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ON THE LESS COMMON FORMS, GENESIS AND HORMONAL CORRELATIONS OF FEMINIZING OVARIAN TUMOURS

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In the past 30 years a number of reports have been published on the genesis, histomorphology, pathology, hormonal relations, therapy, relationship to uterine and breast cancer, etc. of the granulosa and theca-cell tumours of the ovary. In spite of the remarkable wealth of data, the problems involved have not been elucidated in full detail. Some statements have evoked fierce arguments, while others have proved to be unsubstantiated. In recent studies in animals, interes has been focussed upon the hormonal relations of these tumours, a problem still awaiting clinical elucidation. The few and rather conflicting evidence reported by BATIZFALVY and DUBRAUSZKY, SCHUSCHANNIA, HODGSON, KULLANDER, RUZICSKA, STERNBERG, KNIGHT, DEMPSEY—BASSET and others has failed to clarify the eventual hormon production (oestrogen, progesteron, etc.) of these tumours and their relationship to the anterior lobe of the pituitary although animal experiments have shown it is in these relations that the onkogenetical factor should be sought for. Along with RIISFELDT, SCHUBERT, we, too, have been unable to confirm the claim that hormonal changes in the endometrium such as glandular cystic hyperplasia as an indicator of oestrogen production, would be always associated with these tumours (see later) and the views on the histogenesis of these growths are also conflicting (R. MEYER, NOVÁK, KOVÁCS, ROBINSON, MCKAY, and others.).

Further studies both clinical and experimental, are required for a fuller elucidation of the problems involved. Valuable information may be derived from estimation of hormones in tumour tissue or in blood of human subjects. The lack of evidence in this field is due in part to the fact that the methods are too complicated and that histological data on the properties of tumours usually become available only after the lapse of some weeks after operation, at a time when hormonal relations may have completely changed. This is why recidiv feminizing tumours, and, in general, cases differing from the typical form appear to be particularly suitable for clinical studies.

A total of 23 feminizing tumours of the ovary detected in Szikszó and in Gyula during the past ten years were studied with regard to the above points of view. In each case, we made a histologic study of the tumour, of the

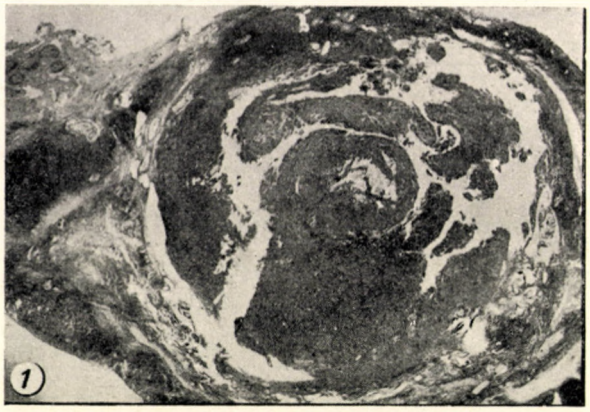
endometrium (and in some cases, also of the vaginal smear) to determine their structure and to demonstrate eventual interrelations. Morphological characteristics and hormonal correlations were sought for, the former being important with respect to histogenesis and the latter with respect to onkogenesis. Changes in hormonal relations were usually approached by means of examining the endometrium, the indicator of sexual hormonal effects but in the presence of a few recidiv granulosa cell tumour the blood and urine of patients were repeatedly examined for level of hormones (oestrogen and gonadotropic). The histological examinations and diagnoses were made by DR. V. HEIM and by DR. GY. HABÁN but synthesis and analysis of the entire material was our work, relying on histological evidence. The hormonal studies were carried out by DR. B. ZEMPLÉN, leader of the Biological Laboratory, Kőbányai Gyógyszerárugyár. Unfortunately technical difficulties prevented us from making hormonal studies of tumour tissue, although DEMPSEY—BASSET and KNIGHT emphasize that the production and storage of hormones in feminizing tumours is still an open question. When evaluating the results, all evidence derived from a total of 23 cases of feminizing ovarian tumours (19 granulosa and 4 theca cell tumours) were considered. In the present report, however, only such cases will be presented in which rarity, peculiar structure, hormonal correlations and effects, etc. have appeared to merit particular attention, or from which evidence contributing to our konwledge of the nature, histo- or oncogenesis of such tumours could be derived.

The cases showing these characteristics were the following :

1. Microgranulosa tumour. Malignant folliculoma

(Record No. 67—XII/952.) 58 years old multipara (7 births). Ab. ∅. After 10 year- of amenorrhoe uterine bleeding appeared. Abrasion was done and ample, marrow-like material was obtained. The uterus was found to be enlarged, Histology : Glandular cystic hyperplasia, with richly nucleated stroma.

Since bleeding recurred, laparatomy was done 6 weeks later. The goose-egg sized uterus and the apparently normal adnexa were removed. *Histology:* In the left ovary, a structure similar in appearance to a big follicle was found. Instead of follicular fluid luteinized epithelium was found too (Fig. 1, 2). Among and around this there were nests if small cells of thecal origin divided into a few lobes by scarce connective tissue. The tumour was almost microscopic in size and caused no enlargement of the ovary (Fig. 1). Since it did not invade normal ovarial tissues, it could be classified as a malignant folliculoma (KAHLDEN, ROBINSON). The ovary bearing the tumour contained no follicles. The stroma of the other ovary was more voluminous and contained a few primordial follicles. The endometrium was 10 to 15 mm. thick, hyperplastic with cystic glands and a richly nucleated hypertrophied stroma (Fig. 3). In some areas the arteriovenous sinuses described by FARKAS were detectable between the dilated glands. The glands were lined with a single layer of epithelium but the nuclei were distributed in different levels at many sites. In a few areas several layers of nuclei and variable hyperchromasia were found (increased nuclear activity, praecancerous state). The basal membrane was intact. In other glands, vacuolisation of glycogen etc. printed to secretory activity. The endometrial connective tissue was also hypertrophied and rich to nuclei almost similar to embryonic tissue. These changes did not extend to the connective tissue of the myo- and perimetrium, indicating that only the endometrium was susceptible to the oestrogen produced by the tumour.



