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Some Observations on the Fine Structure of Human Granulosa Cell Tumors

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Summary. The ultrastructural features of three granulosa cell tumors are presented. The neoplastic non-luteinized granulosa cells are characterized at sub-microscopical level by severely indented nuclei with prominent nucleoli, sparse to moderately developed predominantly granular endoplasmic reticulum, scanty lipids and lysosomes, small mitochondria with lamellar cristae and abundant intracytoplasmic filamentous material. The luteinized cells display a strongly developed tubular agranular endoplasmic reticulum and mitochondria with tubular cristae.

These findings are compared with those of previous reports and discussed in relation to the well-known hormonal activity of these tumors.

Key words: Granulosa cell tumors – Ultrastructure.

Introduction

Granulosa cell tumors are uncommon ovarian neoplasms of low grade malignancy. They are, as a rule, hormonally active and usually produce oestrogens. However a few reported cases of granulosa cell tumors have been shown to be androgenic, causing virilization of the patients.

Their histological features show great variations, many growth patterns being represented within the same tumor. There seems to be no present justification for separating these neoplasms into benign and malignant subgroups according to their microscopical appearance.

The origin of the granulosa cells and of their derived tumors is still disputed. Granulosa cell tumors have been experimentally induced in rodents by several procedures but no convincing evidence of their histiogenesis was found (Hamlett et al. 1971; Volfson 1976).

In the literature there are a few reports of the fine structure of benign and malignant granulosa cell tumors, all dealing with a single case (Toker

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1968; Gondos 1969; Pedersen and Larsen 1970; Gondos and Monroe 1971; Bjersing et al. 1973; Waisman et al. 1975; Gallipi et al. 1976). The findings of these authors are similar in many ways but also reveal several discrepancies. MacAulay et al. (1967) studied the ultrastructural features of a granulosa cell tumor and tried to relate them to its steroid biosynthetic pathways. The purpose of this study is to present additional data concerning the fine structure of these interesting neoplasms and to discuss them in relation to their hormonal activity.

Material and Methods

The tumors studied here were obtained from three patients operated upon at the Department of Gynecology of the University Womens's Hospital in Zürich.

Case 1 (D.G., EM 24/77)

This 60 year old patient was sent to the hospital by her physician following the acute onset of severe lower abdominal pain. Laboratory data were unremarkable. At laparotomy a ruptured left-sided ovarian tumor was found, measuring about 10 cm in diameter. The tumor was resected and sent for frozen section examination. It was diagnosed as a granulosa cell tumor. A total hysterectomy and bilateral adnexectomy were performed as well as a resection of the omentum and a peritoneal biopsy. Histological examination of the uterus revealed a marked endometriosis interna and a glandular cystic hyperplasia of the endometrium. The right ovary and the omentum and peritoneum were free of tumor. The patient underwent post-operative radiotherapy and is well three years thereafter.

Case 2 (H.D., EM 2/78)

This 31 year old patient who had always presented irregular menses and who had had occasional spotting prior to admission was sent to the clinic by her physician. He had incidentally palpated a retrouterine mass and suspected an adnexal neoplasm. At laparotomy a ruptured left-sided ovarian tumor was found and resected together with the tube. A wedge-biopsy was taken from the right ovary. Histological examination of the neoplasm revealed a focally luteinized granulosa cell tumor. The ovarian tissue of the opposite side displayed some degree of stromal hyperplasia as well as marked oedema. No further therapy was undertaken and the patient had a normal delivery one year after operation. One year later there are no signs of local recurrence or metastasis.

Case 3 (B.O., EM 46/79)

This obese 71 year old patient was admitted in the Hospital because of recurrent vaginal bleeding post-menopausally. Physical examination revealed the presence of a large left-sided adnexal mass. At laparotomy a ruptured haemorragic tumor measuring $12 \times 7 \times 6$ cm was resected and sent for frozen section examination. It was diagnosed as a granulosa cell tumor. A total hysterectomy and bilateral salpingo-oophorectomy were performed. The omentum was resected and a peritoneal biopsy was taken. Histological examination of the uterus revealed glandular cystic hyperplasia of the endometrium. The right ovary displayed marked hyperplasia of the cortical stroma and of the hilus cells. Omentum and peritoneum were free of tumor. One month after operation an intraperitoneal instillation of colloidal P32 was performed. Four months thereafter the patient is well.

