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Mixed Germ Cell Tumours (Gonadoblastomas) in Normal and Dysgenetic Gonads

Case Reports and Review

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Gemischte Keimzellgeschwülste der Gonaden

Zusammenfassung. Gonadoblastome sind primäre Keimzellgeschwülste, welche eine reaktive Wucherung der Sertolizellen oder Granulosazellen ausgelöst haben. Dies kommt im normalen Hoden nur ganz ausnahmsweise vor (2 Fälle). Etwas weniger selten ist diese Reaktion in normalen Ovarien (8 Fälle), wo die Reaktion in schon bestehenden Stromawucherungen beobachtet wird. Die Reaktion variiert in Form und Grad. Sie kann verbunden sein mit Oestrogensekretion und schließlich einen geschwulstartigen Charakter annehmen. Sie kommt besonders häufig und in charakteristischer Form in dysgenetischen Keimdrüsen vor (50 Fälle), wo sie entweder von den Samenkanälchen oder von wenig ausdifferenzierten Keimzellen und Granulosazellnestern, und zwar unmittelbar angrenzend an das Keimgewebe ihren Ausgang nimmt. In dieser letzten Form verhält sich das Gonadoblastom wie eine in bezug auf den Geschlechtscharakter nicht voll ausdifferenzierte Geschlechtszelle, doch vorwiegend in Richtung männliches Geschlecht mit hormonalfunktionellen Auswirkungen in der Pubertät. Letztere scheinen vom Hypophysenvorderlappen-Gonadotropin abhängig zu sein, wie auch der Übergang in eine Neubildung.

Summary. There are described (1) a seedling gonadoblastoma (gonocytoma III) in a girl of 19 with primary amenorrhoea, an XO/XY karyotype and dysgenetic ovaries: there were no testicular rudiments and the tumour made no connection with any other structure; (2) a large gonadoblastoma (gonocytoma II) in a chromatin positive girl of 16 with puberty menorrhagia, showing diverse interrelated patterns including dysgerminoma, fibroma, granulosal cell tumour and embryonal carcinoma; and (3) a seminoma in a normal man of 23 with 4 small foci of intratubular gonadoblastoma at the tumour margin.

A survey of the literature, classification and main features of the tumour suggest that: (1) 50 cases are classifiable as gonocytoma III and 10 as gonocytoma II; (2) tumours arising in normal ovaries are histologically diverse whilst the rest resemble one another; (3) the tumour arises as a primary germ cell neoplasm in either testicular or ovarian tissue, evoking an enveloping Sertoli cell response in the former and a stromal response with subsequent granulosal metaplasia in the latter; (4) it can probably arise from dysgenetic structures lying at the periphery of malformed testis and the centre of malformed ovary; and (5) pituitary gonadotrophin promotes both its development and endocrine effects.

The present article describes 3 tumours consisting wholly or partly of the pattern described by Scully (1953) as "gonadoblastoma". They arose respectively in a dysgenetic ovary, a normal ovary and a normal testis and differed somewhat from one another in structure. The literature is reviewed, and parts of it suggest (tentatively) that these differences of structure and origin may be correlated. The

conceptual unity of the tumour and a previous attempt to subdivide it (Teter, 1960a) are considered in relation to this, as is the debatable neoplastic status of the non-germinal elements.

Case 1. Miss L. D., aged 19, attended the endocrine clinic in October, 1967 with a complaint of primary amenorrhoea. She had lived in Beirut between the ages of 7 and 18, and investigation there had shown her to be a chromosomal mosaic. She had been on cyclical premarin since 1965.

Clinical examination showed a pleasant and intelligent girl: she was very slim, with thin long limbs and fingers, 160 cm in height and 170 cm in span. Her voice was feminine. The breasts were very small with no nipple development. There was moderate *pectus excavatum.* There was no axillary hair and pubic hair was scanty, though of female distribution: it had been absent before treatment with premarin. The vulva was normal, with no clitoric enlargement: the hymen was intact and vaginal examination difficult owing to vaginismus.

Investigations. The buccal smear was chromatin negative. The chromosomes of cells from a short term peripheral blood culture and from a fibroblast culture (set up from a skin biopsy) were examined and confirmed that the patient was a mosaic. The complement in 90 dividing cells was 2 with 44, 41 with 45, and 47 with 46 chromosomes. Twenty mitoses with 45 chromosomes were examined in detail and showed 15 chromosomes in group C (6-X-12, Denver system) instead of the normal female 16, corresponding to the 45XO karyotype typically found in Turner's syndrome. Twenty-eight mitoses with 46 chromosomes so examined showed the same karyotype plus a small acrocentric chromosome which was larger than the other group G chromosomes (nos. 21—22). In some cells its morphology was typical of a Y chromosome, in that the long arms were poorly stained and were more parallel than those of nos. 21 and 22. This cell line therefore had a male karyotype of 46XY, and the patient was consequently a 45XO/46XY mosaic. Gynecography showed an apparently normal sized uterus: the ovaries were not clearly visualised. A gonadotrophin stimulation test was negative, showing that there was no functioning ovarian tissue.

Laparotomy on 5. 3. 68. showed a normal-sized uterus. The ovaries were represented by thin white fibrous cords. Bilateral salpingo-oophorectomy was performed, removing as much of the broad ligament as possible. Convalescence was uneventful and the patient was discharged on the 11th post-operative day. She was later seen twice as an outpatient and found to be well, with a well-healed scar. She was advised to continue cyclical premarin therapy.

Pathology. The excised objects consisted of 2 small tubes and flattened wormlike ovaries (L. $1.5 \times 0.4 \times 0.2$ cm; R. $3.0 \times 0.5 \times 0.2$ cm) with no gross evidence of tumour. The left was made into 3 blocks and the right into 4. The routine sections showed no tumour, but extra ones cut revealed a seedling gonadoblastoma at the medial pole of the right ovary. The remaining material on both sides was then reduced to serial sections.

Microscopically, the serially cut part of the tumour (probably over three quarters) measured $3.5 \times 3.5 \times 1.5$mm: it was spheroidal and occupied most of the ovarian cross-section (Fig. 3). Proximally it reached the mesovarium and medially the beginning of the ovarian ligament: distally it was enclosed by somewhat compressed ovarian stroma. It was uniform in structure throughout and composed of separate tumour nodules (save for a single pair connected by a narrow bridge), all either spheroidal or accommodating a concave contour to a spheroidal neighbour. Each was occupied to a variable degree by rounded concretions and consisted otherwise of 2 cell types, not always clearly distinguishable. Typically these were (a) large pale glycogen-rich cells (interpreted as germinal) with rounded nuclei of varied size and staining depth, showing occasional mitoses, and (b) small dark cells with scanty cytoplasm (for convenience to be called "granulosal") of varied form — ovoid, rodlike, arcuate and triangular. The 2 types were combined in various ways. A common one had the form of narrow branching granulosal cords with included germ cells (both single and clustered), ringed round to suggest primordial follicles (Fig. 4). These continued into broader trabeculae — some mainly germinal, with a narrow granulosal hem (Fig. 5, lower), whilst others were darker, with a higher content of granulosal and indeterminate cells and a Pagetoid sprinkling of germ cells (Fig. 5, upper).

