

# True Hermaphroditism<sup>\*)</sup>

## Two cases with chromosome analysis

*J. P. Hart Hansen & Marner Simonsen.*

A true *hermaphrodite* is an individual with both male and female gonadal tissue. According to Greek mythology, Hermaphroditus was a child of Hermes and Aphrodite, the goddess of love, and inherited the attributes of both parents, so that the sex of the child could not be determined. Ancient artists often depicted Hermaphroditus as a female with male genitalia (Fig. 1). In the course of time hermaphrodites have played a great part in man's imagination, and this found expression in literature, art, and legislation of ancient times<sup>1</sup>. *Pseudohermaphroditism* is a congenital condition, in which the gonad of the individual is either of a male or a female character, whereas the external genitalia more or less resemble those of the opposite sex. *Intersexuality* is a collective term designating all conditions in which the sexual development is essentially different from normal, so that the actual sex of the individual cannot be recognized immediately, and conditions in which the gonads and internal genitalia do not corre-

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<sup>\*)</sup> From the surgical department (Head: Th. P. Dahl), Landssjúkrahúsið, Tórshavn, Faroe Islands and the department D (Head: J. C. Christoffersen), Bispebjerg Hospital, Copenhagen, Denmark.



*Fig. 1. Statue of Hermaphroditus.*



spond to the external genitalia, which may be of a completely normal appearance.

In ancient literature a true hermaphrodite is described as an individual with both male and female gonads — testes and ovaries — and fully developed male and female external genitalia, which are able to reproduce the individual both as a man and as a woman and, from a theoretical point of view, capable of auto-fertilization. However, no such individual has ever existed, although strange cases are to be found even in more recent literature<sup>1</sup>.

### *Sexual development.*

Sexual differentiation and sexual development are determined genetically. The genital anlage appears in the embryo during the fourth week after conception, and this anlage is identical in male and female embryos till the seventh week of intrauterine life. This genital anlage may potentially develop into either a male gonad — a testis — or a female gonad — an ovary. The differentiation is determined by the genes of the sex chromosomes. The X-chromosome contains the feminizing genes and the Y-chromosome the masculinizing genes.

The genital primordium consists of a cortex and a medulla. Under the influence of the normal female composition of the sex chromosomes with two X-chromosomes (XX-), the cortex will develop into the ovary, whereas the medulla degenerates in such cases. If the sex chromosomes are composed by one X-chromosome and one Y-chromosome (XY-), as in normal males, the testes develop from the medulla, whereas the cortex degenerates. Hence, the gonadal differentiation and development are determined by a balance between the cortex and the medulla in the genital primordium, depending on the genetic sex of the individual. It is supposed that this balance is determined by hormonal cortico-medullary substances, which are antagonistic, and which are different from the adult sex hormones. It was suggested that these substances should be desig-



*Fig. 2. Case No. 1.*

nated corticine and medullarine<sup>2</sup>. Under the influence of the genes of the XX-chromosomal pattern it is assumed that the cortex produces the morphogenetic substance which transforms the cortex into the ovary and arrests the development of the medulla. In the male individual the genes of the XY-chromosomal pattern will further the formation of testicular tissue and inhibit the development of the cortex.

The formation and development of the remaining internal and external genitalia are controlled hormonally from the gonadal anlage, these primordia being potentially capable of male or female development. In the female the so-called Müllerian duct is developed, which first differentiates into the uterine tubes on either side and secondly fuses more distally



to form the uterus, the cervix, and the uppermost part of the vagina. The Wolffian duct in the male becomes the epididymis, the vasa deferentia, and the vesiculae seminales. In either sex the duct which is not developed will degenerate, although rudiments of these structures will be found in the adult individual. In the female the non-developed and degenerated Wolffian duct forms the epoophoron, the paroophoron and Gärtner's ducts. In the male the appendix testis and the utriculus prostaticus are remnants of the Müllerian duct<sup>3</sup>.

During the first weeks the development of the external genitalia is determined by the hormone production of the gonad, and the urogenital sinus and the genital tubercle develop into the external genitalia in either sex. At later stages, however, this development depends very much on a normal balance between the production of hormones by the pituitary gland, the adrenals and the gonad. It is well-known that certain steroids exert an androgenic influence. They stimulate the male development of the external genitalia, and such influence may produce female pseudohermaphroditism in female individuals during the development, the external genitalia exhibiting a more or less pronounced masculine appearance in spite of the presence of a female gonad. This condition may be seen in a female embryo in case of an abnormally increased production of adreno-cortical hormones, in connexion with certain hormone-producing tumours in pregnant women, and if the mother has been treated with certain types of hormones during pregnancy<sup>4</sup>.

