Virchows Arch. A Path. Anat. and Histol. 389, 103–117 (1980)

Virchows Archiv A

XY (H-Y$^+$) Gonadal Dysgenesis

Morphoiogical Examination of 4 Cases by Light and Electron Microscopy

Heinz Pickartz[1], Lothar Moltz[2], and Eberhard Altenähr[1]

[1] Institut für Pathologie und [2] Klinik für Gynäkologie und Geburtshilfe, Klinikum Steglitz, Freie Universität Berlin

Summary. The gonads of 4 phenotypically female individuals with XY chromosomal constitution and signs of virilisation were examined by light microscopy. Electron microscopic examination was also performed in two cases. Serological analysis of H-Y antigen titer yielded positive results. The matrix of the gonads is shown to be ovarian stroma, in which tubular and follicular structures are embedded. The epithelia of the follicles resemble granulosa cells of the ovary, the tubular epithelia are resemble Sertoli cells. Tubules and follicles both show extensive regressive changes. A varying number of Leyding cells/stroma lutein cells were found in each gonad. The different degree of development of testicular and ovarian structures in the dysgenetic gonads might be explained by a defect of the gonadal specific receptor for the H-Y antigen, this defect varying in time of occurrence, duration and severity.

Key words: Gonadal dysgenesis – H-Y antigen – Ultrastructure.

Introduction

The term "gonadal dysgenesis" (GD) refers to a differentiation disorder of the gonads which may occur in cases of chromosomal anomalies but which may also occur if no disorder in the chromosomal set is detectable. GD is associated with different phenotypic characteristics.

The understanding of the aetiopathogenesis of GD requires knowledge of current hypotheses of the differentiation of the gonads and of the sexual phenotype, which will be described briefly.

In 1955 Eichwald and Silmser described a histo-compatibility antigen with weak antigenicity occurring in male inbred mice, which they called "histocompatibility antigen Y" (H-Y antigen). Goldberg

Offprint requests to: Dr. med. Heinz Pickartz, Institut für Pathologie, Klinikum Steglitz der FU Berlin, Hindenburgdamm 30, D-1000 Berlin 45

0340-1227/80/0389/0103/$03.00

et al. (1971) succeeded in producing a humoral antibody against this H-Y antigen in female mice, the cytotoxicity of which could be titrated on spermatozoa and epidermal cells of male mice. This antibody facilitated the detection of the H-Y antigen by means of absorption tests. Studies performed with this test (Wachtel et al. 1975) showed that the male cells of all mammals tested (including man) absorbed H-Y antibodies specifically in vitro, whereas the female cells of all animal species tested failed to do so and were thus shown to have no H-Y antigen.

Ohno et al. (1978) showed that differentiation of the indifferent gonad into testis in cultivated testicular cells of mice was determined by the H-Y antigen. Thus cultivated male gonadal cells reorganize, after blockage of the H-Y antigen by H-Y antibodies and form ovarian structures. Further investigations (Wachtel et al. 1976; Cattanach et al. 1971; Fredga et al. 1976; Zenzes et al. 1978; Gosh et al. 1978) revealed that both H-Y positive individuals with XX chromosomal constitution and H-Y negative individuals with XY constitution occur in mammals and man. The gonads of these individuals possess – independent of the genetic sex – testicular structures in cases of positive typification for the H-Y antigen, and ovarian structures in cases lacking this antigen.

Human genetic findings led Wolf (1976, 1978, 1979) to advance the hypothesis that the H-Y antigen is coded by an autosomal structural gene, which itself underlies the control of a regulatory gene on the X and Y chromosome (3 gene hypothesis).

These ideas concerning the differentiation of the gonads are supplemented by Jost (1946–1947, 1972), Josso (1972, 1973, 1974) and Blanchard and Josso (1974) who reported on the differentiation of the secondary sexual organs. They showed that the maturation of the Wolffian duct takes place under the influence of testosterone and that the development of the Müllerian duct in human males is impeded by a substance not yet isolated, which is called anti-Müllerian-hormone (AMH) or Müllerian-inhibiting-factor. The maturation of the secondary sexual organs in XX individuals takes place as a matter of course in the absence of AMH and testosterone, after the gonad has differentiated into an ovary in absence of the H-Y antigen.

Material and Methods

4 cases of GD were examined. Both gonads were available in case No. 1, the uterus and bilateral adnexae in case No. 2, the right adnexae in case No. 3 and the uterus with both tubes and the left gonad in case No. 4 (Table 1). Light microscopic examination was performed on paraffin-embedded, formaldehyde-fixed tissue and in semithin-sections after embedding in Mikropal (Fa. Ferak, Berlin). The sections were stained with the following staining methods: Haematoxylin-eosin, elastic – van Gieson, PAS, Ladewig, trichrome – Goldner and Giemsa.

For the electron microscopic examination gonadal tissue from cases No. 3 and No. 4 was fixed in 3% glutaraldehyde and in 2% OsO_4, each for two hours. After dehydration in alcohol, the specimens were embedded in Mikropal. Ultrathin sections were contrasted with uranyl acetate and lead citrate. Examination was performed by an electron microscope 101, Fa. Siemens at 60 or 80 KV.

Table 1. Specimens available for microscopic examinations

	Case 1	Case 2	Case 3	Case 4
Uterus		+		+
Right gonad	+	+	+	Fibroma ten years ago
Right tube		+	+	+
Left Gonad	+	+	Dysgerminoma six years ago	-
Left tube		+		+

The chromosomal analyses were done on lymphocytes of the peripheral blood, on epithelial cells of the oral mucosa and on gonadal tissue by Frau Dr. E. Struck (Institut für Humangenetik der FU Berlin). The determination of the H-Y antigen was performed by Prof. Dr. U. Wolf (Institut für Humangentik und Anthropologie der Universität Freiburg i.Br.) on serum.

The genetic findings in the 4 cases reported on in the present paper have been published recently by Wolf (1979), (cases No. 33, 34, 35, 36), the clinical and endocrinological findings by Moltz et al. (in press).