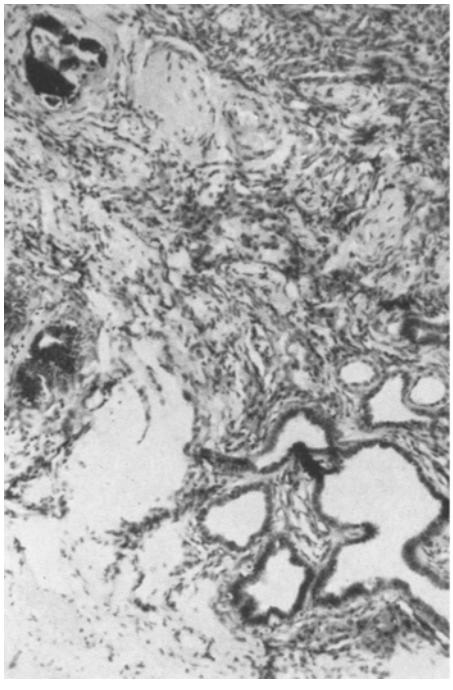


Fig. 1

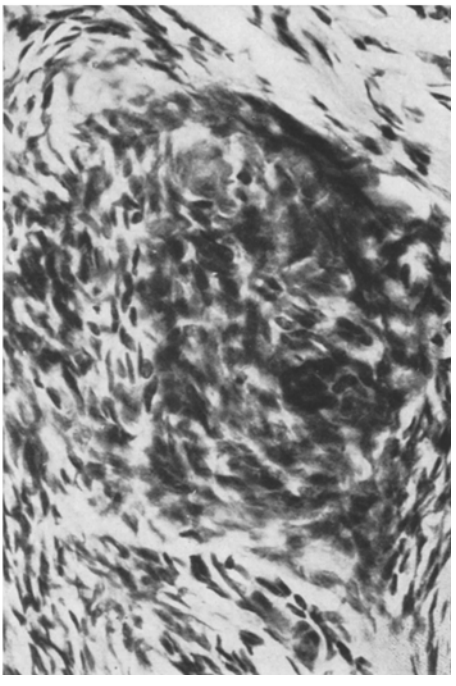


Fig. 2

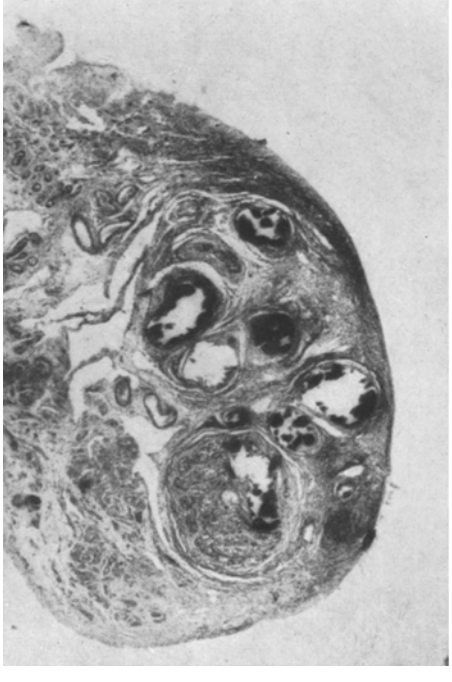


Fig. 3

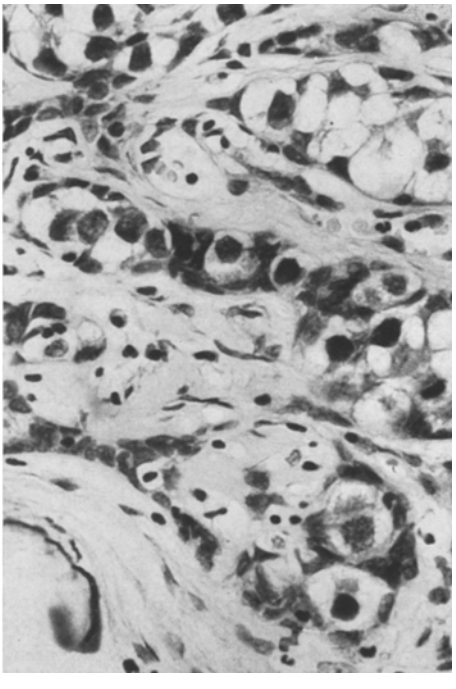


Fig. 4

The margins of these masses were often sharply defined, both externally to the adjacent connective tissue and internally to numerous hyaline eosinophil inclusions which were surrounded in microfolliculoid fashion. These inclusions were strongly PAS-positive and mostly rounded, but some were elongated, branching or flask-shaped: they were easily seen to be hyaline expansions of entering fibrous septa (Fig. 5, left) and to be largest near the sites of such entry, where the entering reticulum faded out into a diffuse and weakly argyrophil ground substance. Within and between the nodules clusters of interstitial lutein cells were present. The stroma was mostly poorly cellular but contained a few cellular patches continuous with the surrounding ovarian cortex. At no point did the actual tumour elements show continuity with any other structure. The larger concretions were bordered by fibrous connective tissue: the smaller lay sometimes free in the hyalinising stroma and sometimes were bordered by granulosal cells, their antecedents being indiscernible. They stained for calcium but not for iron: their ground substance stained with Alcian Blue.

The left ovary and the rest of the right showed a few surface inclusions, a narrow tunica and cortex (up to 0.8 mm thick) and a variably developed medulla (up to 1.5 mm thick) of interleaved stroma and vessels. Little whorled stromal condensations were common (Fig. 2) as were various hyaline knots (Fig. 1) and granulosa-like cords blending with the stroma; but there was nothing certainly of follicular origin nor any testicular tissue. Concretions were present scantily on the left, commonly on the right, being large and numerous near the tumour. Some were in groups and others quite isolated (as in Fig. 1): the smallest lay bordered by stroma in the condensations noted and might show a central darker rounded area suggesting nuclear remains (Fig. 2, upper). At the hilar border were many irregular medullary canals (Fig. 1): between or near them were many clusters of small lutein cells (Fig. 1, centre). Large clusters of hilus cells were present in the mesovarium: rete and epoophoron were well-developed and the tubes without particularity.

Case 2. Miss B. K., aged 16, had had menorrhagia since the menarche at 13 with periods of bleeding of 10 up to 90 days. She had no hirsutism. She was curetted and a large right ovarian tumour was removed. Five months later there was massive and inoperable peritoneal recurrence. The left ovary and tube were removed and the uterus left in-situ.

Pathology. A dome-shaped segment of the tumour ($30 \times 14 \times 14$ cm) was available for study. Its convex outer surface was smooth and slaty-white with a few low knobs. Its cut surface was whitish, solid and rather fibrous, apart from some softer marginal areas and a few small cysts up to 3 cm in diameter. Twenty blocks were made from all parts and multiple sections cut. In addition a few sections were available of the uterine curettings and of the left ovary.

Microscopically the tumour showed 5 main patterns, falling roughly under the heads of dysgerminoma, fibroma, gonadoblastoma, granulosal cell tumour and "embryonal carcinoma". There were transitional forms between the first 4 and the present account is largely concerned with these.

Classical dysgerminoma was present at parts of the tumour margin. It had the usual appearance of spawnlike islands and cords (Fig. 6, upper left) with poorly cellular septa which were often infiltrated with lymphocytes and an occasional Langhans giant cell. Similar areas were also found more deeply, but here the islands were often separated by a vigorous

Fig. 1. Case 1. Hilar region of right ovary showing edge of mesovarium at bottom left, medullary canals, cords of small lutein cells, hyaline knots, concretions and ovarian stroma. $\times$ 85. H & E

Fig. 2. Case 1. Whorled stromal condensation, from peripheral bottom right in Fig. 3 at higher power, showing tiny early concretion at upper pole with possible central nuclear remeins. $\times$300. H & E

Fig. 3. Case 1. Medial pole of right ovary at low power showing small gonadoblastoma, with 9 concretions visible and rims of tumour tissue to 3 of them, mesovarium to left and narrow capsule of ovarian stroma to right, compressed above. $\times$ 17. H & E

Fig. 4. Case 1. Part of large lower nodule in Fig. 3 at higher power, showing narrow cords of granulosal or Sertoli cells enclosing large pale germ cells, singly or in groups, with 2 structures like ill-formed primordial follicles and part of concretion below. $\times$300. H & E