By foetal castration experiments in mammals<sup>5</sup>, it has been proved that female internal and external genitalia will develop when the gonad is removed. Hence, the presence of ovarian tissue is not necessary for the development of female genitalia, whereas it has been shown that the presence of a male gonad is necessary for the differentiation of the male genitalia during foetal life. Thus, castration of a female embryo does not interfere with the formation of the female genitalia and male embryos develop into females when castrated at an early

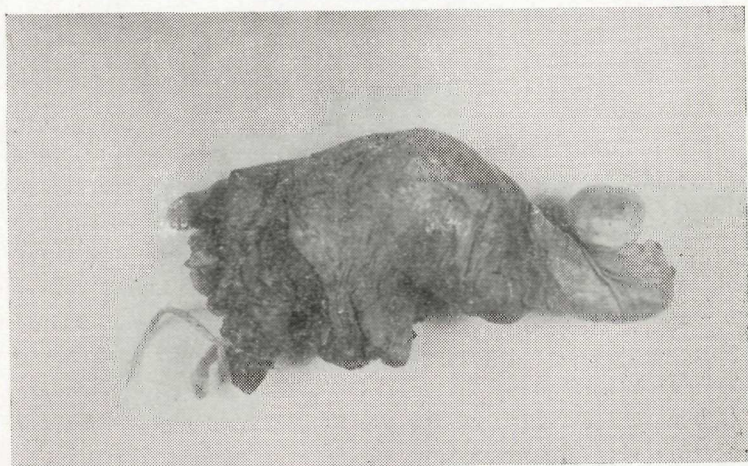


Fig. 3. Operative specimen from Case No. 1. Peritoneal-covered structure and the gonad upwards to the right.

stage. The later in foetal life the embryo is castrated, the greater the number of intersexual conditions with progressively increasing masculinization.

#### *Sex chromatin.*

In 1949 *Barr and Bertram*<sup>6</sup> found that in female cats a chromatin body was situated at the nuclear membrane in the nerve cells, which was not the case in male individuals. Later this phenomenon was demonstrated in human cells from skin biopsies, from scrapings of the oral mucous membrane, in leucocytes, and in many different kinds of tissue sections. The phenomenon has been very valuable in the clinical examination of sexual and chromosomal developmental disturbances and abnormalities, since the cellular sex can be determined by this investigation. It is supposed that the Barr-body is formed by one single X sex chromosome, so that the number of Barr-bodies in a cell is always one below the total number of X sex chromosomes in a cell<sup>7</sup>. Actually, in certain conditions chromo-



somal abnormalities can be observed, in which more than two X sex chromosomes and thus more than one Barr-body are present.

### *Chromosomes.*

Up to 1956 it was supposed that the number of human chromosomes was 48. In 1956, *Tjio and Levan*<sup>8</sup> were able to correct this. They showed that man has 22 autosomal chromosome pairs and either two X sex chromosomes or one X sex chromosome and one Y sex chromosome. By studying cells in the metaphase after treatment with colchicine, the various chromosomes were isolated and classified as pairs of homologous chromosomes, the so-called Denver system being employed in most parts of the world for the purpose of classification and nomenclature. Under the Denver system the chromosomes are classified according to decreasing size. *Fig. 8* presents a survey of the chromosomes of a cell according to the Denver system.

Chromosomal abnormalities may include changes in number and structure of the sex chromosomes and the autosomes. The so-called mosaic formation designates a condition in which cells with various chromosomal patterns, XX/XY, XX/XO, XO/XY, XX/XXX, etc. appear in the same tissue. A chimaera is an individual in whom various tissues present different chromosomal patterns<sup>9 25</sup>.

During recent years it has been shown that many abnormalities of the development of the gonad and the genitalia are results of an abnormal number and structure of the sex chromosomes. Only few autosomal chromosome abnormalities are known as yet. In mongolism (Down's syndrome) duplication of one of the smallest autosomes is found and consequently, the total number of chromosomes will be 47<sup>13</sup>. In connexion with chronic myelogenous leukaemia a reduction of the structure of one of the smallest chromosomes has been described, and in cases of multiple congenital malformations abnormal structure or number of the autosomes has also been

