R2	1	7	55	—	1	—	XX

All four cultures contained predominantly cells with 46 chromosomes. The sex chromosomes are interpreted in all four cultures to be XX (see Fig.). The few counts other than 46 can be accounted for as technical errors. In three of the cultures the chromosomes were, so far as one can say from this sort of examination, normal female. In the fourth (R2), however, there occurred in about 7% of the cells an abnormally long chromosome. Careful analysis of several of these cells showed that this could be explained as a reciprocal translocation between members of chromosome pairs 3 and 4 (in order of size). All the cells of this culture were in other respects normal female. Had this abnormality been present in the original tissue it is felt that it would also have been observed in the other culture from the same biopsy. This was not found, though several hundred cells were carefully examined. It is considered, therefore, that this aberration had arisen in culture, though the possibility of its presence in the patient

Ideogram prepared from a photograph of a skin culture cell showing 46 chromosomes. The two X chromosomes cannot be identified with certainty, but only as two of a group of six chromosomes. ($\times 870$.)

cannot altogether be ruled out. It can be concluded that the cells of these two skin biopsies from widely separated sites contained chromosomes characteristic of the normal female. In corroboration of this Dr. J. E. Gray, of the Department of Anatomy, King's College, Newcastle, has examined the skin adjacent to the biopsy sites and found both to be chromatin-positive.

Miss P. A. Jacobs, of the Medical Research Council Group, Western General Hospital, Edinburgh, has examined the chromosomes of cells from a bone-marrow culture and agrees with the finding that they are of the normal female pattern.

Discussion

From the aspect of technique two points arise from these results. It is of interest that successful cultures can be established with regularity from the skin of a

patient 70 years old. Secondly, the finding of an easily recognizable and viable chromosome change occurring at an early stage of culture, while it does not detract from the usefulness of this technique, does indicate that results should be interpreted with caution.

Hungerford *et al.* (1959) have published a full study of a true hermaphrodite bearing one testis and an ovotestis, in which the great majority of cells which they examined from the peripheral blood were reported to have 46 chromosomes. The sex chromosomes were interpreted as XX. These findings agree very well with ours, and both results together pose some interesting developmental problems—for example, how can cells which seem genetically determined to form a female organism differentiate into a testis and lead to the formation of a predominantly male phenotype? One must consider the possibility that these patients are mosaics—that is, are made up of two or more clones of cells of different genetic constitution. This has been suggested for true hermaphrodites, but this is not supported by the evidence obtained from observations of the sex chromatin (Grumbach and Barr, 1958). This test, however, would not locate an XX/XXY mosaic, and Hungerford *et al.* do not exclude the possibility that their patient could fall into this category though no XXY cells were found. In our case after examination of bilateral skin biopsies and bone-marrow there is no evidence to suggest that the patient is a mosaic. It would, however, have been very interesting to examine the cells of the right gonad to determine whether the cells which had differentiated into a testis really did have two X chromosomes and no Y, but this is not now possible.

The primary defect in this case is a developmental error which may or may not have been genetically determined. The medullary component of one gonad has somehow become dominant in spite of the presence of two X chromosomes which would normally ensure the dominance of the cortex. The subsequent masculinization of the genital tract is probably a consequence of this primary error. Grumbach and Barr quote several examples of reversal of gonadal development in other vertebrates induced by hormone treatment. Especially interesting is the bovine freemartin, where the presumptive ovary differentiates into a testis under a hormonal influence of unknown origin. It seems reasonable to suggest that some similar, and likewise unknown, hormonal influence may be acting in cases such as the one reported here. This study emphasizes the point, which has been made before but perhaps not sufficiently stressed, that the phenotype of an individual is the resultant of an interplay between several factors, some genetically determined and others probably not. In sex differentiation, as distinct from sex determination, this is of great importance. In this particular case the possession of the female pattern of sex chromosomes has not proved sufficient to determine the phenotype and has not prevented other factors, which may or may not have been genetically determined, causing masculinization of what should apparently have been a female individual.

Summary

The chromosomes of a human true hermaphrodite have been studied and found to be 46 in number, the sex chromosomes being interpreted as XX. There is no evidence of mosaicism. The importance of the interaction of genetic and non-genetic developmental factors in the development of the phenotype is noted.

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UNUSUAL CASE OF GONADAL DYSGENESIS (TURNER'S SYNDROME)

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Turner's (1938) syndrome is characterized by infantilism, shortness of stature, webbing of the neck, and cubitus valgus, but numerous other congenital abnormalities have been described. Turner made no mention of the condition of the gonads. Varney, Kenyon, and Koch (1942) and Albright, Smith, and Fraser (1942) demonstrated in this disorder a high urinary excretion of gonadotrophin, and from this concluded that the infantilism was due to primary ovarian insufficiency. Previous authors, tabulated by Wilkins and Fleischmann (1944), had described similar cases in which rudimentary ovaries had been found at laparotomy or at necropsy. Wilkins and Fleischmann (1944), observing that the "ovary" consisted only of a primitive genital ridge composed of stroma-like cells and showing no proliferation of the epithelium nor primordial germ cells, proposed the term "ovarian agenesis" for this condition.

Subsequently Grumbach, Van Wyk, and Wilkins (1955) showed that most of their patients with this disturbance had a male chromatin sex pattern, and considered that the condition exemplified an extreme form of male pseudohermaphroditism. On this account Wilkins (1957) applied the term "gonadal aplasia" for this disorder, using the wider term "gonadal dysgenesis" for the entire group of defects in the development of the gonads. Ford *et al.* (1959), however, subsequently found that a patient with gonadal dysgenesis and chromatin negative possessed 45 chromosomes instead of the normal 46. They concluded that the sex-chromosome constitution of the patient was XO, and emphasized that such a person should not be referred to as a chromosomal male, as she was a female with an abnormal genotype.