In all three cases, tissue for light microscopy was fixed in 10% buffered formalin, processed by conventional methods and stained with haematoxylin-eosin and PAS. Van Gieson's stain and

Table 1. Light microscopic features

	Case 1	Case 2	Case 3
Microfollicular	–	++	+
Macrofollicular	–	–	–
Trabecular	+	–	+
Diffuse	++	+	++
Cysts	–	few	few
Focal luteinization	+	+	+
Thecal elements	++	–	+

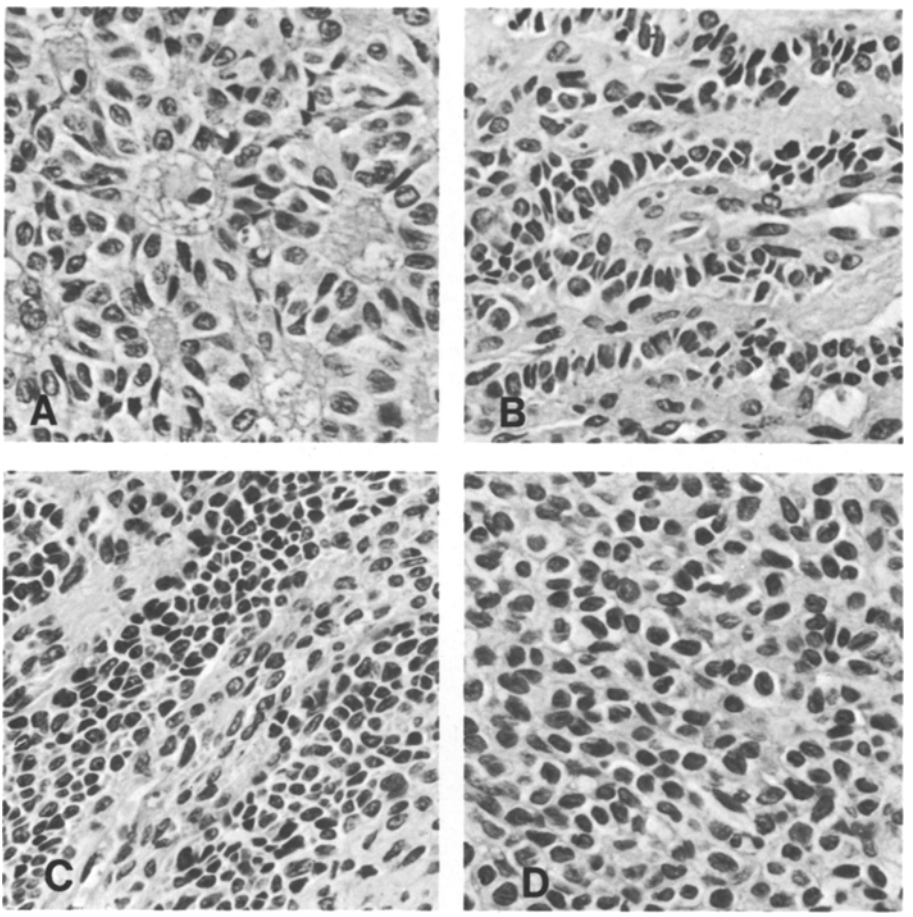

Fig. 1A–D. Light microscopic features of granulosa cell tumors. **A** microfollicular area with Call-Exner bodies. **B** cylindromatous pattern. **C** trabecular pattern. **D** so-called pseudo-sarcomatous or diffuse pattern. Note the focal luteinization of tumor cells. HE, ×400

Gomori silver impregnation were also achieved. For electron microscopy small blocks of tumor tissue were immediately fixed by immersion in cold buffered 2% glutaraldehyde and post-fixed in s-collidine-buffered 1% osmium tetroxide after washing in phosphate buffer. The samples were then dehydrated in series of ethanol and embedded in Epon. Semithin sections for orientation were stained with toluidine blue. Ultrathin sections were cut with an Ultrotom III and after staining with uranyl acetate and lead citrate, they were examined in a Philips 201 electron microscope[1].

Results

The main histological features of the three tumors are summarized in Table 1 and illustrated in Fig. 1.

At ultrastructural level the tumor cells are generally round or polygonal, most often in close apposition to one another (Fig. 2). The cell membranes