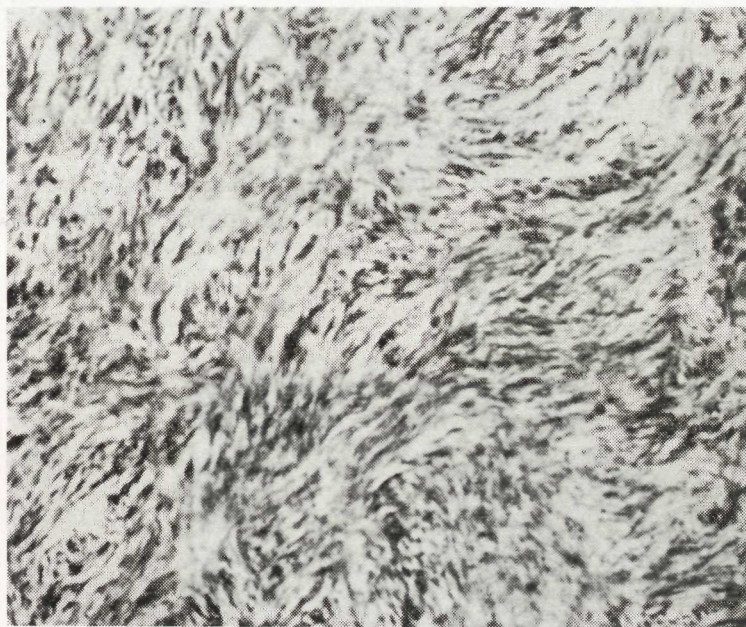


Fig. 4. Section of the ovarian part of the gonad from Case No. 1. Dense wavy connective tissue, but no ova. About 1000 x.

found. Hence, chromosomal abnormalities are not rare. In about 4 of each 1000 newborn infants, a chromosomal abnormality will be found — either abnormal sex chromosomes or mongolism<sup>9</sup>.

#### *Sex chromosomal abnormalities.*

In 1942, Klinefelter *et al.*<sup>10</sup> described a typical clinical entity. Later it appeared that in spite of masculine habitus, male internal and external genitalia, and masculine social position, these patients have a positive sex chromatin test. The disease is often discovered at examination because of infertility. The positive sex chromatin finding is caused by a chromosomal abnormality, the cells in these individuals con-



taining 47 chromosomes or more<sup>11</sup>. To produce a positive sex chromatin test, two X sex chromosomes are required, and to give a male phenotype one Y sex chromosome is necessary. Thus, in most cases the sex chromosomes are XXY. However, other sex chromosomal patterns have been found — XXY/XX, XXY/XO, XXXY, XXYY, XXY/XXXY<sup>12</sup>.

In a patient with gonadal dysgenesis (Turner's syndrome), the female genitalia are immature and other characteristic congenital somatic abnormalities are present. These individuals are most often sex chromatin negative<sup>2</sup>, and chromosome analysis reveals only one sex chromosome. This sex chromosome is an X sex chromosome. On rare occasions patients with Turner's syndrome have two X sex chromosomes or mosaics, but in such cases one of the X sex chromosomes is often defective. Complete absence of sex chromosomes is most likely incompatible with life on account of loss of genes<sup>14</sup>.

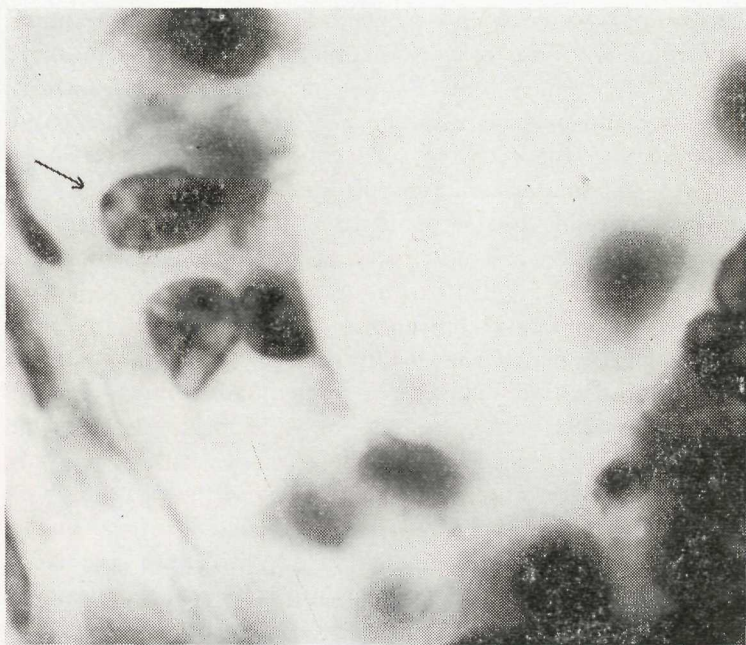
A disorder which often shows familial occurrence, is Morris' syndrome or the so-called testicular feminization, in which a negative Barr-phenomenon and normal male chromosomal arrangement — XY — are found in a phenotypical female. In these patients testes will often be present in the inguinal canal.