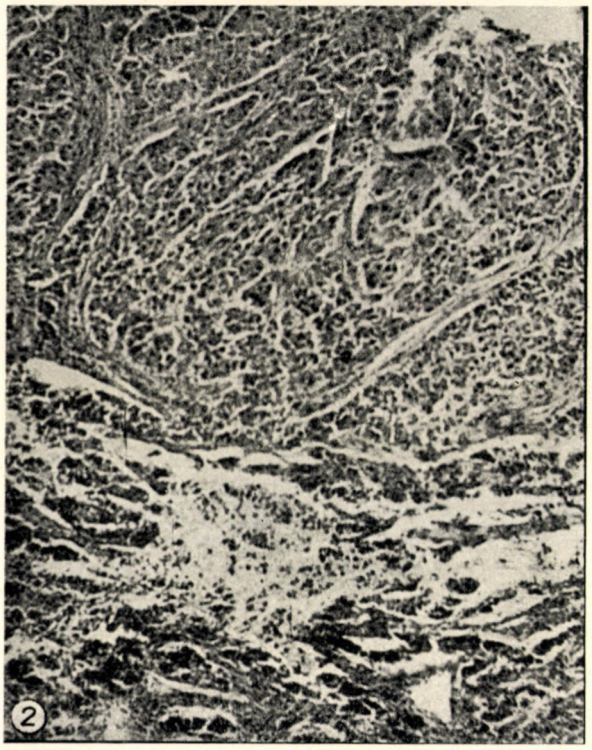


Fig. 1. Microscopic appearance of a trans-sected ovary with microgranulosa tumour. The centre of the granulomatous epithelial proliferation, which resembles a large follicle, is still cavernous, with residues of follicular fluid and cavity (From a 58 years old patient, after 10 years of amenorrhea).

Fig. 2. High power view of Fig. 1. Luteinized granulosa nests, with interposed smaller theca cells surrounded by fascicles of granulosa

The case merits attention in view of the rarity of the condition and with respect to the histogenesis and hormonal relations of granulosa tumours. Only one or two such cases have been described in the literature. According to McKAY and others, such tumours usually grow at a very slow rate and cause symptoms (haemorrhage, etc.) only late, so that they are not infrequently

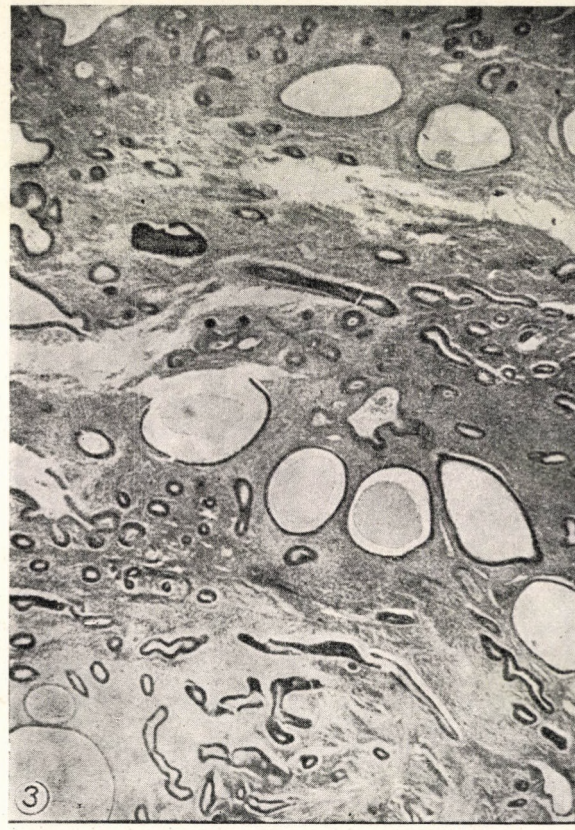


Fig. 3. Glandular cystic hyperplasia of endometrium from a case of microgranulosa tumour. Alongside the cystic-hypertrophic dilatations of glands, conspicuous hyperplasia of both the glands and the stroma can be seen, with embryonal like connective tissue islets. In a number of glands the nuclei are multi-layered, polymorphous, hyperchromic but not invasive, thus cannot be considered cancerous

fist or head-sized at the time they are discovered. Under the name „folliculoma malignum" KAHLDEN described in the ovary a follicle-sized accumulation of granulosa cells, that proved to be a feminizing tumour in its effect, too. The theca cell tumour removed by KYANK was microscopic in size, those removed by NOVAK, KOVÁCS, and SCHEYER were plum-sized granulosa cell tumours, and the theca-cell tumour removed by BATIZFALVY and DUBRAUSZKY was of

the size of a nut. According to BEHRENS, careful examination will reveal that the gl. cystic hyperplasia after the menopause is caused by microscopic hormon-producing tumours of the ovaries much frequently than commonly believed.

The fact that glandular cystic hyperplasia occur not only in the presence of larger tumours but of a microscopic one indicate that oestrogenic effect and changes in the endometrium depend not so much on the volume of the tumour (KOVÁCS) but rather on its functional activity which is also dependent on the structure of the tumour. It has been stated by NOVÁK, GORDON, MARVIN, and others that theca tumours produce more actively oestrogen than granulosa. DEMPSEY—BASSET went even farther, claiming that the hormone production would be the property of the internal theca cells only. In most cases (including ours) theca and granulosacells are mixed in the tumours. Growths — in turn — consisting apparently of granulosa cells only do not confirm the hormonal inactivity of such tumours.

It can be assumed that the oestrogen produced by the feminizing tumour is ineffective on the activity of the anterior pituitary (the follicle stimulating hormone, in the first place), because this gland is not susceptible to the oestrogen secreted by the tumour cells. GARDNER and also others, have namely found in animal experiments that the cause of the tumourous proliferation of granulosa cells in the ovary transplanted into the spleen, would consist in a disturbance of the above hormonal correlations. We have found in our patients that large doses of dienoestrol may decrease the size of granulosa cell tumours, or even make them to regress. (V. Case 6). Dienoestrol is known namely to inhibit the activity of the anterior pituitary.