Results

The 4 cases of GD described represent differentiation disorders of the gonads which occur in chromosomally male and phenotypically female individuals. The serological determination of the H-Y antigen was positive in all cases. The patients were 25, 29, 35 and 40 years old. The inner genitalia consisted of uterus and tubes in all patients. In cases No. 1, 2 and 3 the uteri were clearly hypoplastic. The gonads of these cases were situated in the site of the ovary. The uterus of case No. 4 was slightly hypoplastic, the left gonad was located in the pelvis retroperitoneally. Cases No. 1, 2 and 3 had streak gonads, their size was up to $50 \times 10 \times 10$ mm. Case No. 4 had a firm ovoid gonad, $20 \times 12 \times 12$ mm in size. In cases No. 3 and 4 the right gonad had been removed 6 and 10 years ago respectively, because of a dysgerminoma (case No. 3) and a fibroma (case No. 4) (Table 1). Histological examination of these gonadal tumors was made by other pathologists and the reports do not contain any information on residual tumor-free gonadal tissue. In reviewing the slides we could not find any residual gonadal tissue.

All patients with at least one intact streak gonad had elevated plasma and urinary androgens when compaired with healthy ovulating women; plasma estra-

Table 2. Urinary and plasma testosterone (T), 17β-estradiol(E_2), basal and stimulated plasma pituitary proteohormones in 4 patients with XY (H-Y$^+$) GD. Values in parenthesis indicate normal ranges, i.e., upper normal limits for the early follicular phase of healthy ovulating women, mean + 2 SD

	Case 1 I.K. 40 yrs.	Case 2 B.P. 35 yrs.	Case 3 G.O. 25 yrs.	Case 4 E.M. 29 yrs.
Urinary T (<10 mg/24 h)	6.8	13.8	13.4	38.7
Plasma T (<0.5 µg/ml)	0.28	0.21	0.84	1.74
E_2 (<20 pg/ml)	14.0	37.6	27.6	46.0
LH basal (0.8–4.0 ng/ml)	5.9	6.4	8.2	19.9
LH Δ_1 (<8 ng/ml)	11.4	12.4	15.2	42.6
LH Δ_2 (<12 ng/ml)	5.2	7.4	12.5	36.8
FSH basal (1.1–4.2 ng/ml)	10.7	17.3	28.9	24.9
FSH Δ_1 (<3.5 ng/ml)	10.9	21.2	34.9	11.8
FSH Δ_2 (<5.0 ng/ml)	8.5	36.4	36.0	16.6

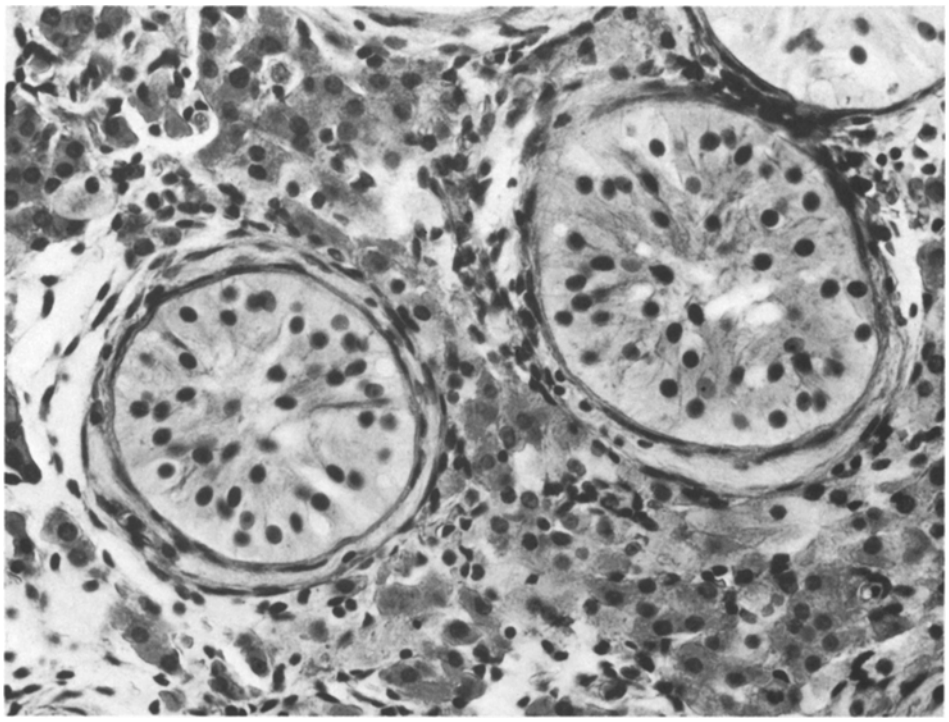


Fig. 1. Gonad no. 4. Seminiferous tubules with multilayered prismatic Sertoli cells. No germ cells, no signs of spermatogenesis are detectable. Between the tubules are numerous Leydig cells. ×280

diol was higher than the upper normal limit for the early postmenopause. Basal and stimulated gonadotropin release (LH and FSH) was similar to that observed during the postmenopausal period (Moltz et al., in press). For endocrinological data see Table 2.

Light Microscopy

In cases No. 1 and 2, the gonads show nearly identical findings on both sides. The matrix of all gonads is an ovarian stroma which is variably fibrotic.

Gonads No. 1 and 2 contain sparse perihilar tubules embedded in the ovarian stroma. These are lined by cylindrical epithelium and show narrow lumina. The cytoplasm is slightly basophilic, the nuclei are monomorphic and ovoid. In gonad No. 3 these tubules occur in larger numbers and are also seen in superficial cortical areas. There are also some cortical tubules which contain multilayered epithelium, which resemble the seminiferous tubules of the infantile testis. Gonad No. 4 contains a large number of such tubules (Fig. 1). Their epithelium us usually arranged in a radiate manner. This architecture is focally disturbed by stratification of the cells. In these areas the tubules change their character and become similar to ovarian (secondary) follicles. The ovarian stro-

ma of gonad No. 4 is marginated, and at one pole there is a cap-like broadening of this stroma border.

Gonad No. 1 and especially gonad No. 3 show solid nests of medium sized polygonal cells with rounded nuclei. The cell nests often enclose one or more hyaline eosinophil globules and are separated from the adjacent ovarian stroma by a distinct, often hyalinized basement membrane (Fig. 2). The globules show a strongly positive reaction with PAS-staining, and are occasionally focally basophilic in haematoxylin eosin stained sections. They resemble the Call-Exner bodies of ovarian follicles. In semithin sections the cytoplasm of tubular epithelia and of cells with a follicle-like arrangement reveals a moderate number of lipid-droplets. The tubular cells in gonad No. 4 show numerous vacuoles of varying size, up to 3 micron or more (Fig. 3).