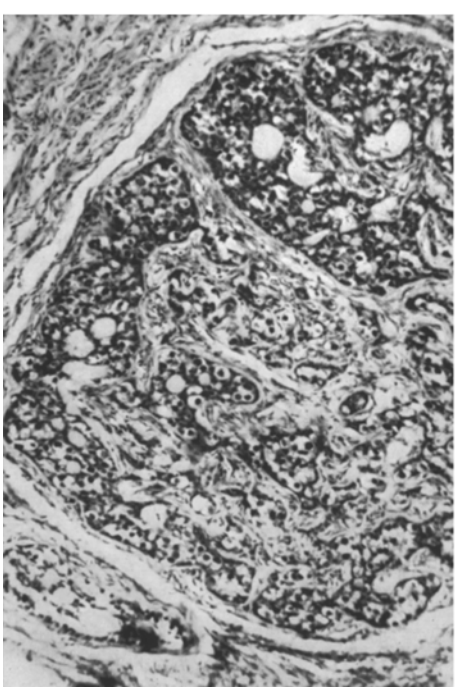


Fig. 5

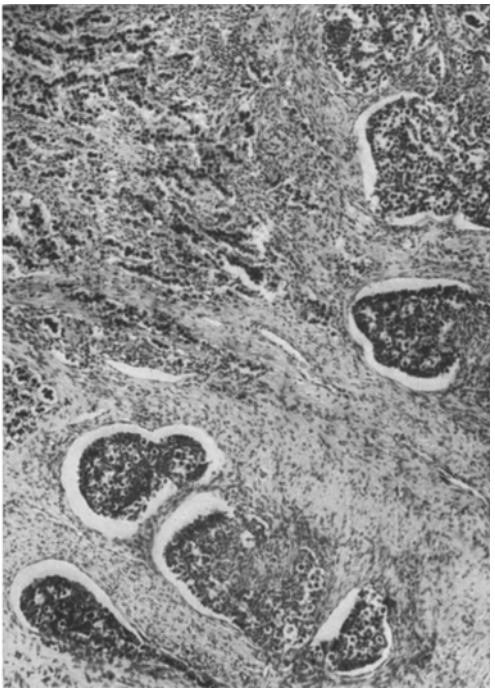


Fig. 6

Fig. 5. Case 1. More luxuriant part of the tumour showing sharply hemmed granulosal masses with multiple pale included germ cells and microfolliculoid formations with hyaline centres continuing into adjacent tumour stroma in places, especially on left. × 85. H & E

Fig. 6. Case 2. Peripheral region of tumour showing dysgerminoma cords with scattered lymphocytes at top left, and adjacent fibrous connective tissue containing 6 glomeruloid nodules of gonadoblastoma speckled with included germ cells, shrinkage spaces and cellular stroma entering basally in 2. × 35. H &E

Fig. 7. Case 2. Somewhat deeper part showing nests of germ cells separated by proliferating stroma below and by a network of granulosal cells above: these surround the germ cells and in places blend with the stroma. ×90

Fig. 8. Case 2. Details of a nodule like those of Fig. 6 showing stroma entering below and relating tangentially and circumferentially to the germ cells to give structures like primordial follicles with more epithelioid continuation above enclosing and limiting nests of germ cells. ×300. H & E

Fig. 9. Case 2. An area (upper left) in which granulosal cells predominate and pale germ cells are few, showing the stylised microfolliculoid pattern of a mature granulosal cell tumour, continuing into another (lower right) where germ cells are more numerous and the stylisation is lost. ×85. H & E

Fig. 10. Case 2. A field of luxuriant gonadoblastoma in closely packed islands and cords with both cell types equally prominent, suggesting foetal testis and ovarian carcinoma with "ovum-like cells". ×90. H & E

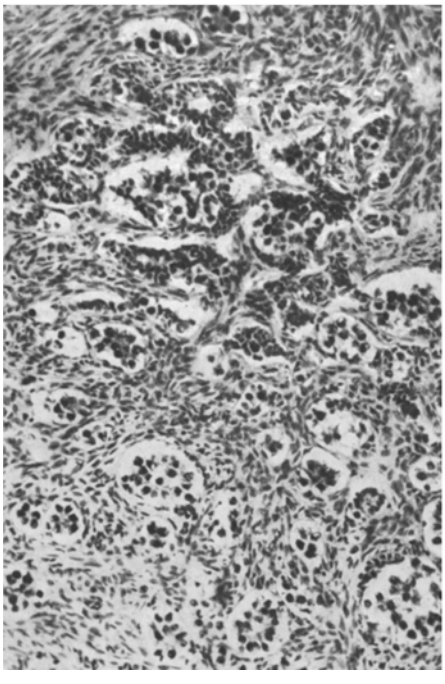


Fig. 7

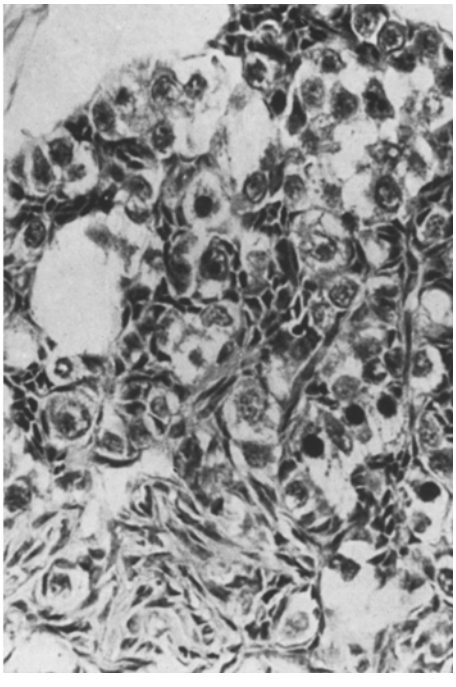


Fig. 8

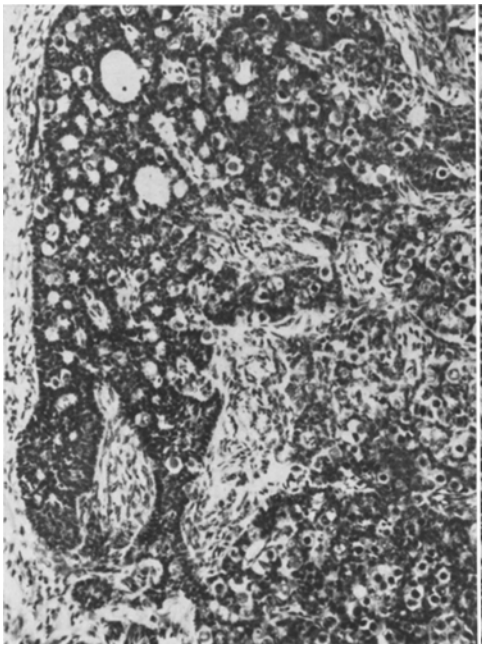


Fig. 9

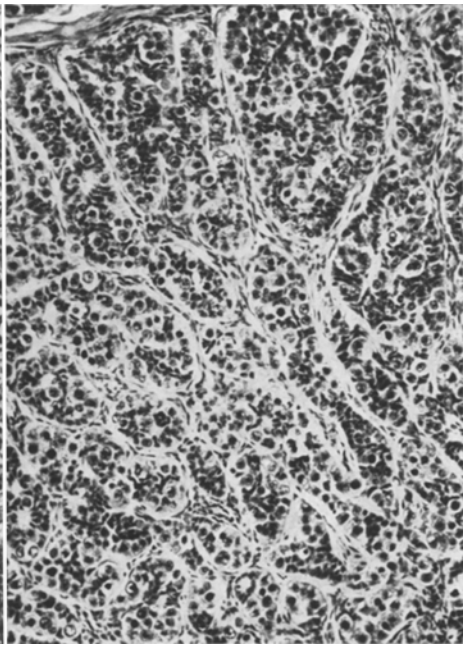


Fig. 10

stromal proliferation (Fig. 7, lower) and some had a slightly rosette-like form. Much of the tumour resembled pure fibroma, ranging from highly cellular to almost acellular, with irregular calcific foci.

Gonadoblastoma patterns showed their most rudimentary (and presumably earliest) form in the areas noted where germ cell clusters were separated by stromal proliferation. In some places small dark granulosal trains surrounded the clusters like a hem, or were more extensive and replaced the stromal bands between them (Fig. 7, upper), penetrating and dividing up the clusters. These granulosal attendants blended with the adjacent stroma at many points and appeared to derive from it. In other places the granulosal reaction was more vigorous forming multiple rounded and discrete islands: these often had a glomeruloid form, being tethered at one side by entering stroma and showing an artificial cleavage space opposite (Fig. 6, lower). Part of a small island of this type is shown in detail in Fig. 8. Many large pale germ cells are seen: they have fluffy amphophilic cytoplasm and rounded prominent nuclei — some being large and stippled and others smaller and dark. The stroma entering from below rings round several individual germ cells to form structures resembling primordial follicles: its continuation above is more epithelioid and forms small stellate granulosal clusters with interconnections, which surround groups of germ cells and form an incomplete limiting layer interrupted by them. In this and similar nodules reticulum fibrils ceased abruptly at the point where the cell form seemed to change from stromal to granulosal.