Our case of microscopic granulosa tumour supplies new clinical evidence to the histogenesis of feminizing tumours too and that is in agreement with the results of animal experiments. Opinions vary in this respect, too. R. MEYER believes that these tumours originate from residual bundles of primordial granulosa, the precursor of folliculogenesis. In contrast with this, MCKAY, WOLL and others are of the opinion that the arisal of theca tumours in this way cannot be confirmed. According to WOLL, the arisal of these tumours would be related with the stroma hyperplasia in the senil ovary. NOVÁK suggests that both types of feminizing tumour would originate from the primitive genital mesenchyma which had differentiated to show feminine characteristics, i. e. from the progranulosal and prothecal phases, of which granulosa and theca cells may equally develop, while KOVÁCS attributes this role to the granulosal and thecal phases. According to ROBINSON and MCKAY, mature granulosal epithelium in atretic follicles would play a part in the genesis of granulosa cell tumours too. In some cases the pattern of folliculoma malignum resembles a mature Graafian follicle, some of them even contain a degenerated ovum. In later cases the tumorous growth of granulosal epithelium begins with the degeneration of the ovum, then with a luteinization of stroma and theca cells,

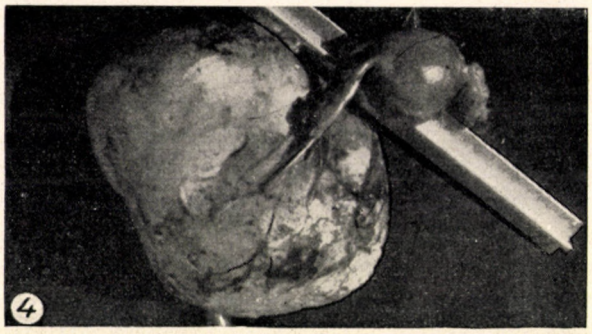
the follicular epithelium is not destroyed, but proliferated although according to KOVÁCS and R. MEYER, no tumour develops from the mature granulosar epithelium of Graafin follicles. MCKAY pointed out, that in the ovary transplanted into the spleen of castrated mice, the tumour would originate from the mature granulosal epithel of atretic Graafian follicles and the formalgenesis would proceed as outlined above. It appears that in women also any stage of the differentiation of feminine mesenchyme may serve as a starting point for the development of feminizing tumours. The differences in the stages might account for the benign or malign nature of these growths. The histomorphology of the case under discussion, with the presence of intertwining luteinized and ingrowing thecal cells, appears to demonstrate that the tumour arose from the granulosal epithelium of an atretic follicle, as it has been suggested by ROBINSON, and MCKAY. Had we examined the tumour earlier at the time irregular bleeding had first occurred, the degenerated ovum could have been perhaps also detected.

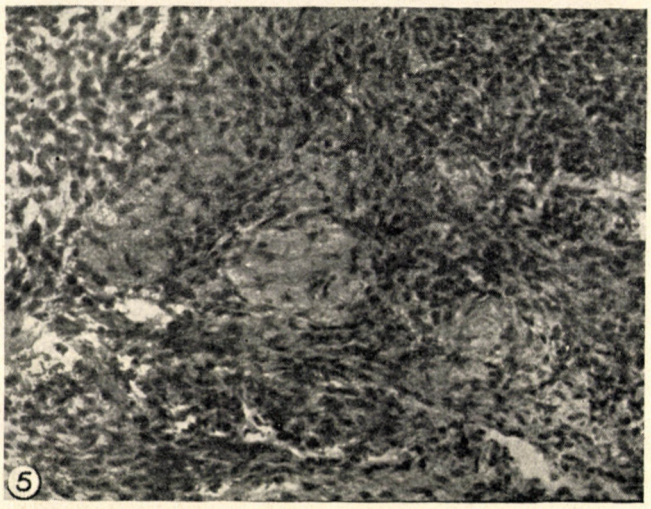
Amoung our cases there were two paraovarian theca cell tumours each of the size of a head. This appears to indicate that feminizing tumours may develop also from aberrant primitive genital mesenchyma. These cases merit attention and are therefore described in brief.

2. Paraovarian theca cell tumour

Record Nos. 58-II. and 107-III (1953) 46 years old II para. Last menstruation had occurred one year ago. The stout woman has lost considerable weight in recent month, with weakness and loss of appetite. She thought that she was pregnant, as she found her breasts swollen. On examination nothing contributory could be detected. Palpating through the fatty abdominal wall, an uterus similar in size to one in the 5th month of gravidity was found. The mucosa of the vagina and the portion was loose and livid. The frog reaction yielded a negative result. At X-ray examination no foetal bone contours could be seen. Gravidity was still suspected and the patient was sent home. She returned two weeks later, complaining of increasing weakness and of a further increase in abdominal circumference. Gravidity tests were persistently negative. This time however, a large volume of ascites was demonstrable and both pleural sinuses were filled with exudate but there was no sign of lung disease or fever. MEEIGS' syndrome was diagnosed and laparotomy performed. A pailful of ascites was removed and a dense paraovarian fibroma of the size of an infants head was found beside a goose eggsized uterus and small ovaries. The growth had a thin root in the left infundibulopelvic ligament, was supplied by vessels from the spermatic artery and from the mesenterium. The tumour was completely isolated from the both ovaries and from the uterus (Fig. 4). The genital organs with the tumour were removed. Histology revealed that the yellowish tumour was a mature *fibrosarcoma* and at places rich in cells (Fig. 5), with double refracting fat stain in the plasm.

These latter and the presence of gl. cystic hyperplasia of the endometrium after 1 year of the menopause, lividity of the vagina, etc., suggested that the tumour is a thecoma. In single glands the epithelium showed increased mitotic activity (Fig. 6). The connective tissue was also hyperplastic but not in the myo- or perimetrium, as in case 1. Both atrophied ovaries contained degenerated follicles and hyperplasia of the stroma. Otherwise, it has not been proved beyond doubt that the double refracting fat stains detectable in the theca





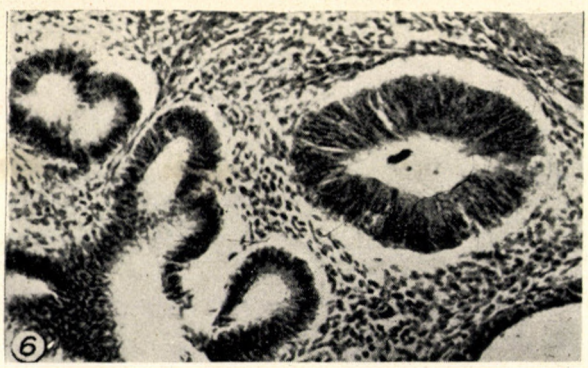


Fig. 4. Paraovarial theca cell tumour, with swollen uterus and atrophied ovaries, not invaded by tumour. From a 46 years old patient, after 2 years of amenorrhea