In gonad No. 3 we found some large cells rich in cytoplasm with large round nuclei and comparatively poor in chromatin between the smaller follicular cells.

Tubules and follicle-like structures in all gonads show various regressive changes. In gonad No. 3 the ovarian stroma is interspersed with small, convoluted hyaline cords which correspond to obliterated seminiferous tubules. A small number of these structures is also present in the gonad of case No. 4 (Fig. 4 and 5). The majority of the follicles in cases Nos. 1 and 3 also show partial or complete hyalinization. The regressed follicles also show agglomerated micro-calcifications. The single calcified particles display onion shell-like concentric layers after decalcifaction (Fig. 6). Some hyalinized follicles have wave-like contours and resemble atretic follicles.

Solid nests and small rows of medium sized polygonal cells similar to Leydig cells or luteinized theca cells are present between the tubules (cases No. 3 and 4), in the ovarian stroma (case No. 3) and in the hilar region of the gonads (cases No. 1 and 2). The cytoplasm of the cells is eosinophilic and granulated (Fig. 7) and in case No. 4, a number of Reinke crystals are visible in their cytoplasm. The crystals a re mainly small and were detected only in the semithin sections.

Essential light microscopic findings are summarized in Table 3.

In 3 cases the hila of the gonads contain rudiments of the Wolffian duct. In case No. 4 we found variably differentiated mesonephric structures, in the hilus and mesosalpinx, which correspond to the ductuli efferentes and the ductus epididymidis in the male.

Electron Microscopy

Ultrastructurally the Leydig cells is characterized by an abundant smooth tubular endoplasmic reticulum. The numerous mitochondria have tubular cristae, a dark matrix and an ovoid shape. There is quite a number of small and large lipid droplets visible in the mitochondrial matrix. Giant mitochondria are often found, with their tubules frequently arranged in bundles oriented in different directions. Golgi-fields are prominent in the perinuclear region. In addition the cytoplasm contains variable numbers of lipid droplets, lipofuscin

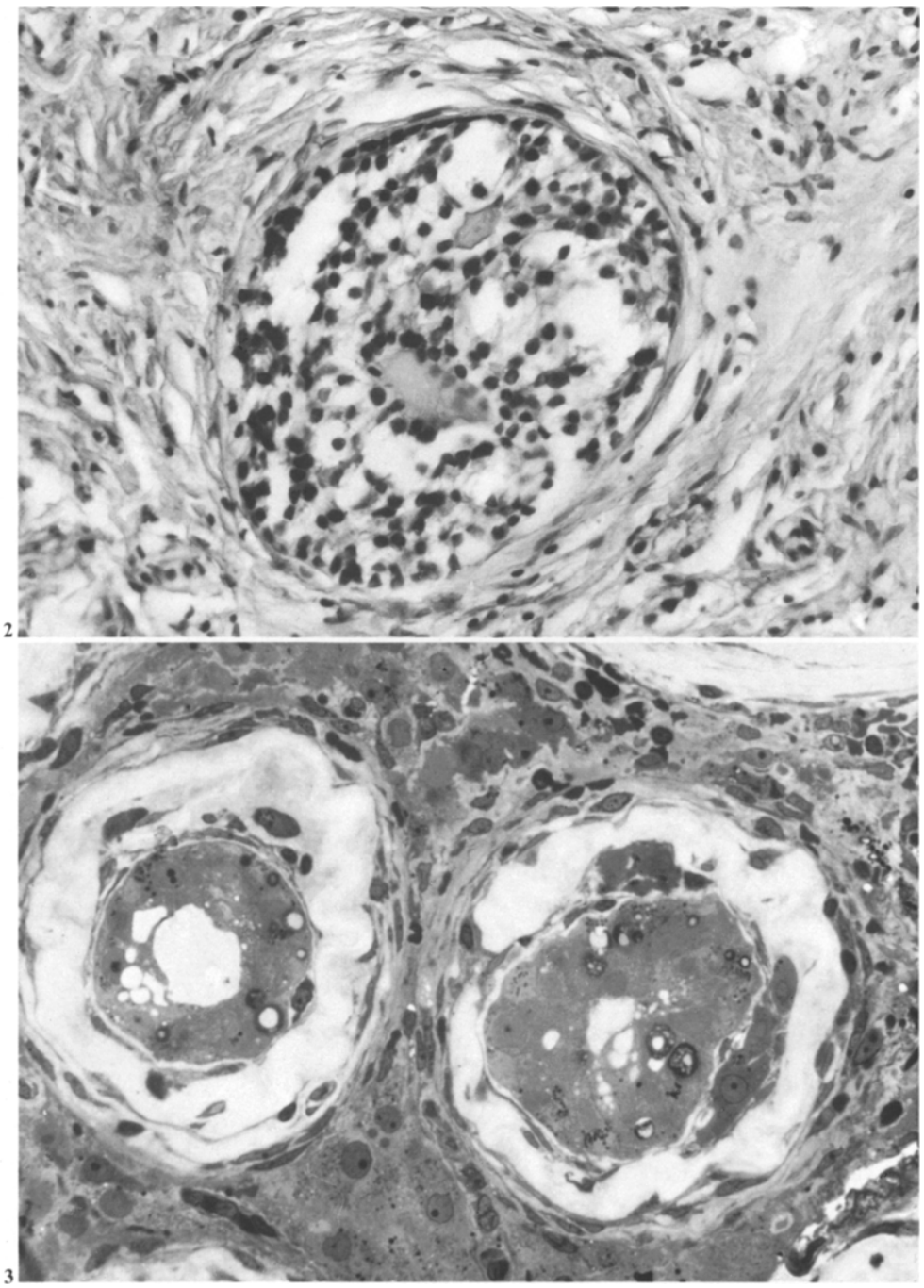


Fig. 2. Gonad no. 3. Follicle-like cell nest with focal hyalinizations. The surrounding cells are arranged in a rosette-like fashion. Thus the picture resembles the Call-Exner bodies of the ovarian follicle. ×280