The triple-X syndrome or the so-called super-female syndrome is a disorder in certain females, in whom two Barr-bodies and three sex chromosomes — XXX — will be found.

#### *True hermaphroditism.*

True hermaphroditism is a rare condition. Since 1900, a total of 118 cases has been reported in the literature. In 25 of these cases chromosome analysis was carried out<sup>13</sup>. In order to establish the diagnosis with certainty, both testicular and ovarian tissue must be demonstrated histologically.

On examination it appeared that 80% of the patients in whom chromosome analysis was carried out were sex chromatin positive, and that 70% of those examined had a normal female sex chromosomal pattern — XX. Two of the sex chro-



*Fig. 5.* Section of mesonephric duct from the gonad (Case No. 1). Columnar epithelium is seen. Arrow indicates a nucleus with sex chromatin. About 2000 x.

matin negative individuals exhibited the pattern XY as in normal males, and besides mosaic formation was found on rare occasions — XX/XXX, XX/XY, XY/XO, and XX/XXY/XXYYY<sup>26</sup>. That mosaic patterns were not found more frequently must be due the fact that in most of the cases the troublesome and time-consuming chromosome analysis was not carried out on more than one type of tissue. Otherwise it is difficult to explain how cells which according to their chromosomal arrangement should be female, can lead to the formation of testes and to the development of a primarily male phenotype<sup>15</sup>.

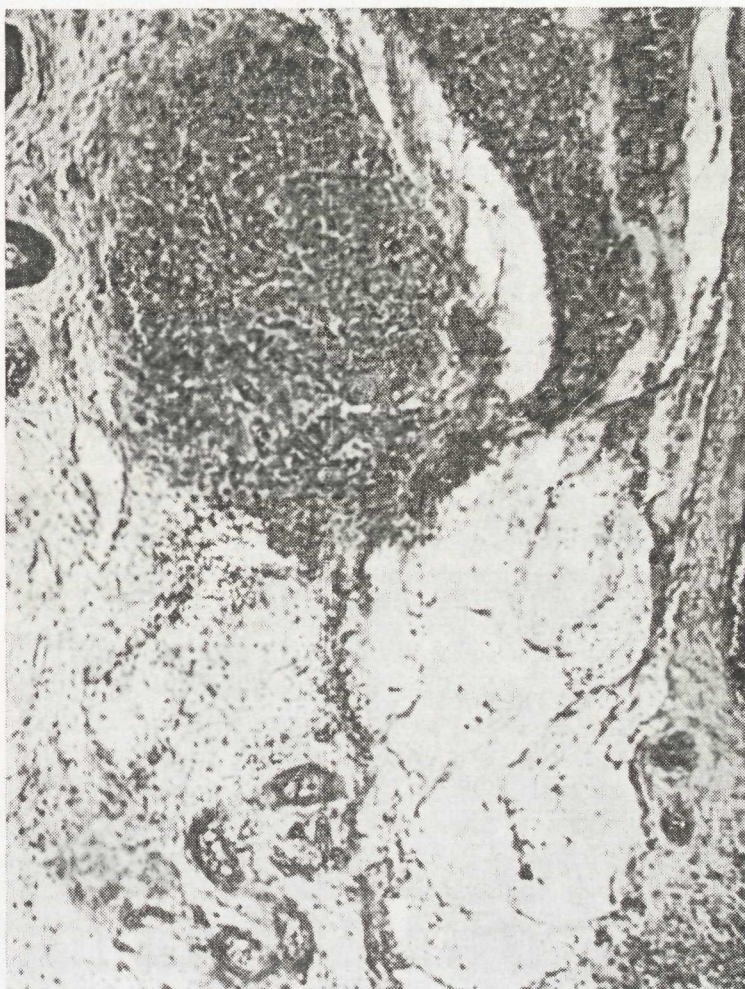
In true hermaphroditism the appearance of the internal and



external genitalia may present many varieties. The gonads may be formed as a testis on one side and an ovary on the other. According to *Hinman's* classification<sup>16</sup> this is designated *lateral* hermaphroditism. Often a *bilateral* hermaphroditism with testicular and ovarian tissue on the same side will be found, sometimes in the form of an ovotestis. The most frequent finding is *unilateral* hermaphroditism characterized by an ovotestis on one side and an ovary or a testis on the other<sup>17</sup>. The external genitalia are most often of masculine appearance. A characteristic finding is gynaecomastia after the age of puberty and the frequent development of inguinal hernia (43%), during the repair of which the condition is most often revealed<sup>18</sup>. There is often hypospadias, and sometimes urethroscopy will reveal a small vaginal opening in the posterior urethra, through which menstrual bleeding may mix with the urine at monthly intervals in some cases. Sexual asymmetry of the body has been described. Unilateral gynaecomastia associated with an ovary on the same side and ovotestis on the other has been observed<sup>19</sup>, and this condition is analogous with the gynandromorphism which is seen in some insects.