Fig. 5—6. Histologic appearance of theca cell tumour and of a section of endometrium, showing richly nucleated stroma, multiple layers of hyperchromic nuclei in the glandular epithelium and typical cystic hyperplasia

cell tumours would actually be identical with or representatives of the feminizing hormone. Recent studies (DEMPSEY, BASSET, KNIGHT, and others) seem to indicate that theca or granulosa cells do not store but only produce substances or hormonal activity. This accounts for the failure of attempts to demonstrate major quantities of hormone in such tumours (KNIGHT and others). Other observations also support the view that the feminizing nature of an ovarian tumour is determined not only by its histomorphology but also its clinical or hormonal activity and a tumour that resembles a simple fibrious neoplasm in that it contains no double refracting fatty granules (ovarian fibroma) may actually be capable of producing feminizing hormone (R. MEYER, HUSSLEIN and others).

No post-operative irradiations were done. The patient made a complete recovery. The pleural exudate was absorbed and ascites did not recur. As no relapse has occurred after 2 and a half years, it seems justified to claim that the tumour was not a common type of sarcoma.

As regards the relationship of hormonal correlations and feminizing tumours, this case too, has shown that tumour produced oestrogen does not inhibit pituitary function that could slow down the rate of tumours growth and stop unrestricted oestrogen production. The Case 2. is remarkable not only because a theca cell tumour arising from paraovarian tissue is a rarity but also because it proves that, in accordance with the view advocated by KOVÁCS, NOVÁK, and others, a feminizing or thecal tumour may arise from primitive genital germ cells, dispersed along or residual at the genitophrenic ridge.

Four cases of theca cell tumour have been observed by us during the past 8 years, all in the post-climacteric or the senile period. The oestrogenic effect manifested itself in each case with glandular cystic hyperplasia of the endometrium. Of the four cases in two, the one described above and that of an 55 years old patient (Record No. 2. VIII/953) did we find a paraovarian origin. In the latter case the tumour originated and was supplied from the right sacrouterine ligament, was independent from the ovary and was similar to two fists in size. There were atrophy of both ovaries, glandular cystic hyperplasia of the endometrium. The structure of the tumour was as in Case 2. Total hysterectomy was performed, no post-operative irradiations were given. The patient is free of complaints.

3. Theca cell tumour and cancer of the corpus appearing after irradiation

There was one among the four theca cell tumours which appeared to support the view advocated by WOLL and others, that some relationship exist between the genesis of thecomas and the stroma hyperplasia of the senil ovary, that the growth of the tumour is promoted by radiation injury to the ovaries

and by the upsetting of genital hormonal balance in old age. This case has been described in detail in *Nőorvosok Lapja* No. *10.* (1952).

The case presented the following interesting features. A 66 years old woman, had 6 years earlier undergone X-ray and radium treatment for advanced stage III simple epithelial cancer of the collum. The irradiations had destroyed the tumour, causing atresia of the cervical canal. Six years afterwards she was operated on in *Szikszó* because of the presence of a carcinohaematometra and theca cell tumour of the ovary. We had to assume that the cancer of the corpus and particularly the thecoma had begun to develop after the irradiations and that these had played a substantial role in the genesis of the corpus cancer. At the time of the irradiations no thecoma had been palpable beside the small uterus. The cancer of the corpus removed 6 years later was definitely glandular in structure.

Numerous authors (SCHEYER, NEUMANN, SCHILLER, STUDDIFORD, GORDON, KAMINESTER, DOCKERTY—CARTY, PALLOS, BATIZFALVY—DUBRAUSZKY) have described granulosa and theca cell tumours arising or begun to grow months or years after castration or therapeuthic irradiations. A relationship was therefore suspected between irradiations and the arisal of tumours or, at least, it appeared that these tumours or their precancerous phases are not destroyed but even stimulated by irradiation. Animal experiments by GARDNER, TRAUT, BUTTERWOERTH, and others indicate that granulosa tumours may develop not only in consequence of hormonal imbalance but also as a result of radiation injury.

These 3 ovarian feminizing tumours had an intensive oestrogenic effect on the endometrium, as manifested in the development of a glandular cystic hyperplasia and in recurrent bleedings. This is in support of the view that such tumours are oestrogen-producing but the changes described are not *sine qua nons* of the presence of such tumours, since their development depends on many factors, such as the susceptibility of the endometrium, the quality of the oestrogen produced, the age of the patient, etc. According to JAYLE, ovarian oestrogens (including oestradiol, oestriol and oestrone) differ in their effects both qualitatively and quantitatively. The endometrium is particularly influenced by oestradiol while the anterior pituitary mainly by the oxidation products of the hormone (oestriol, oestrone). In fertile age the endometrium responds to feminizing tumours less frequently with the development of glandular cystic hyperplasia, then in the post-climacteric and senile periods. In such cases the other non-tumorous ovary may modify the oestrogenic effect of the grows, although, according to NOVÁK and others, the nontumorous ovary does not show cyclic functions, as it is apparently supported by the low incidence of gravidity in the presence of hormone-producing ovarial tumours (DIDDLE, O'CONNOR, WEBBS, and others). Glandular cystic hyperplasia could be detected in only two (Record Nos. 2793/950, 3362/948) of the total of 7 patients with granulosa tumour under the age of 46 years and still showing regular menstruation, as compared to the more or less marked proliferation in the rest of the cases. Irregular bleeding was present in 1 case only, while