More developed fields of gonadoblastoma might cover an area several centimetres across. Some were in the form of large, sharp-bordered and close-lying islands suggestion an untidy microfolliculoid granulosal cell tumour (like Fig. 5) stippled with included germ cells. Others took the form of meandrine or undulant cords suggesting foetal testis or a poorly differentiated carcinoma with "ovum-like cells" (Fig. 10). In a few areas granulosal cells greatly predominated and included germ cells were reduced to occasional: these developed the stylisation of pattern commonly found in mature granulosal cell tumours (Fig. 9, upper left) — and lost it in contiguous fields where germ cells were more numerous (Fig. 9, lower right). A few such areas showed macrofolliculoid spaces (often containing effused blood), both within the massive zones and at their margin (Fig. 11). The last often developed a distinct lining of cubical epithelium with ground-glass eosinophil cytoplasm and budded into the adjacent fibrous tissue to produce a small adenofibroma: this is beginning at the right hand edge of Fig. 11.

The pattern designated "embryonal carcinoma" formed about $^2/_5$ of the whole and showed patterns too numerous to illustrate properly: Figs. 12 and 13 show two of them. They included leashes of bubble-like spaces and various adenoid, adenopapillary, cribriform and solid epithelial structures, ranging from wild and amorphous to sharply defined and quiescent. Cytoplasmic staining varied from dark to pale and hypernephroid, ground-glass or granular eosinophil protoplasm being common (Fig. 12). Lining epithelium varied from endothelioid through hobnail and cubical to conspicuously tall and columnar, with disparate types sometimes side by side. There were some syncytial areas containing bubbles, suggesting trophoblast. The more exuberant adenopapillary areas (as in Fig. 13) showed many diastase-fast PAS-positive globules, large and small, both within and beside the epithelium. Stroma varied in quantity from scanty to predominant: in the latter areas it was often slightly regimented (Fig. 12). There were many areas of haemorrhage and necrosis.

No clear inference-loaded relation of the last set of patterns to the rest could be seen, though there were three inconclusive ones. (1) Some of the more quiescent gland spaces (as Fig. 12, upper left) were similar to those of Fig. 11 (right) without definite continuity. (2) There were a few areas of intermingling, with gonadoblastoma islands spilling their clear cells into surrounding carcinoma, but the appearance was wild and suggested collision with secondary fusion. (3) In one area dysgerminoma islands mingled with fibrous tissue, went beyond the rosette-like form of Fig. 7 and produced a definite lumen. There were three of these gland-like spaces, not further developed or continuous with any other structure.

Glycogen was present in the germ cells and in the carcinoma cells. Sudanophil and doubly refractile lipoid were found in the stromal septa of the gonadoblastoma areas, where there were plump fibroblastic cells but no actual luteinisation, and there was sudanophil lipoid in the carcinoma cells. Diastase-fast PAS-positive material was present in the microfolliculoid spaces, in the macrofolliculoid spaces of Fig. 11, in their lining cells and in the

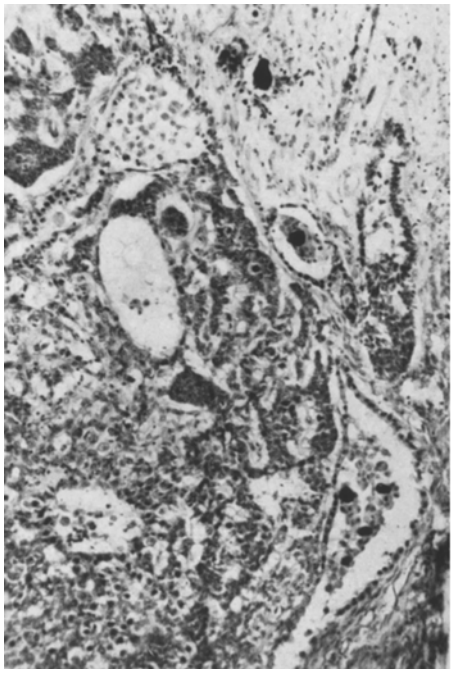


Fig. 11

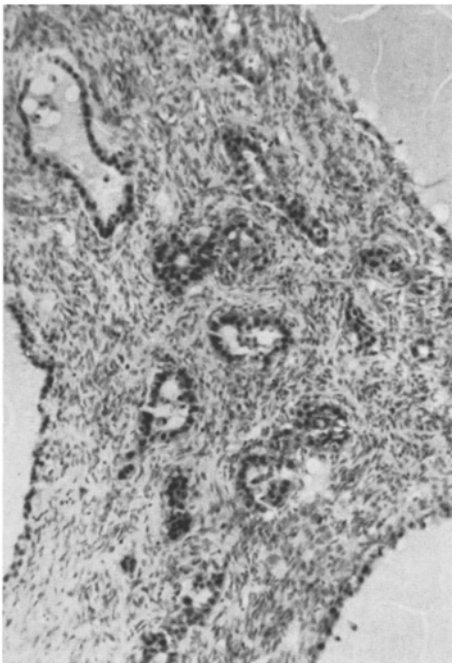


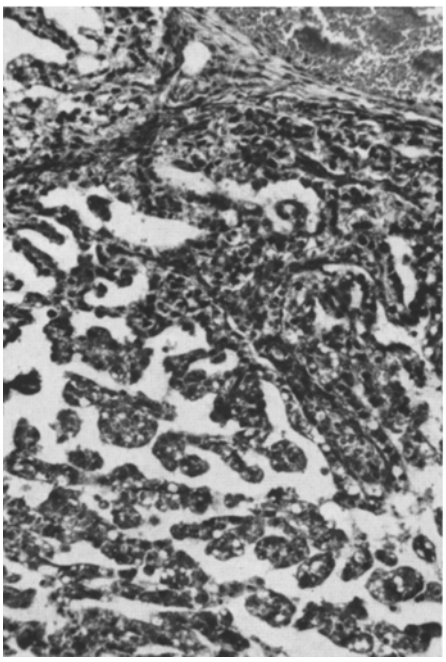
Fig. 12

Fig. 11. Case 2. Edge of large gonadoblastoma mass of woven granulosal cords speckled with germ cells, with 2 included macrofolliculoid spaces and 2 at the margin containing concretions, developing a cubical epithelial lining and extending into the surrounding fibrous connective tissue. ×75. H & E

Fig. 12. Case 2. An area of relatively inactive embryonal carcinoma, showing nests, cords, acini and cysts with granular eosinophil epithelium and plentiful cellular fibrous stroma with slight nuclear regimentation. ×85. H & E

carcinoma. A few small concretions were present in the gonadoblastoma areas, most frequently in the budding marginal spaces (Fig. 11), and in some similar unrelated gland spaces of uncertain affinity: their staining reactions were similar to those of case 1, but they had nothing like their size and frequency. Mitoses were found in all the cell types of the tumour but were most numerous in the germ cells.

The fragment of left ovary showed normal cortical stroma, a few primordial follicles with degenerate oocytes and a single atretic follicle 3 mm in diameter. The deeper cortical stroma showed clumps of germinal cells like those of the main tumour and was developing an early granulosal envelope to some of them (much as in Fig. 4): whether these clumps were metastatic or an early secondprimary could not be judged. There was also a large deposit of embryonal carcinoma of adenopapillary pattern (Fig. 13). The curettings from the first operation were scanty and showed a proliferative phase endometrium with a few mitoses. Sex chromatin counts were made on these and on tumour material in Feulgen and buffered thionin preparations with the following results: granulosal cells 54/100 and 71/100; epithelium of the type of Fig. 12, 29/100 and 36/100; stroma in such areas 55/100, 55/100 and 63/100; stromal cells in dysgerminoma septa 54/100 and 52/100; endometrial epithelium 61/100, endometrial stroma 65/100, both indifferently 64/100; endocervical stroma present in curettings 65/100. Slightly higher counts were found in thionin than in Feulgen preparations. No sex chromatin could be detected in the germ cells in either dysgerminoma or gonadoblastoma areas.