The aetiology of true hermaphroditism is unknown and undoubtedly multifarious. It may be theorized that the underlying cause is gene mutations, unknown intrauterine causes, disturbances of the cortico-medullary balance, or chromosomal abnormalities arising during meiosis or mitosis and resulting in abnormal numbers of chromosomes, abnormal chromosomal combinations or arrangements. Only once familial occurrence of true hermaphroditism has been reported<sup>27</sup>.

Diagnostic aids include the chromatin and chromosome studies previously discussed and a general physical examination including hormone analysis and the important gonadal biopsy<sup>24</sup>. As is the case in any disorder where the genitalia deviate from normal, the investigations must aim at determining 1) the genetic sex, 2) the gonadal sex, 3) the somatic sex, 4) the hormonal status, and 5) the psychical structure<sup>20</sup>.



*Fig. 6.* Section of the testicular part of the gonad (Case No 1). At the top an abundance of Leydig cells. At the bottom to the right a brighter section consisting of hyaline seminiferous tubules almost without any cells. About 150 x.



An early diagnosis is important in order to decide upon the sex of rearing to be adopted. Sex determination depends on the appearance of the external genitalia and on the nature of the gonads. Any external genital malformations must be corrected surgically as early as possible, and if it is equally easy to change the genitalia surgically into either sex, attempts must be made at determining which of the two types of gonadal tissue is best developed, whereupon the tissue which shows the poorest degree of development is removed<sup>21</sup>. In most cases the surgical correction must be supported by hormone treatment during the period of puberty. If the disorder is diagnosed at a later time of life, the appearance of the external genitalia and the sex of rearing must be decisive of the treatment to be adopted, considering the severe psychical problems which may be present. In some cases a combination of surgical and hormonal therapy will help the patients to lead fairly normal lives, but in other cases where the condition is not diagnosed till after the time of puberty, it will most often be better to abstain from interfering.

It has been stated that many cases of true hermaphroditism are disclosed in connexion with operations because of inguinal hernia. Apart from the risk of incarceration of inguinal hernia, which occurred in our two cases, other complications of hermaphroditism may arise. Several cases of malignant neoplastic changes in undescended testes have been described and cystic degeneration of ovaries has been reported<sup>19</sup>. Furthermore, *Hanley*<sup>22</sup> described one patient with normal masculine external genitalia, but with uterus, vagina and uterine tubes and salpingitis developing because of prostatic hypertrophy. Finally, on several occasions endometriosis following surgery in hermaphrodites has been reported, as was the case in our second patient<sup>23</sup>.

*Case 1.* Our first case is a 70 years old person, registered as a male, who had regarded himself as a male his whole life and lived accordingly. He was the only child of normal parents who died from natural causes. In the family there were no known cases of malformations of any kind.

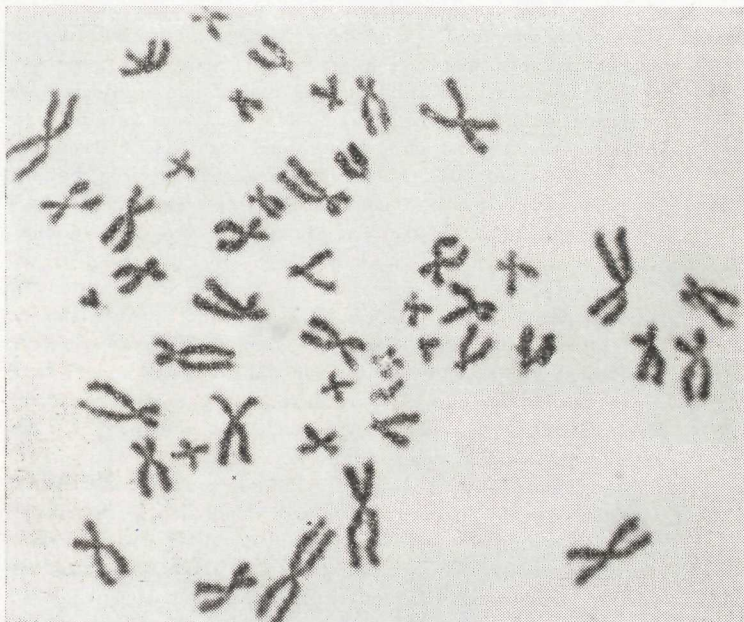


Fig. 7. Cell during division. Cultivated from skin biopsy from Case No. 1. 46 chromosomes are seen. About 2000 x.