in 3 cases (Record Nos. 3362/948, 3282/948, 1275/951) amenorrhoea, in another 3 (Record Nos. 1685/951, VI. 22/951, 67—IX/953) cyclic bleedings were present. Of the 16 patients with feminizing tumour, who were older than 46 years or were in postclimacteric or senile age (11 granulosa and 4 theca cell tumours), in 5 of the atrophy mucosa was detected, associated with bleeding in 3, with glandular cystic hyperplasia in 11 (of these in 8 with bleeding) and with cancer of the corpus in 1 case. Thus, even postclimacterial and senile patients responded to the oestrogens of these tumours with endometrial proliferation in only 66,7 per cent, although histomorphologically each tumour was a typical, differentiated granulosa tumour and in some patients vaginal smears showed marked oestrogenic influence. This observation is in agreement with the report by *Hodgson et al.*, that among 62 postclimacterial patients the incidence of glandular cystic hyperplasia was as low as 67 per cent. Thus, in a certain proportion of cases, the uterus — and mainly the endometrium — the „target organ" of oestrogenic effect, has lost its susceptibility to the effects of these tumours (KOVÁCS). Our observations show clearly that functional changes, proliferation and, particularly, hyperplasia of the endometrium do not accompany feminizing tumours of the ovary in each and every case. It could be also demonstrated that the effect of the oestrogen produced by such tumours may manifest itself not only with proliferation, excessive growth of the mucosa, but also with uterine bleeding, which may be independent of the functional state of the endometrium. A case of granulosa tumour associated with mucosal atrophy and appearing after the climacterium was reported also by RIISFELDT and SCHUBERT. We have observed 2 patients, both in the senium (case Record Nos. 102—VII/952, 64 years old and No. 3074/951), 66 years old with atrophied bleeding endometrium associated with a differentiated granulosa tumour of follicular structure. This may be explained by a direct action of oestrogen on the blood vessels, or by a neurovascular effect. One of these cases is described in the following.

4. Granulosa tumour associated with atrophied, bleeding endometrium

Record No. 3074/951, 66 years old, 10 deliveries, no abortion, last menstruation 20 years earlier. Since a few month she has been feeling that a tumour is growing in her abdomen, and thus had slight bleedings. She noticed no changes in her breasts. Laparatomy was performed and a right ovarian tumour the sized of a child head was removed. The uterus was enlarged and the left adnexum atrophied. The tumour was a differentiated, mature, follicular and fasciculate granulosa tumour (Fig. 7). The endometrium was thin, with one or two narrow glands and local bleedings detectable in it (Fig. 8). The patient made an uneventful recovery and was given no postoperative irradiations. She has been free of complaints and has shown no recurrent growth now for four years.

The latter cases are in agreement with the observations reported by RIISFELDT and SCHUBERT, the view that proliferation or glandular cystic hyper-

plasia are not regularly associated with granulosa tumours, even if the latter is more mature, follicular in structure. Thus, the absence of proliferation in post-climacterial or senile age doest not yet prove the non-oestrogenic nature of the ovarian tumour if its structure is characteristic and other clinical features are present.

The development of endometrial changes depends, among other factors, also on the suspectibility of the endometrium to these tumour effects, which in different periods may differ even with the same tumour.

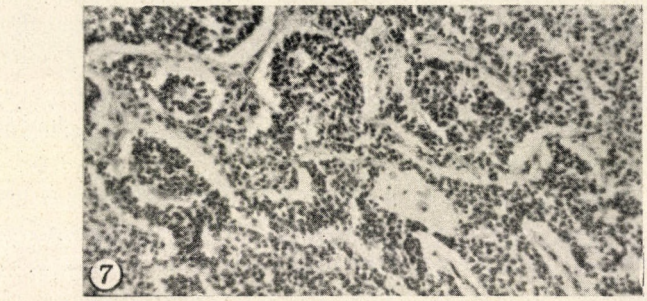
The following case reveals much of the effects of tumours, of changes in the endometrium due to hormonal effects, and of the nature of hormonal correlations.

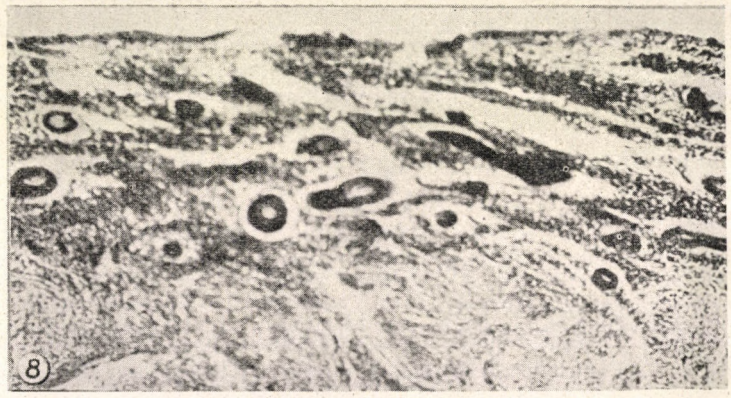
5. Variability of endometrial changes in a case of recurrent granulosa tumour

Record No. 3362/948, 33 years old, no gravidity. After 1 year of amenorrhea, in 1947 it was removed a right ovarian tumour the size of a man's head. We have been unable to obtain the histological findings. One year later she was admitted again, this time to our hospital in *Szikszó*, still complaining of amenorrhea. At operation a slightly enlarged uterus, a normal left ovary, and multiple tumours, varying in size from that of an egg to that of a nut, yellowish in colour, were found located to the vesical, uterine, pelvicomental and mesenterial surfaces of the peritoneum. After removal of about 6 litres of ascites, all visible tumours were excised. No follicle or luteinisation were visible in the ovary. The breasts were tense and on pressure yielded a small amount of serous fluid. The endometrium showed a richly nucleated stroma and glandular cystic hyperplasia, as in Cases 1 and 2 (Fig. 10). Histologically the growth proved to be a granulosa cell tumour follicular and gyriform in structure (Fig. 9), with cellular polymorphism and hyperchromic nuclei. Some mitoses were also present. Intensive irradiation therapy was carried out but the recurrent growth showed further progression.

On several occasions abdominal punctures had to be made to remove the collected fluid. The patient died at her home in 1950.