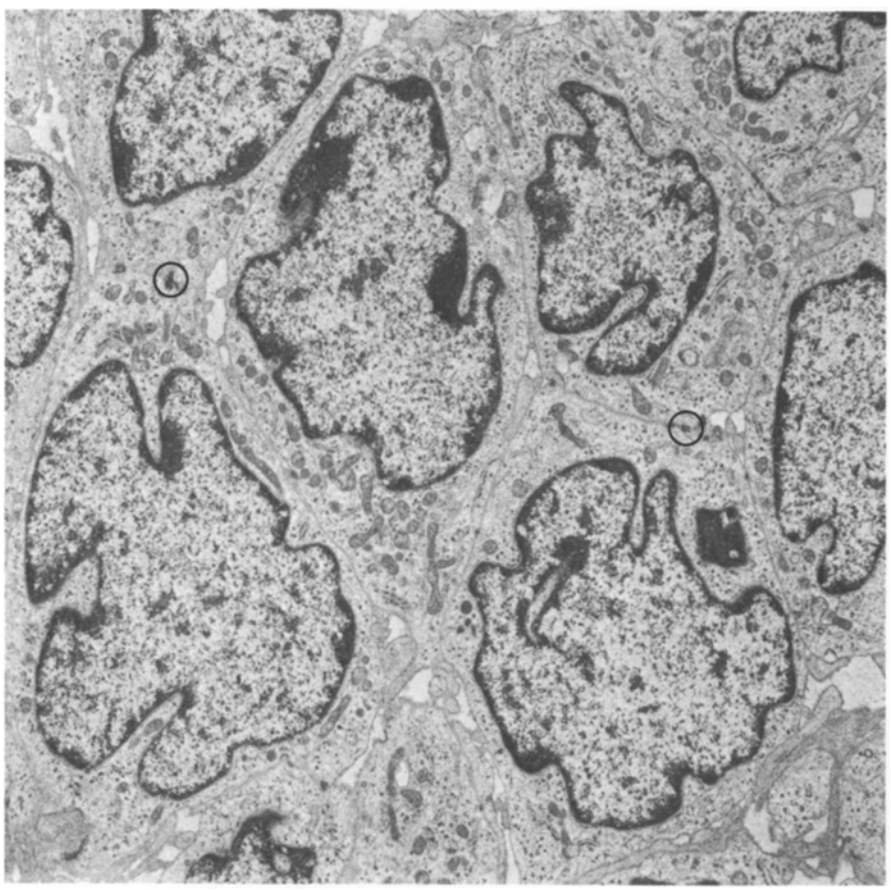

Fig. 2. Low magnification electron micrograph of neoplastic granulosa cells. The cell membranes are distinct, running mostly parallel one to another, some desmosomes being present (○). Note the deeply indented nuclei with irregular peripheral condensation of the chromatin. A few cytoplasmic projections extend into small widened intercellular spaces. ×6,400

[1] I am greatly indebted to Miss Silvia Heeb for her technical assistance

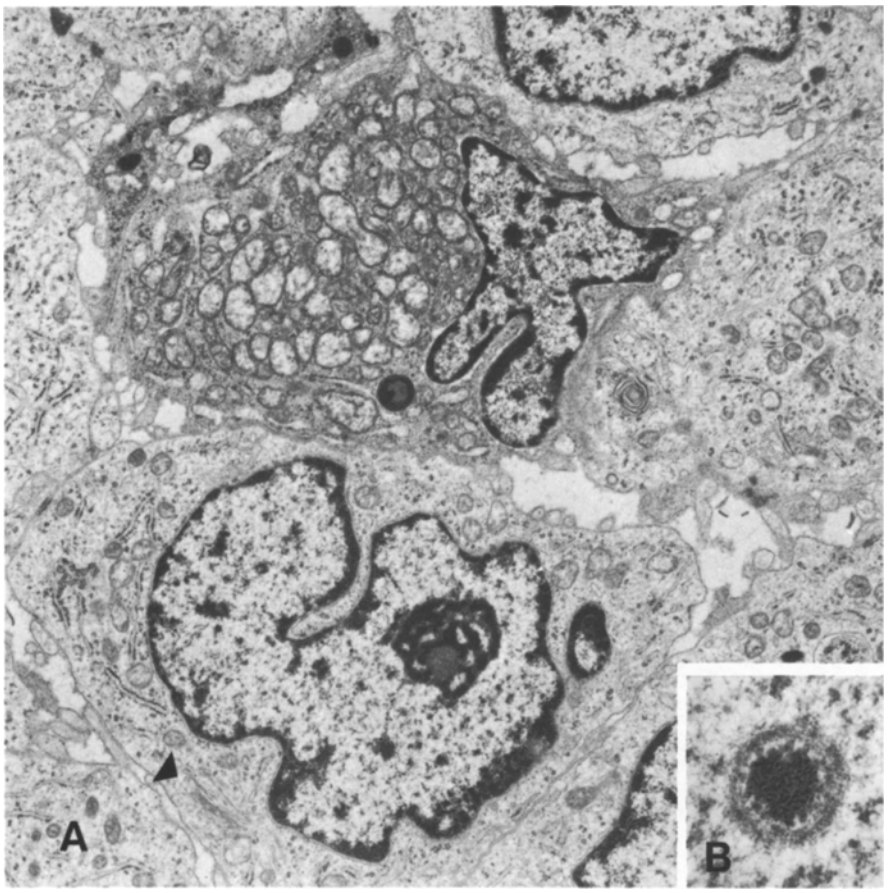

Fig. 3. A Widened intercellular spaces in which protrude numerous short cytoplasmic projections. The dark cell displays swollen and partly disrupted mitochondria, shrunken nucleus and cytoplasm. In the clear cells are a few parallel stacks of granular endoplasmic reticulum, small round mitochondria and inconspicuous Golgi (►). ×9,600. **B** Rare intranuclear inclusion found in some tumor cells of Case 2. ×29,600