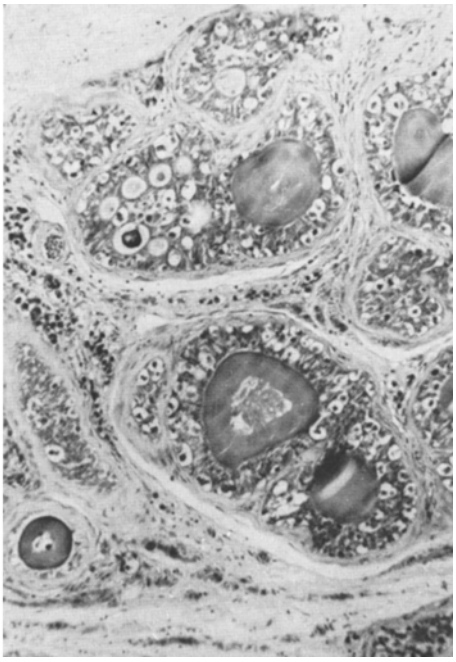


Fig. 13 Fig. 14

Fig. 13. Case 2. L. ovary showing metastatic nodule of more active embryonal carcinoma with scanty stroma, adenopapillary pattern, and rather pale epithelium containing dark globules of PAS-positive material. ×100. H & E

Fig. 14. Case 3. R. testis, showing cluster of seminiferous tubules containing proliferating Sertoli and germ cells, many expanded, and containing microfolliculoid spaces and concretions, with some narrow cords of seminoma cells infiltrating between them. ×85. H & E

Case 3. An anatomically normal man of 23 had a swelling of the right testis: this was removed, together with 7 cm of cord. About $^3/_4$ of the testis was occupied by a typical seminoma 4 cm in diameter. Eleven blocks were made, comprising most of the tumour. The residual testicular tissue showed normal spermatogenesis in many tubules and unusually frequent Leydig cell clusters: the nuclei in the latter showed no sex chromatin. Near the tumour many tubules showed germinal arrest with proliferation of stem cells of all degrees from nil up to intra-tubular seminoma. In some areas just outside the main tumour mass narrow cords of seminoma cells infiltrated between the tubules; and in these areas or just within the main mass were four foci of intra-tubular Sertoli cell proliferation with included germ cells, folliculoid spaces and concretions, each about 1 × 1 mm in cross-section. Fig. 14 shows the most compact of these: it resembles a typical gonadoblastoma, with slightly more cytoplasm than usual in the non-germinal elements. The concretions stained similarly to those in the first two cases. One of the foci showed a grossly swollen spermatogonium with laminated hyaline change and granular calcific foci: it recalled the early concretion of Fig. 2. Five years later the patient was well, free from recurrence and had become the father of two children.

Discussion

This falls under three heads: comments on the case reports individually, the concept and classification of gonadoblastoma, and its origin.

Comments on Case Reports

Case 1. The essential item (Fig. 3) was probably a small tumour rather than a malformation as its mitotic activity, rounded form and surrounding compression suggest incoordinate growth. It was grossly unsuspected and sharply localised. We have found a similar localisation with other aberrant structures and with scanty follicles in these ovaries: they are not homogeneous and should for preference be multiply and totally blocked.

An earlier article (Hughesdon, 1970) discussed the morphogenesis of the dysgenetic ovary and cited 7 cases where concretions have been reported in the absence of tumour or with tumour on the other side only. Hence the presence of concretions (for example, in the septa of a dysgerminoma) is only suggestive, and does not warrant a firm inference that a gonadoblastoma was or is present somewhere. This point emerges from case 1 where there were many concretions outside the tumour. Some were grouped and may have been burn't out accessory tumour remains; but others were small and isolated (as in Fig. 1) and cannot have arisen so.

Their origin is obscure. In case 1 they were all rounded when small, suggesting that some rounded structure had calcified. The two obvious candidates are the germ cells and the centres of the microfolliculoid spaces (Fig. 5). The latter we discount, as these centres were actually hyaline collagenous stems cut across and often had other shapes. This leaves the germ cell alternative for which there is other evidence. The small concretion of Fig. 2 has a centre suggesting nuclear remains, as did a similar one in case 3. Bieger *et al.* (1965) made the same observation on testicular concretions and ascribed them to degenerate spermatogonia. We have also seen hyaline basophilic spherules (not convincingly staining for calcium) surrounded by granulosa in neonatal ovaries, suggesting that small oocytes may undergo a comparable change.

Case 2. The lack of sex chromatin in the germ cells probably reflects the difficulty in heteropyknosis of the second X chromosome that large nuclei engender (Mittwoch, 1967). It is unlikely that this chromosome was absent, as all the other data indicate that the patient was a normal female. Amongst illustrated studies of the sex chromatin in dysgerminoma Hienz (1961) found Barr bodies in only 2 out of 10 cases, in proportions of 20 and 24%; whereas Talvalkar found them in 14 out of 16 cases, but the bodies figured seem rather faint. Analogous sex chromatin discrepancies between patient and tumour are noted by Hörmann *et al.* (1961).

The part designated "embryonal carcinoma" was (we think) a primitive ovular or teratoid tumour. Some of the untidier adenopapillary, cribriform and syncytial formations distinctly recalled embryonal carcinoma of the testis and the ovarian equivalent described by Abell *et al.* (1965). There was extreme variegation of pattern, differentiation and epithelial form, with contrasted types sometimes lying side by side; and there was a marked tendency to new gland formation by the dissociation of solid islands rather than budding of existing glands. The sex chromatin findings suggest a genetic difference from the rest of the tumour. We cannot classify the tumour with the variously named tumour of Teilum (1965), despite the presence of PAS-positive globules; for so-called

"endodermal sinus" formations were lacking and clustered labyrinthine spaces poorly developed and occasional only.

Case 3. This seems to be the first reported case in a scrotal testis (Scully, 1968). The only other case in a testis insufficiently abnormal in form or context to be described as "dysgenetic" is that of Collins and Schoenenberger (1962). They reported a seminoma 2.5 cm in diameter in a right inguinal testis of a chromatin negative boy of 9 with hypospadias. Parts of the tumour showed concurrent Sertoli cell proliferation, rosette formation and concretions: there were no hormonal effects.

The Concept and Classification of Gonadoblastoma

The original accounts (Scully, 1953; Morris and Scully, 1958) described 2 chromatin negative women with dysgerminoma, primary amenorrhoea and virilism. The last was ascribed to aberrant areas in the tumour composed of 2 cell types — namely, large pale cells — identified as germinal, and small dark cells — identified as granulosal or Sertoli cells.

The first identification turned mainly on the resemblance of the cells to those of the associated pure dysgerminoma and partly on their prominent rounded nuclei. The latter feature has usually been lacking in the many "ovular cells" described previously in ovarian tumours (as in the case of Aschner, 1922, who reviews the literature), but seems less reliable on its own. The second identification turned mainly on the pattern: the implied homologuy of granulosal and Sertoli cells with their interconvertibility in tumours will not be here discussed (see Neubacker and Breen, 1962). In Scully's 2 cases (described in detail) the granulosal cells were arranged in coronal fashion round the germ cells, in microfolliculoid fashion round small hyaline foci and in single file at the edge of the combined cell masses. In the 5 cases culled from the literature some of these details were lacking; but it is their presence — especially the multiple eyelike effect of the ringing-round of various elements — that has stamped the tumour with a readily recognisable character in most later descriptions. In addition the second case showed areas of interstitial luteinisation of Leydig cell type; but as the first showed only plump spindle cells the former feature cannot be taken as essential, as Teter (1960a) implies. Reviews have been given by Fine *et al.* (1962) and Scully (1968).