Similar cases are rare examples of human autobiological experiments. In patients having recurrent feminizing tumour the organism is flooded for prolonged periods by such excessive quantities of oestrogen which cannot be attained either by experimental methods or by administering hormones or by ovarian implantation (KOVÁCS). Accordingly such cases offer a deeper insight into the relationship between the oestrogen and malignant or benign structural changes in the endometrium than those obtainable by any kind of arteficial hormonal experiment. Our patient remained amenorrhoic, not in consequence of the irradiations but in consequence of disturbed hormonal correlations. It was found namely that these differentiated granulosa tumour was resistant to X-rays, it showed further growth, formed further metastases and produced hormone. After five weeks, and then after another six weeks lively proliferation and development of glandular cystic hyperplasia could be seen in the endometrium. Still 3 month later, the histologic examination taken by abrasion showed quiescence but the specimens obtained 3 and 6 month





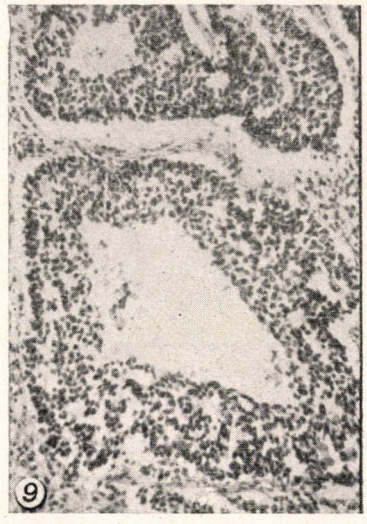


Fig. 7—8. Granulosa tumour, exhibiting follicular, gyriform, cylindriform, etc., patterns in different areas, with atrophied haemorrhagic endometrium. From a patient, whose last menstruation had occurred 20 years earlier

Fig. 9—10. Recurrent, metastasis-forming granulosa tumour with remarkably mature, follicular structure, from a 33 years old patient (last bleeding before 2 years). The endometrium of the same patient exhibit multiple layers of nuclei, hyperchromism, polymorphism (but no malignance in the glandular epithelium, and a richly nucleated stroma. (Specimen obtained 2 years after removal of primary tumour)

afterwards exhibited the same glandular cystic hyperplasia, precancerous nuclear activity, and richly nucleated stroma as had been found at the first operation.

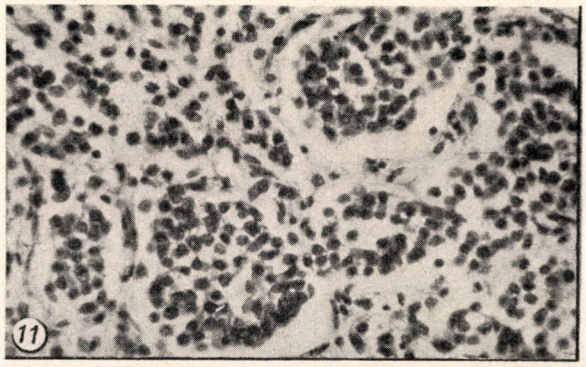
Thus, the prolonged presence of a granulosa tumour, i. e. hyperoestrinism of almost 3 years duration did not produce a malignant proliferation in the endometrium. Even in the specimen from the last curettage the cells in the glands were distributed in a single layer and the basal membrane was intact everywhere. The changes in the vaginal smear were not different from those characteristic of follicle hormone action, i. e. a discharge containing flat epithelium but no tumour cells. Apart from swelling, the breast showed no other alteration too. Thus, even a granulosa tumour of several years standing, causing excessive proliferation of both stroma and glands and increased nuclear activity, may fail to cause endometrial cancer, although the organism exhibits a tendency to tumour formation, the histomorphology and metastasis-forming ability of the granulosa tumour suggest malignancy, and, under the prolonged influence of oestron, the endometrium is in a precancerous stage, for years. Among other data this too indicates that the role of oestrogens and the significance of the precancerous phase in carcinogenesis cannot be considered as *sui generis*. This is remarkable, since INGRAM, NOVÁK, HODGSON, SZATHMÁRY, DOCKERTY, VÁCZY and others have supposed a close correlation between cancer of the corpus and feminizing tumours. According to NOVÁK, HODGSON and others, feminizing tumours have a carcinogenic effect, especially when they develop postclimacterially. The incidence of endometrial cancer among these tumours has been estimated to vary between 12 and 21 per cent and then the incidence of the cancer of the breast is somewhat lower. This would be more frequent in association with theca cell tumours which for this reason are being claimed to produce more oestrogen and to exert a more intense effect. In Hungary SZATHMÁRY, VÁCZY and the present author described a case of theca cell tumour associated with glandular cystic hyperplasia and cancer of the uterine corpus. As regards the cancerogenic role of these tumours and of oestrogens, respectively, we agree with VÁCZY that they may create favourable conditions for the action of oncogenic substances but the oestrogens (and thus the tumours) by themselves are not cancerogenic (KOVÁCS).

In another patient who because of a recidiv granulosa tumour has been under our observation for 3 years, the level of oestrogen and gonadotropic hormone in blood offered proof that even in the presence of the same tumour and unchanging high levels of oestrogen in blood the endometrium may show different morphological changes (atrophy, quiescence, or proliferation) at different points of time.

6. Record No. 90-IV/1953. A 48 years old patient with 1 delivery and no abortus had 6 years earlier undergone right ovariectomy because of the presence of a tumour. The tumour was a medullary malignant granulosa one. In spite of post-operative irradiations, she still

had the usual menstruations at intervals varying from 6 to 8 weeks. In February, 1953 she complained of prolonged bleeding and of feeling a newer growth in her abdomen. X-ray therapy failed to influence either the bleeding or the size of the tumour. At laparotomy a recidiv tumour invading the intestines, omentum, etc. in the form of a single easily bleeding mass was found which could be removed only partially. Histology revealed a solid granulosa tumour of follicular structure (Fig. 11.). Uterine abrasion was performed ; the specimen examined showed glandular cystic hyperplasia with a richly nucleated stroma (Fig. 12.) like in Case 5. After the operation the patient had no more menstruations. A specimen taken 5 weeks later showed quiescence, while that abrased another 5 weeks later exhibited moderate glandular cystic hyperplasia. The level of gonadotropic hormone was 500 I. U./litre in urine, and 3000 I. U./l. in blood. At the same time, DR. ZEMPLÉN found the level of oestron in urine to be 1500 I. U./litre. Two weeks later, when histology showed quiescent endometrium, the level of gonadotropic hormone was 167 I. U./litre in urine, and 3000 I. U./litre in blood, while that of urinary oestron 1300 I. U./litre. Six weeks later, when the endometrial mucosa was atrophied, similar values were obtained.