Fig. 3. Gonad no. 4. Seminiferous tubules with vacuoles and lipid droplets in the cytoplasm of tubular epithelium. Leydig cells are enclosed in the thickened and hyalinized basement membrane. ×390

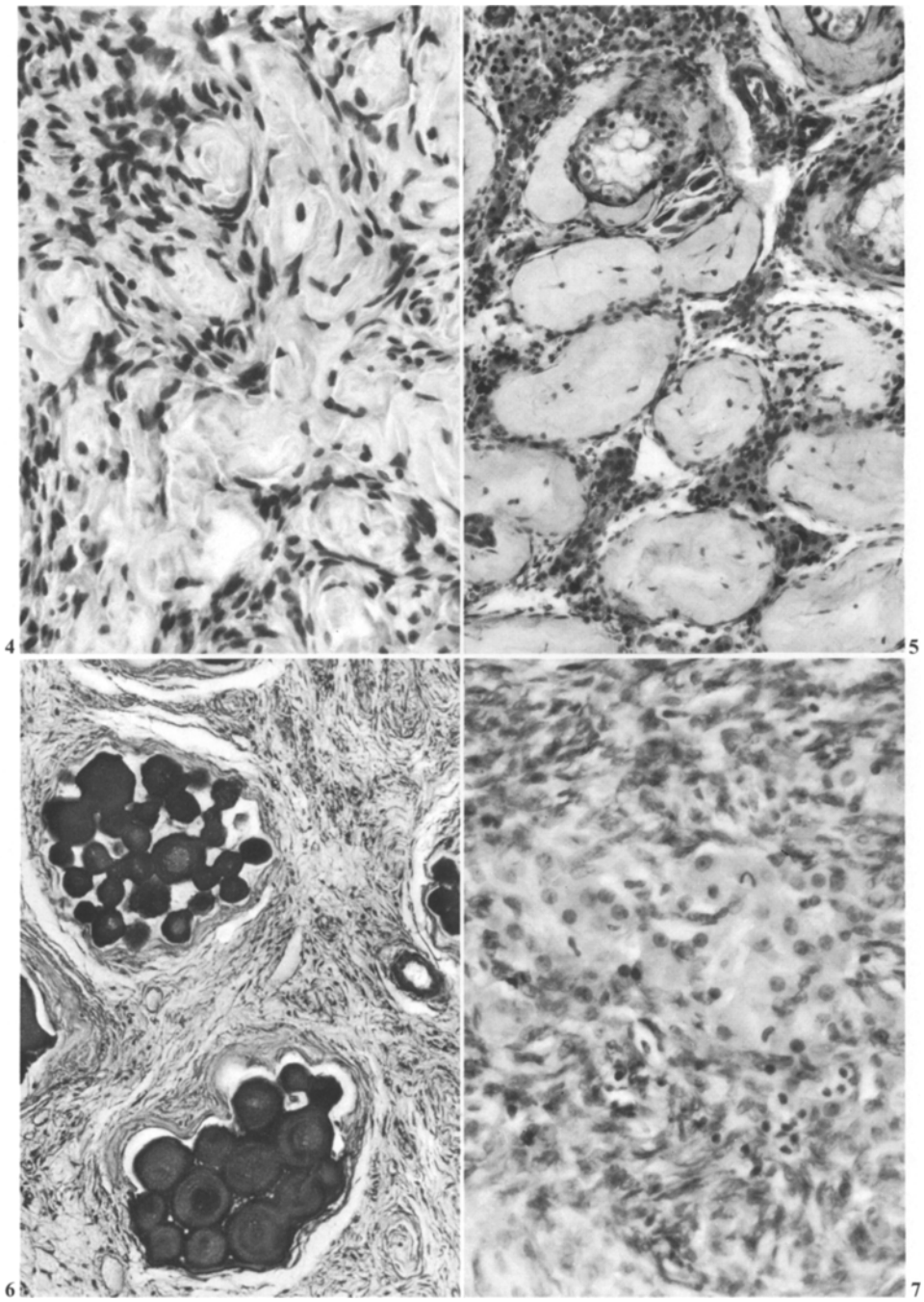


Fig. 4. Gonad no. 3. Tubular residua in the form of small hyalinized cords are entrapped in ovarian stroma. ×280

Fig. 5. Gonad no. 4. A part of the seminiferous tubules has undergone severe regressive changes. The lumina are obliterated, thick hyalinized cords are left. Sertoli cells have disappeared completely. ×280

Fig. 6. Gonad no. 3. Grouped microcalcifications in the end stage of degeneration of follicle-like sex cord derivatives. Note concentric layering of calcified globules. ×280

Fig. 7. Gonad no. 3. Luteinized cells embedded in ovarian stroma. Their cytoplasm contains no Reinke crystals, but apart from this they are not distinguishable from Leydig cells. ×280