The term "gonadoblastoma" reflected the presence in the tumour of the main germinal and non-germinal elements of either gonad and its partial resemblance to foetal testis. The later terms "dysgenetic gonadoma" (Melicow and Uson, 1959) and "tumour of dysgenetic testis or ovary" (Collins and Symington, 1964) are non-specific and beg the question as to whether the tumour is confined to dysgenetic gonads; but Teter's (1960a, 1963) more elaborate regrouping as "gonocytomas I, II, III and IV" attempts to answer it and to define the relation, and so calls for detailed discussion.

Of these 4 categories the last (gonocytoma IV) is in effect a dysgerminoma with endocrine effects ascribed to the presence of lutein foci in its interstitial tissue, marginal gonad, hilus or opposite gonad. As such foci may occur with any ovarian tumour without entailing its reclassification the category seems dubious morphologically, though perhaps functionally convenient. Histologically verified cases include the tumours of Bergstrand (1934), case 5; Plate (1953), revalued by Fine *et al.* (1962); Usizima (1956); Teter and Tarlowski (1960), case 2; and Sohval (1964). Usizima's case contained some smaller cells uncertainly interpreted as either granulosal or shrunken germinal cells so that its classification is also

doubtful. The tumours of Bergstrand and of Sohval contained areas of presumptive embryonal carcinoma and that of Teter and Tarlowski trophoblastic elements, so that the production of luteinising hormone by the tumour might be the root of the matter.

With the first 3 categories the numerals correspond to the number of cell types involved in the tumour, so that gonocytoma I designates pure dysgerminoma, whilst in gonocytoma II there are areas of admixed granulosal cells and gonocytoma III contains foci of interstitial lutein or Leydig cells as well. This splits gonadoblastoma proper into the last 2, and Teter's main contention (justifying this separation on a seemingly small histological point) is that gonocytoma II occurs in normal gonads, lacks concretions and is mainly oestrogenic, whilst gonocytoma III occurs in dysgenetic gonads, shows concretions and is mainly androgenic. This is the central point for discussion and for ordering of the data, choosing for this the character of the gonad (dysgenetic versus normal or not demonstrably abnormal) as the key contrast.

On this basis gonocytoma III is a homogeneous group; but the literature is confused, partly by the inclusion of cases of gonocytomas I and IV owing to the presence of concretions (which we think unjustified for reasons given earlier) and partly by the multiple publication of several cases (with minor variations) and the revaluative comments of later writers with access to the sections. We think the correct list — in approximate order of publication and including some unremarked early cases — is thus:

Schapiro (1927); Reifferscheid (1935); Lindvall and Wahlgren (1940), case 3; Scully (1953), 2 cases; Bradbury and Bunge (1958); Melicow and Uson (1959) and Melicow (1966), 2 cases; Simm *et al.* (1959), Przybora (1960) and Baron *et al.* (1962); Teter (1960b) and Teter and Tarlowski (1960), case 3; Philipp and Stange (1960) and Hörmann *et al.* (1961), 2 cases; Siebenmann (1961); Borghi *et al.* (1962), Giusti *et al.* (1962) and Borghi *et al.* (1965); Teter *et al.* (1962) and Teter (1963), case 3; Fine *et al.* (1962); Flor *et al.* (1962); Teter *et al.* (1964a); Teter *et al.* (1964b); Robinson *et al.* (1964); Frasier *et al.* (1964), 2 cases; Overzier (1964); Cohen and Shaw (1965), 2 cases; Strumpf (1965); Naidu *et al.* (1965); Sirsat *et al.* (1965); Griffiths *et al.* (1966); Caffrey and Casey (1967); McDonough *et al.* (1967); Netter *et al.* (1967); Hervé *et al.* (1967); Cooperman *et al.* (1968); and the present case 1. This list (with 1 case between each semi-colon except as otherwise stated) contains 35 cases with sufficient detail to summarise. We have included the case of Bradbury and Bunge as they describe it as "gonadoblastoma" in their discussion. We omit (owing to paucity of detail) 15 further cases, namely: Santesson and Marrubini (1957); Perrin and Landing (1961); Miller (1964), p. 1120; Collins and Symington (1964), 3 cases; Bieger *et al.* (1965); Melicow (1966), case 3; Jirasék (1967); Guinet *et al.* (1967); Ber (1948), as revalued by Teter (1963); Gough (1938), Potter (1948) and Usizima (1956), as revalued by Fine *et al.* (1962); and an early obscure case of Brauer (1933), making a possible grand total of 50 cases.

Of the 35 cases with adequate detail 3 were of male social sex (Bradbury and Bunge, 1958; Melicow and Uson, 1959), 30 were female, and 2 changed from female to male at puberty (Schapiro, 1927; Overzier, 1964). Ages at operation ranged from 2 to 27 years, 22 lying between 16 and 22 inclusive. The main presenting complaints were primary amenorrhoea — due to the dysgenetic background — and uncertainty as to sex, which is partly due to the tumour: its functional effects however blend with those of an isosexual and/or heterosexual puberty and suggest a like dependence on gonadotrophin. Of the 30 social females 18 were in some degree virilised, and this occurred between 10 and 16 years of

age in 12 and was undated (consisting of clitoric enlargement only) in 6. Nine of the 18 virilised cases had testicular tissue present also and 16 of them showed interstitial lutein cells either in the tumour or the associated gonad: 5 other cases showed such cells unassociated with virilism or any special endocrine effect. Slight breast development had occurred in 12 cases and more marked oestrogenic effects in 7 more, in the form of well-marked breast development (Teter *et al.*, 1962; Teter *et al.*, 1964a; Caffrey and Casey, 1967), occasional menstrual periods (Teter *et al.*, 1962; Borghi *et al.*, 1962), post-operative withdrawal vaginal bleeding (Teter, 1960b), a normal urinary assay (Teter *et al.*, 1964b), or a mature vaginal smear (Strumpf, 1965). Three of these 7 cases had testicular tissue present and 6 of them had interstitial lutein cells.

The tumours themselves ranged from 0.35 to 17 cm in maximum diameter in the 30 cases where this is recorded; but most were of modest size, 20 lying between 2 and 6 cm. Areas of pure dysgerminoma were present in 18, being more frequent in the larger tumours where it was often the main component and is the presumed danger. Such areas were present in 9/13 cases of 5 cm in maximum diameter and over and in only 6/17 tumours smaller than this. No case metastasised, but of the 2 largest that of Sirsat *et al.* ($17 \times 11 \times 10$ cm) was described as infiltrating the left side of the uterus and that of Strumpf ($15 \times 10 \times 10$ cm) was fixed in the pelvis. Pre-operative detection of the tumour by its gross radio-opaque calcification was accomplished in 6 cases: all but 1 tumour (that of Bradbury and Bunge, aged 6) were noted as showing concretions microscopically. The sex chromatin of the patient was negative in the 30 of the 31 cases so investigated and showed a low count in the remaining one (Hörmann *et al.*, 1961). Sex chromosomes were cultured in 18 cases, yielding 13 XY, 3 XO/XY, 1 XX/XY, and 1 XO/X + fragment "which could represent a fragment of Y" (McDonough *et al.*, 1967). In sum, all or nearly all had a Y chromosome, two thirds were either virilised females or social males, just over a half showed some oestrogenic effects (usually minor) and the tumour commonly behaved like a maturing gonad of ambiguous endocrine potential. Parenthetically, whilst virilization by other ovarian tumours has no preferential post-pubertal age incidence, it is rare before puberty (Mathet, 1954), suggesting here also a partial dependence on adequate gonadotrophin.

With gonocytoma II (Teter, 1960a, 1962, 1963) the main difficulty is that the tumours are few in number, variable in form and often briefly described. They were said at first to occur in women of normal sexual maturity or (if young) with premature puberty.

Teter's (1962) formal account is based on 6 cases published more fuly elsewhere and cites 4 further possible cases. To these may be added the 3 early unremarked cases of Peyron (1922); Neumann (1925), case 4; and Kazancigil *et al.* (1940), case 1; as well as the 2 testicular cases noted in the comments on case 3, since Collins and Schoenenberger (1962) cite Teter as allotting their tumour to this group. They will be considered *seriatim*.