During childhood it was noticed that his penis was small. At the age of puberty his mammae started to grow, and his voice only changed little. It remained high-pitched his whole life. He was said to be normally interested in the opposite sex as a young man. Before his first admission to hospital at the age of 46 he had always been healthy. He had never complained of periodical abdominal pains, periodical haematuria or periodical recurring nose-bleeding. Although, at 44 — 45 years of age he complained of »hot flushes« to the general practitioner. The patient lived an active and normal manual worker's life. At the age of 30 he married a woman a few years older. The marital relations were said to be normal and satisfactory. The marriage was childless.

At 46 years of age he was admitted to the County Hospital (Landssjúkrahúsið) Tórshavn, to be operated on for acute appendicitis. On examination during this and later admissions



to the hospital the patient was found to be delicately built with a *feminine distribution of the subcutaneous fat*. The pubes was of *feminine demarcation* and the hair on the body was very sparse. The growth of beard was very thin with a few fair, thin stubbles. The patient had well-developed mammae as in a woman. (Fig. 2). His voice was as a boy's at puberty. Mentally he seemed a normal male. He had marked genu valgum, but there was no cubitus valgus or pterygium colli. The penis was found to be 4 cm of length and there was a slight hypospadias. On the first examination two small intumescences were found in the left side of the otherwise normal scrotal sack, while the right side was empty. No indications of heart, aorta or kidney abnormalities were found by usual somatic and x-ray examinations. Urethroscopy or urethrography were not performed. The excretion in urine of 17-ketosteroids and 17-ketogenic steroids was normal. Only these hormone analysis were performed. During the operation for acute appendicitis a muscular organ was found in the left side of the abdomen resembling an uterus. Upwards and laterally from this organ an one cm thick string was found disappearing through canalis inguinalis together with the spermatic cord, which easily could be separated from the former tissue. This was interpreted as Müller's duct, and no further action was taken and the abdomen closed.

During the following years the patient complained of distress caused by an inguinal hernia on the left side, and at 66 years of age he was readmitted to the hospital with incarcerated left inguinal hernia. During the operation a ligamentum latum resembling structure was found in the hernial sack, covered by peritoneum on both sides. (Fig. 3). In this structure there was felt a pear-shaped intumescens with fundus towards an ovarian-resembling tissue, which apparently showed scars from ovulations. This structure was removed for histologic examination.

The microscopic examination showed the ovarian-resembling structure to be an ovotestis. The pear-shaped structure consisted of a thick muscular wall with a narrow central duct covered with mucosal tissue resembling endometrial tissue. This organ consequently could be an uterus. The microscopic examination of the tissue on the other side of the ovotestis, where macroscopically a little epoophoronic structure and a 4 cm long tuba-resembling structure with fimbriae could be distinguished, showed an epididymis-resembling structure. Besides this a duct quite resembling ductus deferens was found. There was no signs of spermatozoa. Further a small uncharacteristic duct was seen,

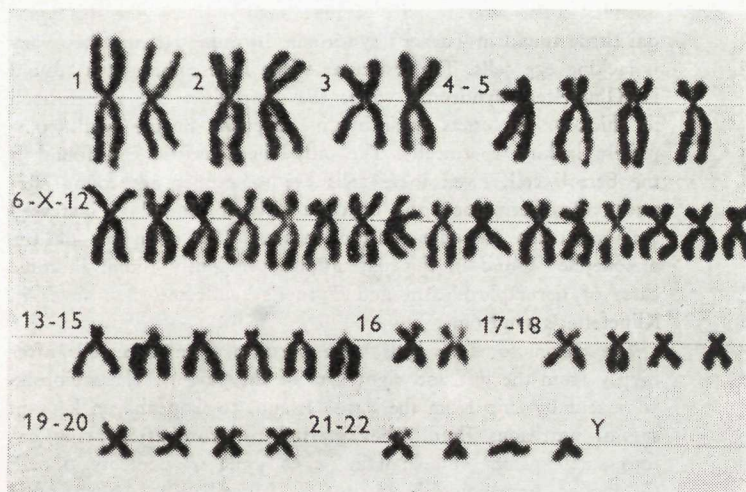


Fig. 8. Same cell as that shown in Fig 6. The chromosomes are cut out and arranged according to the Denver system. The two X-chromosomes are found among the 16 chromosomes in the second line of the system.

slightly resembling a rudimentary tubal duct. The microscopic examination of the ovotestis showed three well-defined areas. First a small area made up of fibrillated connective tissue reminding of the stroma of the ovary (fig. 4). No egg cells were seen. Further a narrow demarcated zone was found consisting of a connective tissue with few cells and vessels. In this tissue a few small ducts were observed, apparently remnants of mesonephros. Fig. 5 shows greatly enlarged a part of this tissue with distinct sexchromatin in one of the nuclei. Lastly a larger area was observed consisting of several components. Here remnants of spermiducts were observed totally destroyed, hyalinized and almost without cells, without any signs of spermatozoa or precursory stages. Further a loose uncharacteristic connective tissue was seen and finally adenomatoid cellmasses, presumably consisting of Leydig's cells (Fig. 6).