Table 3. Histological findings in gonads with XY (H-Y$^+$) gonadal dysgenesis

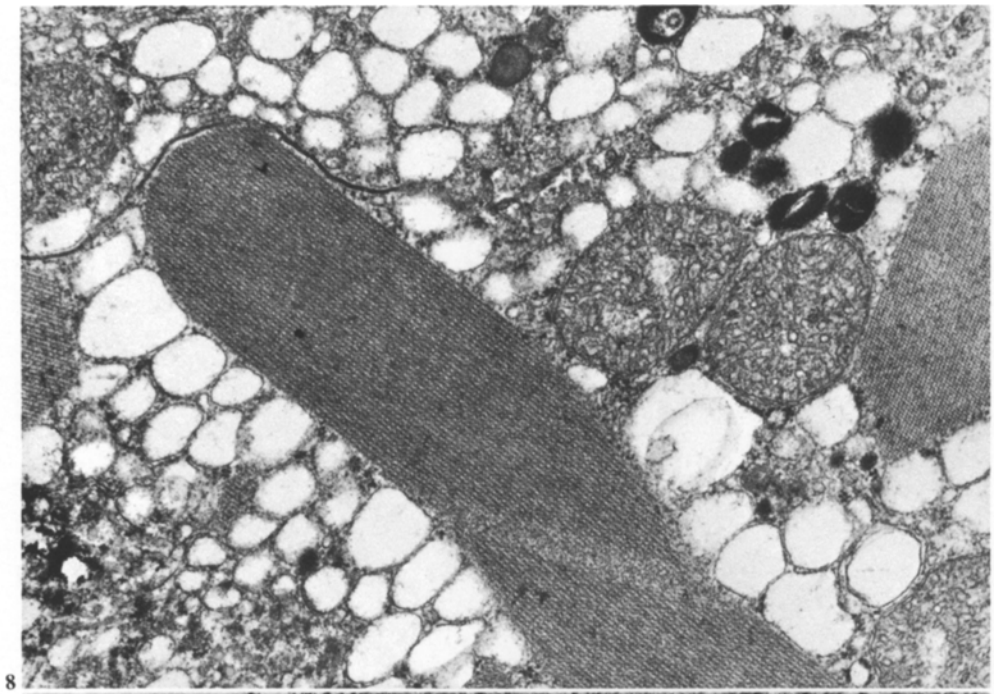
	Case 1 I.K.	Case 2 B.P.	Case 3 G.O.	Case 4 E.M.
Ovarian stroma	+	+	+++	++
Tubules with monolayered epithelium	+	+	++	+
Tubules with Sertoli-like epithelium	–	–	(+)	++++
Cord-like hyalinizations	–	–	+++	+++
Follicles and follicle-like structures	+	–	+++	++
Microcalcification	+	–	++++	++
Leydig/stromalutein cells	+ (hilus)	+ (hilus)	++	++++
Germ cells	–	–	(+)	–
Wolffian duct	rudimentary	rudimentary	rudimentary	partially differentiated

granules and few dense bodies. Reinke crystals show their typical, highly ordered lattice (Fig. 8). The cell surfaces are attached to each other by numerous short and plump interdigitating pseudopodia. Long and slender cell processes are sometimes wound spirally around a central cytoplasmic core, thus producing an image similar to nerve sheaths. The nuclei of the Leydig cells possess marginally distributed heterochromatin and large nucleoli.

The tubular epithelia, if aligned in a radial fashion, have linear cell borders. Their oval nuclei contain mostly euchromatin and large nucleoli with a coarse network. The cytoplasm is endowed with sparse organelles only, e.g., some rod-like mitochondria with lamellar cristae, parallel stacks of granular endoplasmic reticulum, lipid droplets and small Golgi-areas.

In the tubules with distorted radial orientation of the epithelial cells and in the follicle-like cell nests, the ultrastructural characteristics of the epithelium differs clearly from those described above. A well developed smooth endoplasmic reticulum, large and multiple Golgi-areas, and numerous, partly cystic intracytoplasmic spaces are detectable. The latter are filled with an amorphous or fine-granular material. The size of the spaces increases by confluence of Golgi-vesicles. Intercellular gaps are filled with the same material as the intracellular vacuoles. Slender pseudopodia of the adjacent cell membrane protrude into the intra- and intercellular spaces. Neighbouring cells are linked together by deep finger-like indentations of attached cell membranes (Figs. 9 and 10).

The hyaline globules in the follicles consist ultrastructurally of irregularly convoluted and often lamellar lines of a fine-granular material. The formation of these globules seems to start at the basis of the follicle cells by a focally unfolding labyrinth-like convolution of the basement membrane (Fig. 11). The membrane convolutions are located in pocket-like excavations of adjacent cytoplasm. With increasing size a lamellar, partly concentric layering of basement membranes becomes obvious. The inclusions are displaced into a more central



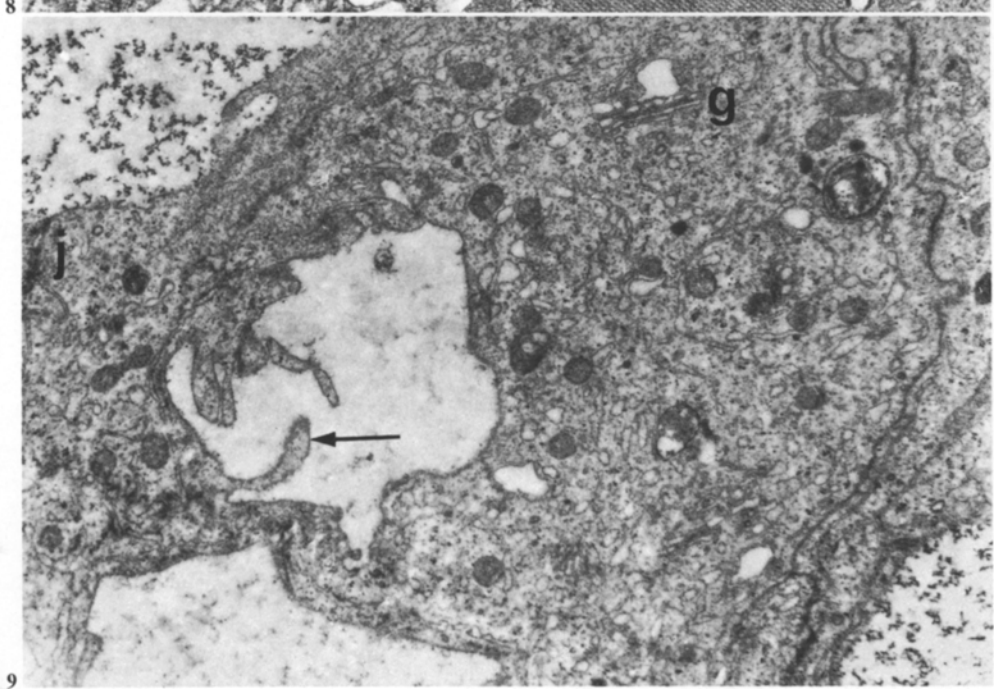


Fig. 8. Gonad no. 4. Cytoplasm of Leydig cells endowed with abundant smooth endoplasmic reticulum, mitochondria of tubular type and Reinke crystals. ×12,500

Fig. 9. Gonad no. 4. Cytoplasm of cells with follicle-like arrangement shows prominent Golgi-areas (*g*) and smooth endoplasmic reticulum. Intracellular blebs display gland-like structures with cell junction complexes (*j*) and slender microvilli (*arrow*). ×20,000