The first 3 cases (respectively Kowalczykowa *et al.*, 1962; Zelikson, 1939, figured by Teter, 1960a; and Hughesdon, 1961, which is also the present case 2) all showed mixed granulosal and germ cell islands of form similar to Scully's original cases. The first (aged 12 at operation) was associated with premature puberty, the third (aged 16) with puberty menorrhagia, and the second (aged 15) was functionless. There follows Tietze's (1931) case, aged 10 with

premature puberty, unfigured and described as a dysgerminoma in which some of the cells were small and dark — tenuous grounds for inferring that they were granulosal. Föderl's (1938) case, aged 51 with cystic endometrial hyperplasia, was poorly figured and reputedly showed dysgerminoma with separate folliculoid granulosal area. Babes's (1929) case, aged 13 and prepubertal, was described as a dysgerminoma with included primordial follicles and a metastatic deposit in the opposite ovary invading a ripening follicle: the author's account offers no real grounds for setting aside this interpretation in favour of a mixed germ cell tumour. Much the same applies to the tumours of Sailer (1940) — as described, a dysgerminoma with an included ripening follicle together with some nebulous and possibly lymphoid septal dark cells — and of Forster (1953), instanced elsewhere (Morris and Scully, 1958). Fauvet (1935) described no granulosal areas but referred to them in previous accounts. Reifferscheid's (1935) case, aged 21, was associated with primary amenorrhoea and the tumour showed concretions: it plainly belongs to gonocytoma III. Schiller's (1934) case, aged 14, had a dysgerminoma with an included microfolliculoid granulosal nodule: this could well have been a ripening follicle cut eccentrically, as Föderl (1938) remarked. Schiller's second case (mentioned *en passant*) was probably the same as Föderl's, as Fine *et al.* (1962) note. Of the added cases, that of Peyron (1922) was a dysgerminoma in a woman of 30 (with no further details): in one area the germ cells were enclosed in a nodule of stromal and granulosal elements as in our Fig. 8. Neumann (1925, case 4) described a woman of 35 with alternating amenorrhoea and metrorrhagia: her tumour contained extensive dysgerminomatous, atypical granulosal and sarcoma-like areas, their interrelations being unclear. Kazancigil *et al.* (1940, case 1) described a girl of 17 (with no further details) with a tumour of part dysgerminomatous and part papillary form: in the former zone were many glomeruloid granulosal nodules recalling our Fig. 6. The 2 testicular cases have been described earlier.

To summarise, there are 10 provisionally acceptable cases — 8 ovarian and 2 testicular. Six of them — the 2 testicular cases and the 4 ovarian cases of Peyron and Teter's first 3 — showed the typical islands of mixed germinal and granulosal and Sertoli cells, and all but Teter's first case showed also areas of pure dysgerminoma or seminoma. Of the other 4, 2 cases (Tietze, Kazancigil *et al.*) were mainly dysgerminomas with small granulosal areas and 2 (Neumann; Föderl) showed substantial granulosal and dysgerminomatous areas side by side. The ages at operation were 9 and 23 in the testicular cases and 10, 12, 15, 16, 17, 30, 35 and 51 in the ovarian. Both testicular cases and 1 ovarian one showed concretions. Maximum diameters of the testis tumours were 2.5 and 4 cm and of the ovarian ones 8, 16, 17 and 30 cm: 3 of the 4 remainder were described as "twice man's fist sized" and as weighing 2 and 3 kgm. One ovarian case metastasised, but the only unequivocal metastasis was "embryonal carcinoma". Five cases were probably oestrogenic and none was androgenic: none showed lutein foci but 3 showed a slight thecal reaction in the stroma.

The last correlation accords with Teter's account — perhaps also with the general relation in ovarian tumours between degree of luteinisation and likelihood of androgenicity (Hughesdon, 1966) — as does the relative lack of concretions; but the case reports are too few and uneven for more than tentative impressions. We here give 4 of our own — namely, that (1) the testis cases (with their small size and prominent concretions) have more affinity with the gonocytoma III group than the present one; (2) the striking features of the 8 ovarian cases are their relatively large size and their variability of form — in contrast to the mutual family resemblance of gonocytoma III cases — thus echoing the variability of many ovarian tumours, including granulosal cell tumours; (3) the stromal and granulosal elements are here potentially neoplastic independently of the

primary germ cell neoplasia, judging by their luxuriance in our case 2 and in Teter's case I and their tendency to outpace the other elements shown in out Fig. 10 — probably fulfilled in Neumann's case as areas of pure granulosal cell tumour; (4) such cases may therefore get diagnosed as granulosal cell tumours, reports of which in early age groups often describe atypical large cells (cf. Zemke and Herrell, 1941), though we can re-classify none with confidence on the illustrations.

As to nomenclature, we suggest that (1) the term "gonadoblastoma" properly applies to the particular patterns of associated granulosal and germ cells, with or without interstitial lutein cells, originally described by Scully and present in all the gonocytoma III and half the gonocytoma II cases reviewed; (2) the terms "gonocytoma II" and "gonocytoma III" (if retained) preferably apply to mixed germ cell tumours arising in normal and dysgenetic gonads respectively, leaving unsettled the number of cell types, the problem yet presented by the small variable "gonocytoma II" group and the possibility that normal ovarian cases alone are distinct enough to warrant a separate category; (3) the term "mixed germ cell tumour" (used by Teter, 1963) is a convenient non-committal one for any tumour in which germ cells are combined with other types, regardless of the details, leaving open the possibility that there are further categories not certainly related to the foregoing, as reported by Masson (1922), Ziegler (1945) and Mostofi *et al.* (1959).

Origin of the Tumour

That the gonadoblastoma pattern can arise from testicular tissue is clear from our case 3, where the intra-tubular location and nearby presence of seminoma *in situ* suggest that intra-tubular germ cell neoplasia is the prime mover, to which an enveloping Sertoli cell response occasionally follows, resulting in the pattern.

Amongst the rest, testicular tissue was noted as present in 15 of the 33 gonocytoma III cases — in 13 on the same side as the tumour, in 2 on the opposite side and in 7 on both sides. In 5 cases it was the only gonadal tissue reported (Lindvall and Wahlgren, 1940; Melicow and Uson, 1959; Robinson, 1964; Overzier, 1964), and in 4 cases tumour tissue was continuous with proliferating germinal and Sertoli cells of the associated testis tubules (Siebenmann, 1961; Overzier, 1964; Teter *et al.*, 1964a, b). This could mean either an origin directly in such tubules (as in our case 3) or an origin in dysgenetic "tubules" of already abnormal pattern which had retained continuity with less affected ones. We think both probably occur.

Such findings and the prevalence of a Y chromosome in these cases have usually suggested that the tumour always arises in pre-formed testicular tissue (Teter *et al.*, 1964a) — and the same view has been taken for dysgerminoma (Fathalla *et al.*, 1966). In 20 cases however no such tissue was described, and in 12 of these there was a quasi-ovarian connective tissue capsule, whilst Hervé *et al.* (1967) described a structure with an oocyte and zona pellucida in their tumour. That testicular tissue was nevertheless present, unobserved or elsewhere, is pure assumption: it is not supported by our case 1 where the tumour was small and most of the material cut serially without finding such tissue.

A variant of this view supposes the tumour to arise, not from pre-formed testicular tissue, but from testicular rudiments that have been blighted (i.e., feminised or oophorised) *in utero* (Philip and Teter, 1964). The post-natal mother tissue of the tumour would then be a small malformation of the same structure as gonadoblastoma. Such structures have been described in association with the tumour (Teter and Boczkowski, 1967), both in the capsule and the opposite gonad; but it is difficult to distinguish malformations from additional small tumours in this context. It would be difficult also to establish such an origin directly, by histological investigation of an established tumour; for the latter could *ex hypothesi* show no transition to any putative antecedent tissue recognisable as distinct from it.