A gonad was consequently found consisting of both testicular and ovarian tissue — an ovotestis. Though, both tissues are abnormal and separately resemble gonadal tissue, which is found



in other characteristic conditions caused by chromosomal abnormalities. The ovarian part of the gonad is much like the gonadal tissue found in Turner's syndrome. In these patients the ovary is lacking egg cells. The testicular tissue is resembling that found in Klinefelter's syndrome, where the spermiducts are transformed to thick-walled ducts with hyaline deposits in the wall, completely lacking sperm cells. The only characteristic cell found is the Sertoli cell. Even these cells are sometimes not found. Between the spermiducts the Leydig's cells are found in increased amount, often in adenomatoid masses. The remnants of the mesonephros found in this patient are previously found in some cases of hermaphroditism and Turner's syndrome, but never in Klinefelter's syndrome.

The chromosome analysis were performed on skin cells after biopsy from the left and right arm of the patient. These biopsies were sent by ship from the Faroe Islands to Copenhagen kept in special nutritious fluid. They started to grow after being cut into small pieces and kept in a constant temperature of 37° Celsius at Arvebiologisk Institut in Copenhagen. After a few weeks the growth was pronounced and several new cells could be observed. By special technique the cell chromosomes were spread, scrutinized, counted and classified. In fig 7 the chromosomes of one of the cells are shown. In fig. 8 the chromosomes are cut out and arranged by size and other characteristics according to the system of Denver. It is shown that the patient has chromosomes as a normal female — 46 chromosomes and among these the two sex chromosomes, XX, seen in the second row of fig 8. Incidentally, it is impossible to distinguish the sex chromosomes from the other autosomes in the same row. The sex-chromatin test was positive as shown in fig. 5.

*Case 2.* This case was previously thoroughly investigated by *Zachariae* and reported in 1955<sup>23</sup>. As chromosome analysis on cells from this patient has not been performed previously, the results of this analysis are reported in connection with case 1.

This second patient was registered and reared as a male. His five siblings and his parents were healthy without any known abnormality. Shortly after the birth it was noted that the penis was small and curved with penoscrotal hypospadias. At the age of 25 he married a normal woman and the marital relations were quite normal. The marriage was childless.

At 28 years of age he sustained an injury which gave rise to haematoma and infection in the right half of the scrotum. Micro-

scopic examination of a lump of ejected necrotic tissue showed necrotic testicular tissue. At 29 years of age the patient was admitted to surgical department D, Bispebjerg Hospital, Copenhagen and operated on for incarcerated left inguinal hernia. The right testis was found to be small and the left testis seemed to be palpable just inside the annulus abdominalis. During the same admission the hypospadias was corrected. He complained now of periodical haematuria lasting five to six days at four weekly intervals. The haematuria started about two months after the injury to the right testis. Urethroscope during a period of haematuria showed a cleft-like opening in the posterior wall of the prostatic part of the urethra from whence a small, bloody lump of tissue protruded. The cells from a skin biopsy were examined for sex-chromatin and the cells were found to be chromatin positive as in a female. The patient was now operated on in order to find and remove ovarian tissue. During the operation an uterus of almost normal size with a normal looking tuba uterina on the left side was found and removed. Further a cystic ovary with corpora lutea was found. From the uterus a little-finger-thick string — vagina — was seen going to the posterior part of the prostata, where the urethroscope had revealed the little opening in the posterior wall of the urethra. Further a small node in the scar from the previous inguinal hernial operation was removed. The patient had complained of transitory pains here following the operation for inguinal hernia. On the microscopic examination the node appeared to be endometriotic tissue, and it is presumed that a suture must have gone through the uterus lying close to the annulus abdominalis during the operation for inguinal hernia.

The chromosome analysis were performed in the same way as mentioned in the previous case on skincells and in this case also on white blood cells. The results showed chromosomes as in a normal female. The sex — chromosome pattern was XX. No mosaic formation was observed.