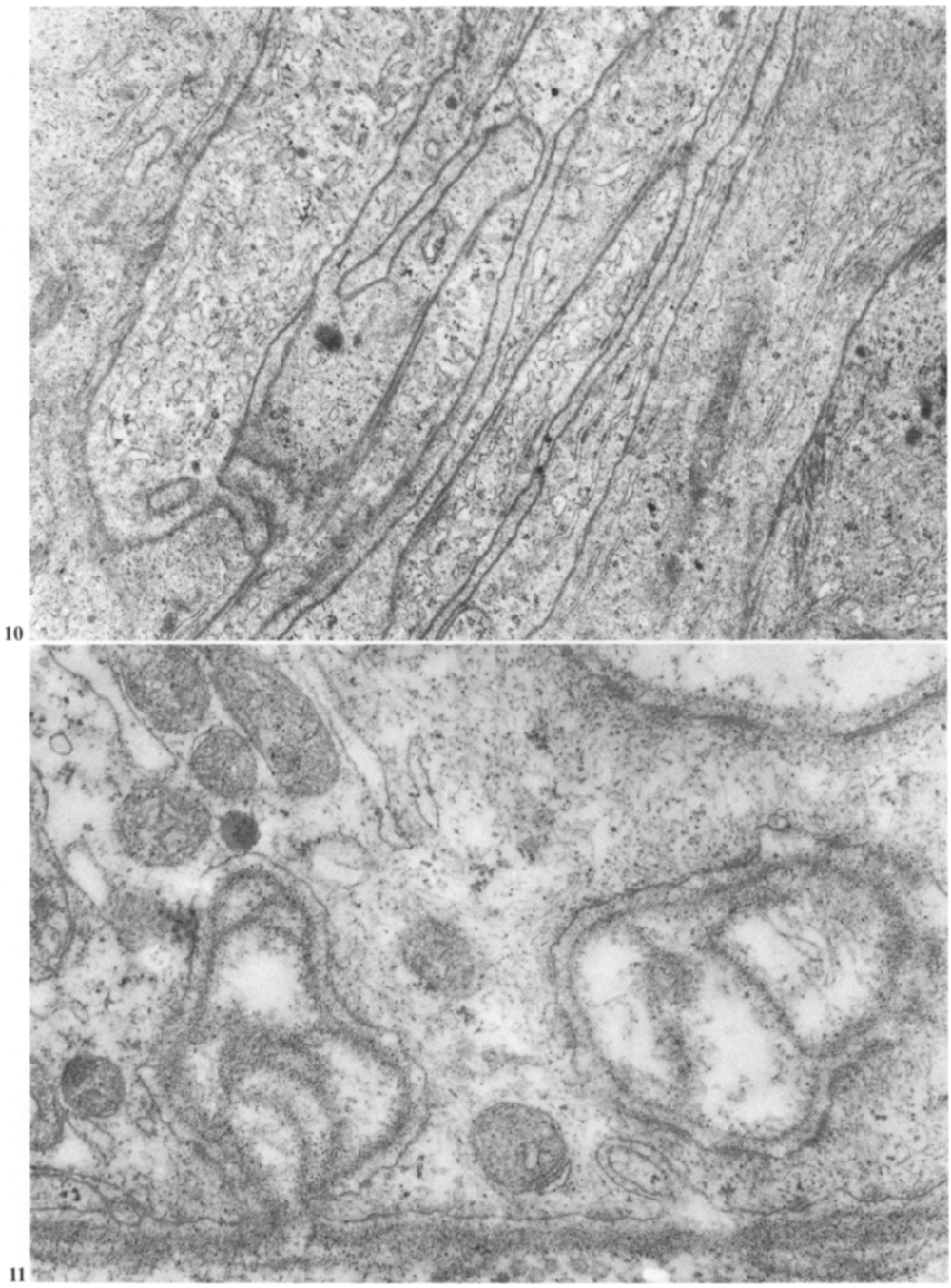


Fig. 10. Gonad no. 4. Cells with follicle-like arrangement are interconnected by long interdigitating processes. ×14,000

Fig. 11. Gonad no. 4. Cell from seminiferous tubule with follicular character. Unfoldings of tubular basement membrane herniate into small pouches of basal cytoplasm. Identical structures are visible in the ovarian follicle. ×20,000

cytoplasmic region and a communication with the cellular surface is no longer detectable.

The cells rich in cytoplasm in the follicles of gonad No. 3 are poor in organelles. They contain medium sized mitochondria and little granular endoplasmic reticulum. The electron lucent cytoplasm shows numerous ribosomes. The nuclei are large and rounded, the chromatin is sparse and the large nucleoli are centrally located.

Discussion

Cases No. 1 and 2 must be classified as "pure" GD because of the identical gonadal histology on both sides (Harnden and Stewart 1959; Shapiro 1977). The classification of cases No. 3 and 4, however, is problematic since in both cases one gonad had been destroyed by a tumor and had been removed. In the dysgerminoma of case No. 3 we found no gonadal rests in the slides placed at our disposal. We have seen, disseminated and grouped microcalcifications however, which Scully (1970) assumes to be evidence for a preexisting gonadoblastoma. In most instances this type of tumor has been detected in dysgenetic gonads (Scully 1970) but also very rarely in ovaries which seemed to be normal (Melicow and Uson 1959; Hughesdon and Kumarasamy 1970). A "mixed" GD (Sohval 1964) therefore seems to be possible in principle.

The slides of the gonadal tumor of case No. 4 show a fibrous, partly myxoid tumor tissue somewhat similar to ovarian stroma. Gonadal rest tissue could not be observed in the slides reviewed by us. In this case an asymmetric gonadal differentiations also seems possible, especially since we did not find epididymis-like structures in the mesosalpinx or the gonadal hilus on the side of the tumor. These structures were developed on the opposite side (Table 3). The presence of a XY constitution, the absence of a mosaic and the symmetrical formation of both uterine horns in cases No. 3 and 4 suggest that these cases should also be regarded as "pure" GD.