Indirect evidence for this view is however furnished by the location of the smaller tumours. Five small tumours in testicular tissue have lain in a subcapsular situation (Schapiro, 1927, R gonad; Bradbury and Bunge, 1958, R gonad; Lindvall and Wahlgren, 1940; Siebenmann, 1961, R gonad; Overzier, 1964): in a sixth case however (Melicow and Uson, 1959, case 5) distribution was multiple, but this was only a small biopsy. On the other hand, in 5 small ovarian cases the tumour lay mainly centrally in a gonad of normal form or only slightly enlarged (Schapiro, 1927, L gonad; Reifferscheid, 1935; Teter *et al.*, 1962; Siebenmann, 1961, L gonad; the present case 1), and in a sixth case (Bradbury and Bunge, 1958, L gonad) the tumour was best developed centrally but extended through to the surface. In 2 further cases (Teter, 1960b, L gonad; Teter *et al.*, 1964b, L gonad) similar tumours lay centrally in dysgenetic ovaries in association with testicular rudiments, whilst the somewhat larger (5 cm) tumour of Naidu *et al.* (1965) had developed peripherally to testicular tissue and had a capsule of spindly ovarian stroma. This pattern of contrasted locations (respectively peripheral and central) in testicular and ovarian tissue is rather striking when present on opposite sides in the same patient (Schapiro, 1927; Bradbury and Bunge, 1958; Siebenmann, 1961) — i.e. in cases of mixed dysgenesis with bilateral tumours. If the old model of the initially bisexual gonad with ovarian periphery and testicular centre (Kohn, 1921) has some application to dysgenetic gonads (though probably not to normal ones), it suggests that the tumour preferentially arises at the margin of the dominant gonadal tissue in that direction where heterosexual tissue would be most likely to appear. One might postulate here a zone of ambiguity prone to aberrant structures which could be seen equally as aberrant seminiferous tubules or aberrant follicles.

The last (in the alternative form of polyovular follicles) have also been suggested as mother tissue to the tumour by Teter (1960a). Such structures often contain immature germ cells smaller than oocytes and so resemble gonadoblastoma: these were called "egg-ball follicles" by Schottlaender (1905) who found them in infants up to 1 year post-partum. They are common in the late foetal and neonatal period in human ovaries (Bacsich, 1946) and in those of various small mammals (Collins and Kent, 1964) where they have been ascribed to the low oestrogen level, being partially corrigible by oestrogen injections (Kent, 1959). If this finding is transferable to human cases, then undue persistence in a dysgenetic ovary with poor oestrogen production seems possible. Comparable

(but more peripheral) structures are Pflüger's tubes (in the special sense of germ cell clusters in a granulosal envelope connected with the surface). These usually die out in the first month or two post-partum (Benthin, 1910) but occasionally persist up to 18 months (Schulin, 1881): aberrant forms are often prominent in neonatal dysgenetic ovaries (Hughesdon, 1970). Their potentiality for neoplasia is suggested by Ziegler's (1945) curious case of bilateral carcinoma of the ovary in a foetus of 30 weeks, which consisted of germinal and granulosal cells in clusters recalling these structures. There is however a large gap in the data needed to establish such progression.

Case 2 provides moreover good evidence that the gonadoblastoma pattern can arise from ordinary mature ovarian tissue. No ovarian remnant was found in the main tumour but the opposite ovary was essentially normal. The relations of stromal and granulosal cells in Figs. 6—8 recall those seen round primordial follicles and in granulosal cell tumours, suggesting a like interconvertibility. There is precedent for these findings: our Fig. 8 is like that of Peyron (1922) in showing apparent stromal to granulosal conversion round the germ cells, and our Fig. 6 recalls Figs. 2—5 of Kazancigil *et al.* (1940) whose multiple granulosal nodules "showed transitions to the adjacent stroma-like tissue". We infer that germ cell neoplasia is again the prime mover; that it may occasionally evoke a vigorous stromal proliferation; and that a granulosal change therein to envelop the germ cells may follow — as biologically appropriate — exactly as a thecal change may follow with other neoplastic epithelia. The earliest stage in the opposite ovary was only a short step from a polyovular primordial follicle. It also resembled the apparent earliest stage noted elsewhere in developing dysgerminoma (Hughesdon, 1959), thus supporting the notion that the ultimate problem (the origin of the neoplastic germ cell) is the same in the 2 tumours.

Given this start, continued germ cell proliferation is likely to evoke that of the enclosing granulosal cells — occasionally their neoplasia — to produce the patterns shown, but the situation is unstable. Neoplastic germ cells can multiply very rapidly: Jackson (1960) recorded a dysgerminoma that grew from virtually nothing to 19 cm in diameter in 3 months. At any stage therefore the germinal component may locally outpace the others, evoking only a leucocytic and granulomatous response and thereby producing areas of pure dysgerminoma. Further, whilst dysgerminoma resembles foetal ovary of about 100 mm in having immature germ cell clusters as structural unit and may evoke similar surface relations (Hughesdon, 1959), the pattern shown here in our Fig. 8 resembles a later stage (c. 150 mm) in having primordial follicles centrally and persistent "egg-balls" peripherally. The whole array of patterns could be seen as an attempt to "gonadize" (mostly "oophorize") neoplastic germ cell clusters, imparting organoid form and supporting the aptness of the term "gonadoblastoma". The further developments in Fig. 11 suggest a surrounding serosal space: they have no precedent in these or in granulosal cell tumours but occur in arrhenoblastoma, where also they may by associated with concretions (Hughesdon and Fraser, 1953).

Finally, Teter (1960a) has suggested that the high FSH output commonly found in gonadal dysgenesis promotes germ cell tumours, much as it promotes granulosal cell tumours in splenic ovarian transplants. He proposes a "dystrophic

background" responsive to this and containing "persistent germ cells (gonocytes) from the embryonic stage". This proviso is crucial, because in adults FSH stimulates granulosal proliferation in the female and germ cell proliferation only in the male. Embryonic reversion might however revise this, since gonadal development (occurring in a highly gonadotrophic environment and perhaps dependent on it) is dominated by germ cell proliferation in the ovary and by that of the other elements in the testis. The scanty collateral evidence however favours atest icular concept of the responding tissue.

Experimental zinc teratoma of the fowl testis depends on adequate FSH output for its production (Bagg, 1936), whilst Twombly *et al.* (1949) claim to have produced such tumours by splenic transplantation of testis. They further suggest that a high FSH output may also promote testicular seminoma where a high output unaffected by removal of the tumour is commonly found (Hamburger, 1958; Symington and Wallace, 1964). Unfortunately we know of no experimental production of pure germ cell tumours by relevant — or any — means and little of the FSH output in dysgerminoma of normal — as opposed to dysgenetic — ovaries. In Hain's (1949) case however a high gonadotrophin output persisted for 3 months after removal of the tumour. The situation is complicated by the positive pregnancy test found in some cases, abolished by removal of the tumour, and usually attributed to areas of trophoblastic differentiation (Burge, 1949; Thoeny *et al.*, 1961). The relevance of FSH might however be deduced from the age incidence. An earlier article (Hughesdon, 1959) deduced the oocytic origin of dysgerminoma of the normal ovary from its cortical architecture. In the light of this the proportionate age incidence might be expected to run parallel to the oocyte count at different ages. This it does from the age of about 18 onwards (compare the respective figures of Mueller *et al.*, 1950; Block, 1952), prior to which the 2 diverge markedly. This discrepancy could be ascribed to ovarian inactivity at the earlier ages, consequent on low FSH output, which seems to rise in sigmoid fashion to adult levels in girls between the ages of 10 and 13 (Johnsen, 1959). This however would imply that FSH exerts a promoting effect on dysgerminoma formation taking 5 years or more to operate; in which case a high secretion might well result in a high incidence whenever germ cells are present to respond.

Conclusion

Gonadoblastoma is a primary germ cell tumour which has evoked a Sertoli or granulosal cell response rather than a leucocytic one. This occurs rarely in normal testis (2 cases); somewhat less rarely in normal ovaries (8 cases) where it develops in an antecedent stromal action, varies in form and degree, may be oestrogenic and can become neoplastic; and most commonly and typically in dysgenetic gonads (50 cases) where it arises either from seminiferous tubules or from ambiguous germinal and granulosal clusters marginal to the dominant gonadal tissue (centrally in ovary, peripherally in testis). In this third form it commonly behaves like a sexually ambiguous maturing gonad (mainly male) showing functional effects at puberty which are probably dependent on pituitary gonadotrophin, as also may be its promotion as a neoplasm.

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