### SUMMARY

The sex-chromatin test and the chromosome analysis are reviewed briefly in relation to the sexual development in normal and known abnormal conditions. Two cases of true hermaphroditism are reported. Chromosome analysis showed normal feminine constitution in both. Microscopical investigation of the ovotestis removed from case I showed the ovarian



stroma without follicles with changes completely as in Turner's syndrome. The testicular elements had features in common with Klinefelter's syndrome. The tubules were completely hyalinized containing Sertoli cells only. Spermatogenic elements were not observed. The Leydig cells were numerous and often found in small adenomas. Case II was reported by *Zachariae* in 1955.

### ÚRTAK

Kynskromatinkanningin og kromosomsundurgreiningin verða handfarnar í stuttum í sambandi við kynsbúningina undir rættvorðnum og kendum órættvorðnum umstöðum. Sagt verður frá tveimur sonnum tvíkyngjunga. Kromosomsundurgreiningin vísti hjá báðum rættvorðna kvennkynssamanseting. Sjóneykukanning av eggrótareistanum (ovotestis), ið tikið var úr tilburði I, bar til sjóndar eina eggrótarvond við ongum eggböllum og við broytingum heilt líkum teimum, ið eru at finna við Turner's syndrom. Eistnupartarnir hövdu drög felags við Klinefelter's syndrom. Tubuli vóru heilt hyaliniseraðir, og í teimum vóru einans Sertoli kyknur. Eingir sáðskapandi kyknulutir vóru at síggja. Leydig kyknur vóru í hópatali og ofta at finna í smáknyklum. Tilburði II hevur *Zachariae* greitt frá í 1955.

The chromosome analysis on both patients was kindly performed by Dr. A. Fröland, Københavns Universitets Arvebiologiske Institut. The histologic examination of the gonads and the internal genital organs in our first case was kindly performed by Dr. Tage Lund, Patologisk Institut, Aarhus Kommunehospital and Dr. A. Fröland. We wish to thank F. *Zachariae*, M. D. for the kind permission to report the second case.

### REFERENCES

1. *Young, H. H.*: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases. Williams & Wilkins, Baltimore 1937.
2. *Sohval, A. R.*: *Physiol. Rev.* 1963: 43: 306—356.
3. *Hamilton, W. J. et al.*: Human Embryology, W. Heffer & Sons, Cambridge 1952.
4. *Bernth & Hagens*: Medicinsk Kompendium, Store Nordiske Videnskabsboghandel, København, 1957.
5. *Jost, A. i Jones, H. W., Jr. & Scott, W. S.*: Hermaphroditism, Genital

- Abnormalities and Related Endocrine Disorders, Williams & Wilkins, Baltimore 1958, pp. 15—45.
6. Barr, M. L. & Bertram, E. G.: *Nature* 1949: 163: 676—677.
  7. Grumbach, M. M. & Morishima, A.: *Acta cytol.* 1962: 6: 46.
  8. Tjio, J. H. & Levan, A.: *Hereditas* 1956: 42: 1.
  9. Fröland, A. & Mikkelsen, M.: *Ugeskr. f. Læger* 1962: 124: 421.
  10. Klinefelter, H. F., Jr. & al.: *J. Clin. Endocrin.* 1942: 2: 615.
  11. Jacobs, P. A. & Strong, J. A.: *Nature* 1959: 183: 302.
  12. Conen, P. E. & al.: *J. Urol.* 1964: 91: 595.
  13. Jacobs, P. A. & al.: *Lancet* 1959 (I): 710.
  14. Conen, P. E. & al.: *Lancet* 1961 (II): 294.
  15. Barr, M. L.: *Surg., Gynec. and Obst.* 1954: 99: 184.
  16. Hinman, F.: *The Principles and Practice of Urology*, Saunders, Philadelphia 1935.
  17. Merrill, J. A. & Ramsay, J. E.: *Obst. Gyn.* 1963: 22: 505.
  18. Shutt, A. J. & Hayles, A. B.: *Mayo Clin. Proc.* 1964: 39: 363.
  19. Gresham, G. A. & Fairgrieve, J.: *Brit. J. Surg.* 1961: 48: 235.
  20. Winkel Smith, C. C.: *Arch. Dis. Child.* 1960: 35: 402.
  21. Wilkins, L.: *Pediatrics* 1960: 26: 846.
  22. Hanley, H. G.: *Brit. J. Surg.* 1953: 41: 217.
  23. Zachariae, F.: *Acta Endocr.* 1955: 20: 331.
  24. Wasserman, D. H. & Klein, E.: *J. Urol.* 1964: 91: 426.
  25. Hungerford, D. A. & al.: *Am. J. Human. Genit.* 1959: 11: 215.
  26. Crossfield, J.: *J. Urol.* 1963: 88: 674.
  27. Rosenberg, H. S. & al.: *J. Clin. Endocrinol. & Metab.* 1963: 23: 203.

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