The hypotheses on the differentiation of gonads and inner genitalia quoted above lead to the expectation that in all these cases testes would have developed. As a consequence of this a male phenotype including male inner genital system would be found. Wolf (1976) explains the formation of a female phenotype, female inner genitalia and of dysgenetic gonads despite XY constitution and positive H-Y antigen in terms of a defect of the gonadal specific receptor of the H-Y antigen. This hypothesis does not explain the extreme microscopic differences found between the individual gonads. These could only arise in the presence of a disturbance in the receptors which varies either in time of occurrence, duration or severity. According to a diminished or completely blocked receptor function abortive or absent testicular differentiation of the gonad is made possible.

Our findings demonstrate clearly that there is no firm negative correlation between the formation of testicular characteristics on the one hand and ovarian structures on the other in the gonads. This may be explained in terms of the temporal gap between testicular and ovarian differentiation during the embryo-

nal period (Jirasek 1971). Since the differentiation of the testis precedes that of the ovaries, a temporary defect of the receptor of the H-Y antigen in this period only might disturb testicular differentiation alone. If, later, delayed onset of receptor function takes place, ovarian differentiation could be impaired or prevented.

Case No. 4 is distinctive because of the prominent development of seminiferous tubules with Sertoli cell-like epithelium and because of the combined occurrence of Fallopian tubes and epididymal structures. The large number of Leydig cells in this gonad may have induced the differentiation of the Wolffian duct during embryogenesis by secreting testosterone. The additional formation of uterus and tubes might be due to a disturbed production or a disturbed action of the AMH which normally causes regression of the Müllerian ducts. This mechanism is proposed by Brook et al. (1973) in considering the syndrome of the persisting Müllerian duct.

The widely spread opinion that dysgenetic gonads do not contain germ cells (Shapiro 1977) has been contradicted by Singh and Carr (1966) who showed an almost normal germ cell migration into the gonadal ridge, in stillborn fetuses with an XO constitution. These authors observed severe subsequent regressive changes in the germ cells, leading to cell death. In accordance with Singh and Carr (1966) we feel that the large cells in the follicle-like cell nests are germ cells. The majority of the follicles revealed severe degenerative changes in which preexisting germ cells might have disappeared. However, we did not observe germ cells in the well preserved tubules of the other cases.

The light microscopic impression of follicle-like cell nests in gonad No. 3 and, less extensively, in gonad No. 4 is supported by the ultrastructural findings. Follicle cells resemble granulosa cells of the ovary in their conspicuous smooth endoplasmic reticulum, in large Golgi-areas and in the formation of large intra- and intercellular blebs, corresponding to the formation of the liquor folliculi by the granulosa cells of the Graafian follicle. Finally the phenomena we have described as leading to the formation of Call-Exner-like bodies lead us to interpret the follicle-like cells nests as the equivalents of the ovarian component of dysgenetic gonads (Crisp et al. 1970; Bloom and Fawcett 1975).

Microcalcifications in the follicles apparently start in the Call-Exner-like bodies and may end in complete deletion of the follicular cells. Both follicles and grouped microcalcifications are identical with the sex cord component of the gonadoblastoma (Scully 1953, 1970) and the gonocytoma (Teter 1960). The occurrence of these structures in dysgenetic gonads supports the assumption that this sex cord component of gonadoblastoma is a female one and originates in dysgenetic ovarian follicles.

The ribbon-like hyalinizations in gonads No. 3 and 4 correspond to completely obliterated seminiferous tubules and suggest that the regression might have started at a very early stage in testicular differentiation, perhaps before the Sertoli cells or other cells were capable of producing the AMH. Gonadal regression starting at an even earlier phase of organogenesis may result in total disappearance of gonadal rests, in aplasia or "agenesis". Such events are taken as the origin of the formation of a female phenotype in spite of XY chromosomal constitution by Abeyaratne et al. (1969) and by Edman et al. (1977). Edman

et al. discuss unknown genetic defects, teratogenic noxae and vascular disorders as causative factors for the gonadal regression and favor genetic defects, in view of the frequent familial occurrence of agonadism. It is still unclear what connections exist between gonadal regression and a defect of the H-Y antigen receptor of the gonadal cells. It seems possible that faulty differentiation of sex cord derivatives and the disturbed integration of germ cells resulting from this, are of importance in this process.

The reports in the literature concerning XY GD with positive H-Y antigen titer (Dorus et al. 1977: 1 case; Wolf 1979: 9 cases) contain only brief comments on gonadal histology. In the case published by Dorus et al. both gonads were destroyed by a gonado-blastoma or a dysgerminoma; in one case bilaterial tumors developed in a time interval of 4 years. In another case a gonadal tumor on one side was diagnosed as a carcinoma-like granulosa cell tumor. The histologic structure of the remaining tumor-free gonads showed a fibrous ovarian stroma, with some mesonephric rests and Walthard's islets.

In contrast to the majority of published cases, the gonads described here have not been destroyed by a tumor. Furthermore, our cases reveal a varying degree of differentiation and regression of testicular and/or ovarian constitutents and we therefore assume a common pathogenetic mechanism for all 4 cases, which varies in its time of occurrence, duration and severity.

Differential diagnosis between the type of GD discussed here and other forms with female phenotype, especially the most common form with XO chromosome constitution, is not possible by morphological analysis of the gonad alone. As a rule the dysgenetic gonads are represented as streaks and previously differentiated sex specific gonadal structures tend to dissapear by regression. However, unambiguous testicular constituents form only if a Y containing cell line is present and/or the H-Y antigen has been produced. Thus, in the case of a XO GD with testicular elements in the streak gonad an undetected chromosomal mosaic or expression of the H-Y antigen in spite of pure XO constitution must be assumed.

Gonadal histology in our case 4 is similar to that in the testicular feminization syndrome (Table 3). For differentiation between both abnormalities – XY GD and testicular feminization in its complete form – the internal genitals are decisive. In testicular feminization uterus and tubes are absent, although some vestigial Müllerian remnants may be present. On the other side, differentiation of Wolffian ducts is prevented by the inherited androgen insensitivity.

Examinations performed routinely in our gynecological department when GD is suspected include chromosomal analysis and the determination of the H-Y antigen. These examinations have yielded 6 cases of H-Y$^+$ GD in the last 4 years. In 4 cases we were able to examine the gonads histologically. Although only 10 cases of H-Y$^+$ have been published to date the fact that 6 cases have been discovered in our Department of Gynecology in this relatively short period of time indicates that this form of GD will be diagnosed with increasing frequency with more frequent determination of the H-Y antigen.