Thus, the results of hormone studies also confirm the validity of our observation that hormonal changes in the endometrium are not a „*sine qua non*"



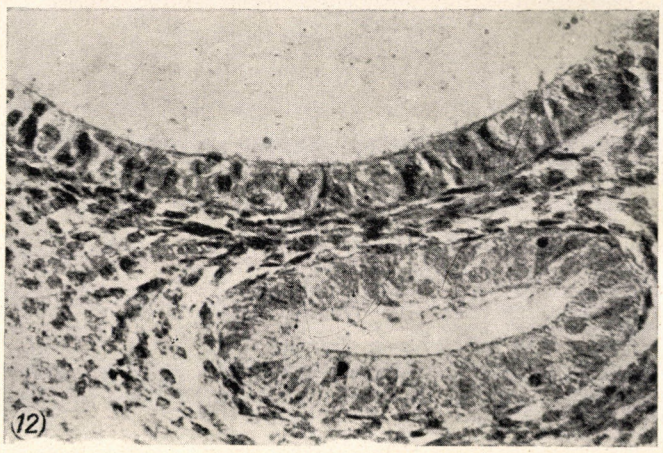


Fig. 11—12. Recidiv, metastasizing granulosa tumour with mature follicular structure from a 48 years old patient, and specimen of abrasion material from her uterus, showing precancerous glandular changes similar to those shown in Fig. 10. Six years after removal of primary tumour, followed by therapeutic irradiations. Chief complaints intermittent bleeding

of the presence of feminizing tumours and that the changes are not always proportionate to the rate of oestrogen production by these growths. Thus endometrial changes may develop uninfluenced by the oestron effect of the tumour. As cited by FEKETE, in 43 out of a total of 47 cases of metropathy described by KALANTAROVA—ORDYNEZ the daily oestron output varied from 1000 to 3000 mouse units per litre, and yet, in 24 of the 43 patients was endometrial atrophy present. In earlier hormonal studies of feminizing tumours (BATIZFALVY and DUBRAUSZKY, RUZICSKA, SCHUSCHANNIA) the results were given in terms of mouse or rat (HODGSON) units. Thus a comparison to our results seems rather difficult. Still, it appears that the values obtained in earlier assays are lower than ours, although these has been found scarcely elevated by DR. ZEMPLÉN. Further investigations are required to clarify this problem. According to KULLANDER, these tumours would cause a decrease rather than an increase in the quantity of oestrogen excreted in urine. In KNIGHT'S case the theca cell tumour weighing 8 kg. contained 0,2 gamma of oestrogen only i. e. 2 I. U. per 100 g.

The patient described above is still under our observation. Following operation, the tumour began to grow again and filled almost the entire abdominal cavity. X-ray irradiations failed to stop growth and had to be discontinued because of grave complaints. In view of the hazards of bleeding and the hopelessness of a radical operation, no third laparatomy was performed. Instead, she was instructed to take 15 to 20 tablets of *dienoestrol* daily over a period of 1 year, assuming that that oestrogenic agent would inhibit the anterior pituitary in the first place. Animal experiments have shown that inhibitors of the anterior pituitary *may inhibit* the *tumorous proliferation* of granulosal epithelium. On this therapy the tumour has not only ceased to grow but even decreased in volume and at present only an egg-sized mass of indefinite outlines can be palpated below the umbilicus, that may be the tumour or adhesions alike. The patient, who had suffered from continuous dsypnoe, is now back at work, feels well.

Summarizing the evidence derived from a total of 23 cases feminizing tumour of the ovary (19 granulosas and 4 thecomas), the following conclusions can be drawn.

Feminizing tumours, especially granulosas, may arise not only in animals but also in women, from follicular atresia (MCKAY, ROBINSON) in the ovaries, or, extraovarially, from germ cells of the primitive genital mesenchyma persisting along the urogenital ridge (R. MEYER, NOVÁK, KOVÁCS), as well as from the stromal hyperplasia of the senil ovary (WOLL). Differences in genesis may play a role in the benign or malignant nature of these tumours. Of our 23 patients in 4 had the granulosa-tumour recidiv (3 patients died). In agreement with animal experiments, clinical data also show that X-rays may play a role in the precipitation of tumorous growth. Of paramount importance in onko-

genesis, however, is a disturbance of hormonal correlations, as confirmed by animal experiments and also by the fact that 70 per cent of all feminizing tumours develop in postclimacterial and senile age, after changes have set in genital hormonal relations, as has been observed also in our material. Apparently the anterior pituitary either loses its susceptibility to oestrogenic effects or the oestrogens produced by the tumour are not effective on the anterior pituitary, do not inhibit FSH and do not initiate LH and LTH production, which could prevent follicular atresia the further production of oestrogen and inhibit the FSH effect promoting the excessive growth of follicular epithelium. Another manifestation of the hormonal imbalance is seen in the fact that sometimes the endometrium responds only slightly, or not at all, to such high levels of oestrogens in blood which occur exclusively presence of feminizing tumours. In several cases the endometrium remains atrophic or bleeds without any functional changes in the mucosa. The nature of changes actually occurring in the endometrium depends on the quality of oestrogen produced by the tumour, just as on the susceptibility of the endometrium to the oestrogen produced and also on the ability of the organism to transform the oestrogens. Any of these factors may vary considerably even in the presence of the same tumour. It is known, for instance, that in fertile age glandular cystic hyperplasia occurs less frequently in association with feminizing tumours, a fact apparently due to a modifying effect of the contralateral, non-tumorous ovary. The significance of endometrial susceptibility is indicated by the observation that changes in its function may show an excessive variability from time to time even in the presence of the same tumour. Thus the presence of glandular cystic hyperplasia or of endometrial bleedings, etc. are not „*sine qua non*" symptoms of feminizing tumours and an absence of the former does not yet mean that a tumour showing the characteristic pattern is hormonally inactive or „silent". This view is supported by our observation that in the same patient the changes of the endometrial mucosa (proliferative, quiescent or atrophic) are not always parallel with the level of the oestrogen and gonadotropic hormone in the blood. We are convinced that an upsetting of hormonal balance, involving oestrogen production, anterior pituitary function, endometrial pattern, etc., play an important role in the genesis of these feminizing tumours and probably also in that of other genital neoplasms. The success of hormonal therapy, especially with oestrogens, of both benign or malignant tumours (BÁRSONY, NOSZKAY, MORLEY, STOLL—RIHM, and others) may depend on how these correlations and the anterior pituitary, in the first place, can be influenced. In animal experiments the development and growth of granulosa tumours arising in the ovary implanted into the spleen may be prevented by oestrogen or testosterone which suppress the function of the pituitary. This problem, which is of obvious importance with respect to both theory (oncogenesis) and therapy is being approached from several angles at our Department.