Acknowledgements. The authors wish to thank Ms. B. Dohse, Ms. K. Hindorf and Mr. D. Born for their skilful technical assistance and Dr. W. Meyer-Sabellek for his aid in translating this manuscript.

References

Abeyaratne MR, Aherne WA, Scott JES (1969) The vanishing testis. Lancet 2:822–824

Blanchard MG, Josso N (1974) Source of the anti-Müllerian hormone synthesized by the fetal testis: Müllerian inhibiting activity of fetal bovine Sertoli-cells in tissue culture. Pediat Res 8:968–971

Bloom W, Fawcett DW (1975) A textbook of histology. Female reproductive tract. Saunders, Philadelphia pp 858–906

Brook CGD, Wagner H, Zachmann M (1973) Familial occurrence of persistent Müllerian structures in otherwise normal males. Br Med J 1:771–773

Cattanach BM, Pollard CE, Hawkes SG (1971) Sexreversed mice: XX and XO males. Cytogenetics 10:318–327

Crisp TM, Dessouky, DA, Denys FR (1970) The fine structure of the human corpus luteum of early pregnancy and during the progestational phase of the menstrual cycle. Am J Anat 127:37–70

Dorus E, Amarose AP, Koo GC, Wachtel SS (1977) Clinical, pathologic and genetic findings in a case of 46 XY pure gonadal dysgenesis (Swyer's syndrome). II: Presence of HY-antigen. Am J Obstet Gynecol 127:829–831

Edman CD, Winters AJ, Porter JC, Wilson J, Mc Donald, PC (1977) Embryonic testicular regression. A clinical spectrum of XY agonadal individuals. Obstet Gynecol 49:208–217

Eichwald EJ, Silmser CR (1955) Communication. Transplant Bull 2:148–149

Fredga K, Gropp A, Winking, H, Frank F (1976) Fertile XX- and XY-type females in the wood lemming (Myopus schisticolor). Nature 261:255–257

Goldberg EH, Boyse EA, Bennett D (1971) Serological demonstration of HY (male) antigen. Nature 232:478–480

Gosh SN, Shah PM, Gharpure HM (1978) Absence of H-Y antigen in XY females with dysgenetic gonads. Nature 276:180

Harnden DG, Stewart JSS (1959) The chromosomes in a case of pure gonadal dysgenesis. Lancet 2:1285

Hughesdon IE, Kumarasamy T (1970) Mixed germ cell tumors (gonadoblastomas) in normal and dysgenetic gonads. Virchows Arch Abt A Path Anat 349:258–280

Jirasek JE (1971) Development of the genital system and male pseudohermaphroditism. The Johns Hopkins Press, Baltimore and London

Josso N (1972) Permeability of membranes to the Müllerian-inhibiting substance synthesized by the fetal testis in vitro: a clue to its biochemical nature. J Clin Endocrinol 34:265–270

Josso N (1973) In vitro synthesis of Müllerian-inhibiting hormone by seminiferous tubules isolated from the calf fetal testis. Endocrinology 93:829–834

Josso N (1974) Müllerian-inhibiting activity of human fetal testicular tissue deprived of germ cells by in vitro irradiation. Pediatr Res 8:755–758

Jost A (1946/47) Recherches sur la différenciation sexuelle de l'embryon de lapin. Arch Anat Microsc Morphol Exp 36:151–200

Jost A (1972) A new look at the mechanisms controlling sex differentiation in mammals. Johns Hopkins Med J 130:38–45

Melicow MM, Uson AC (1959) Dysgenetic gonadomas and and other gonadal neoplasms in intersexes. Cancer 12:552–572

Moltz L, Struck E, Pickartz H, Römmler A, Wolf U, Hammerstein J (1979) Pure XY (HY^+) gonadal dysgenesis. Acta endocr (Kbn) Suppl 225:392

Moltz L, Pickartz H, Sörensen R, Struck E, Schwartz U, Römmler A, Hammerstein J, Wolf U (in press) The H-Y antigen in XY gonadal dysgenesis: an inducer of aberrant testicular differentiation. Obstet Gynecol

Ohno S (1978) The role of the HY antigen in primary sex determination. JAMA 239:217–220

Scully RE (1953) Gonadoblastoma. Cancer 6:455–463

Scully RE (1970) Gonadoblastoma: a review of 74 cases. Cancer 25:1340–1355

Shapiro LR (1977) Disorders of female sex differentiation. In: Blaustein A (ed): Pathology of the female genital tract Springer, New York, pp 420–452

Singh RP, Carr DH (1966) The anatomy and histology of XO embryos. Anat Rec 155:369–384

Sohval AR (1964) Hermaphroditism with "atypical" or "mixed" gonadal dysgenesis. Am J Med 36:281–292

Teter J (1960) A new concept of classification of gonadal tumors arising from germ cells (gonocytoma) and their histogenesis. Gynaecologica 150:84–102

Wachtel SS, Koo GC, Boyse EA (1975) Evolutionary conservation of HY (male) antigen. Nature 254:270–272

Wachtel SS, Koo GC, Breg WR, Thaler T, Dillard GM, Rosenthal IM, Dosik H, Gerald PS, Saenger P, New M, Lieber E, Miller OJ (1976) Serological detection of a Y-linked gene in XX males and XX true hermaphrodites. N Engl J Med 295:750–754

Wolf U (1976) Funktionelle Aspekte der Geschlechtschromosomen beim Säuger. Presented at the 5th meeting of the Cytogenetics Section of the "Gesellschaft für Anthropologie und Humangenetik", Basel, June 17/19

Wolf U (1978) Zum Mechanismus der Gonadendifferenzierung. Presented at the Symposion: "Medical Genetics – Tomorrow" of the Swiss Academy of Medical Sciences, Basel, April 28/29. Bull Schweiz Akad Med Wiss 34:357–368

Wolf U (1979) Gonadal dysgenesis and the HY-antigen. Report on 12 cases. Hum Genet 47:269–277

Zenzes MT, Wolf U, Engel W (1978b) Organization in vitro of ovarian cells into testicular structures. Hum Genet 44:333–338

Accepted July 8, 1980