Summary

A total of 23 feminizing tumours of the ovary has been observed during the past ten years by us. After discussing general principles, a detailed account has been given of some cases which might contribute to the genesis, hormonal correlations, and other aspects of feminizing tumours of the ovary. Evidence has been presented to show that such tumours may originate from follicular atresia in the ovary or from germ cells of the primitive genital mesenchyme persistent along the phrenicogenital ridge, or from stromal hyperplasia of the senil ovary. Radiation effects may also play a role in the genesis of such tumours but, as known from animal experiments, of primary importance from this respect is an upset equilibrium between anterior pituitary and ovary (endometrium). It remains to be elucidated why in women the oestrogen produced by these tumours fails to act on the gonadotropic hormone production of the anterior pituitary, which in animals promotes tumorous growth of granulosal epithelium. The endometrium responds to the oestrogen produced in these growths by proliferation, glandular cystic hyperplasia, or bleeding. None of these changes are, however, „*sine qua non*" symptoms and their absence does not yet prove that the tumour is non-feminizing if its histology and the clinical changes caused by it are otherwise characteristic. A prolonged increase in the activity of endometrial glandular and epithelial tissue may, under the influence of feminizing tumours, create favourable conditions for carcinogenesis but the cases have yielded no evidence suggesting that a feminizing ovarial tumour by itself would exert a carcinogenic effect. Except in one case, the tumour has failed for years to produce uterine or breast cancer, although the patients have undoubtedly been exposed to oncogenetic effects.

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О РЕДКИХ ФОРМАХ, О ПРОИСХОЖДЕНИИ И О ВЗАИМООТНОШЕНИЯХ ФЕМИНИЗИРУЮЩИХ ОПУХОЛЕЙ ЯИЧНИКА

Б. СЕНДИ

Автор наблюдал в течение 8 лет 23 случая феминизирующих опухолей яичника в г. *Сиксо* и *Дьюла*.

Наряду с общими выводами автор занимается особенно с теми случаями, которые предоставляют новые данные о происхождении, о гормональных взаимоотношениях и т. д. феминизирующих опухолей яичника. Эти случаи указывают на то, что данные опухоли могут произойти из заращения фолликула, в яичниках, или из заблудившихся вдоль френикогенитальной складки первичных зачатков половой мезенхимы, или из гиперплазии стромы стареющегося яичника равным образом. В их онкогенезе могут играть роль также лучевые воздействия, но особенно значительную роль играет расстройство гормональных взаимоотношений между передней долю гипофиза — яичником (эндометрий), как это выявлялось также из опытов над животными. Вопрос о том, почему у женщин эстрогенног, вещество этих опухолей не имеет действия на гонадотропную деятельность передней доли гипофиза, которая — согласно опытам над животными — выэывает опухолевое разрастание эпителия гранулезы, нуждается еще в выяснении. Эндометрий реагирует на эстрогенное вещество этих опухолей разрастанием, гландулярно-цистозной гиперплазией или кровотечением. Это, однако, не является безусловным осложнением данных опухолей, и их отсутствие при впрочем характерной структуре и клинических свойствах не доказывает, что в данном случае не имеет место феминизирующая опухоль. Эндометрий является прочной железой и лабильность его эпителия предоставляет возможность для проявления карциногенных действий. Однако, случаи автора не доказывали, что феминизирующую опухоль яичника саму по себе можно было бы рассматривать карциногенной. За исключением одного единственного случая эти опухоли в течение многих лет не вызвали ни рака матки, ни рака грудной железы, несмотря на то, что опухолевые больные бесспорно подвергались онкогенным действиям.

ÜBER DIE SELTENEREN FORMEN, DIE GENESE UND DIE KORRELATIONEN DER FEMINISIERENDEN OVARIALGESCHWÜLSTE

B. SZENDI

(Im Verlauf von 8 Jahren wurden in Szikszó und in Gyula 23 Fälle von femin. Ovarialgeschwülsten beobachtet.)

Neben allgemeinen Erfahrungen beschäftigt sich der Autor besonders mit jenen Fällen, die neue Daten zur Genese, den hormonalen Korrelationen usw., der femin. Ovarialgeschwülste liefern. Diese sprechen dafür, dass die Geschwülste aus der follikulären Atresie, im Ovarium, aus den entlang der phrenicogenitalen Falte verstreuten geschlechtlichen Urmesonchymkeimen oder ebenso aus der Hyperplasie des Grundgewebes der alternden Ovarien entstehen können. In ihrer Onkogenese können auch Strahlenwirkungen eine Rolle spielen, es kommt aber — wie auch die Tierversuche zeigen — dem Umsturz der hormonalen Korrelationen zwischen HVL.-Ovarium (Endometrium) eine besondere Rolle zu. Es bleibt noch zu klären, wieso das Oestrogen der Geschwülste bei Frauen ohne Wirkung auf die gonadotrope Tätigkeit des HVL. ist, was den Tierversuchen nach die Ursache der geschwulstartigen Wucherung des Granuloseepithels ist. Das Endometrium reagiert auf das Oestrogen der Tumore durch Wucherung, glandulär-zystische Hyperplasie oder Blutung. Dies ist jedoch keineswegs eine unbedingte Begleiterscheinung dieser Geschwülste und ihr Fehlen, bei sonst charakteristischen konstruktiven und klinischen Eigenheiten, beweist nicht, dass wir es nicht mit einem femin. Tumor zu tun haben. Das Endometrium ist eine echte Drüse und die Reaktion des Epithels kann unter dem Einfluss solcher Geschwülste zum Durchbruch karzinogener Wirkungen führen ; die beobachteten Fälle haben aber nicht erwiesen, dass die femin. Ovarialgeschwulst an sich krebserzeugend ist. Mit einer einzigen Ausnahme haben sie durch Jahre keinen Gebärmutter- oder Brustkrebs hervorgerufen, trotzdem die mit Geschwülsten behafteten Patienten zweifellos unter onkonegen Einwirkungen standen.

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