are mostly well-defined, presenting some points of attachment provided by well-developed desmosomes. A few micropinocytic vesicles are irregularly distributed. Particularly in two tumors (cases 2 and 3) numerous cytoplasmic projections intermingle in widened intercellular spaces (Fig. 3A). A basement membrane and occasionally some collagen fibers surround the tumor cells either individually or in groups. The nuclei display considerable variation in size and shape and are often deeply indented. Peripheral margination of the chromatin, its interruption at the nuclear pores and its occasional clumping can be readily recognized. Nucleoli are generally prominent, complex in structure, and present a conspicuous pars amorpha. Rare nuclear inclusions are found in Case 2 (Fig. 3B).

The cytoplasm of the non-luteinized tumor cells is of variable electron den-

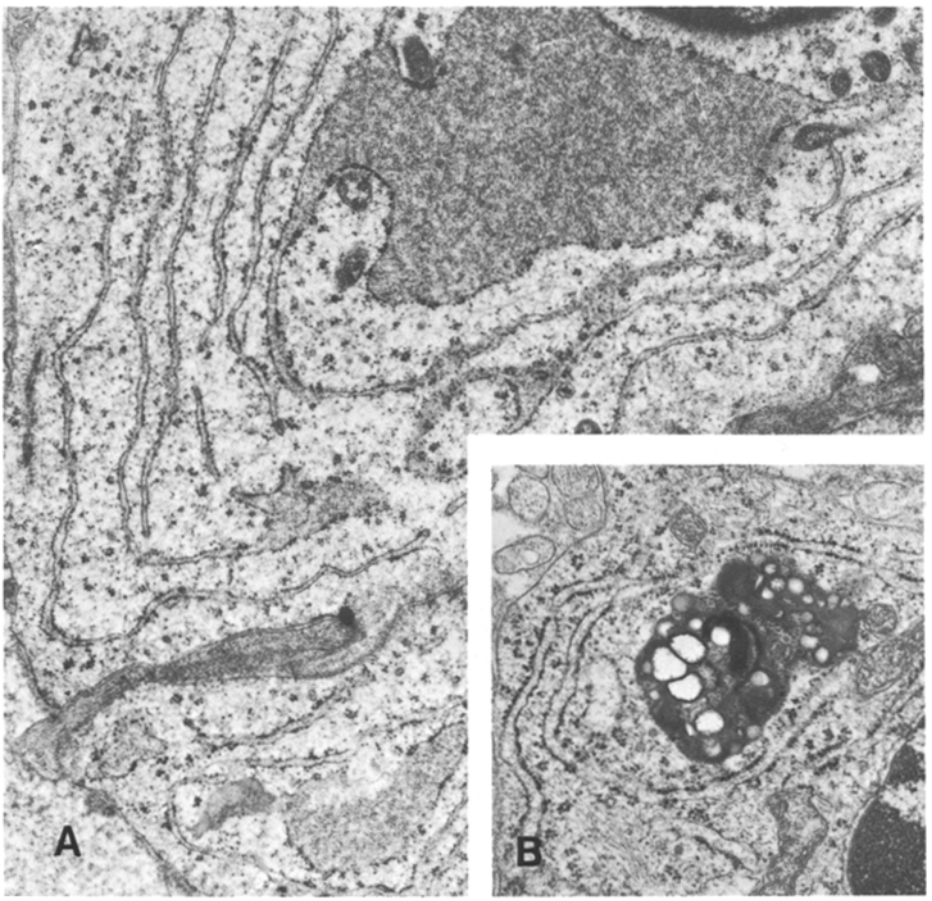

Fig. 4. **A** Tumor cell displaying parallel arrays of partly agranular endoplasmic reticulum, some of which present dilated cisternae filled with fine granular material. In the cytoplasm are a few round mitochondria and free ribosomes. ×13,800. **B** Typical lipofuchsin granule. In the cytoplasm are pleomorphic mitochondria, fibrillar material and some partly agranular endoplasmic reticulum. ×26,500

sity. It contains some ribosomes and polysomes. The Golgi apparatus is rarely found and generally inconspicuous. The endoplasmic reticulum is moderately developed in most cells and predominantly granular in type, often stacked in parallel rows. Dilated cisternae of granular endoplasmic reticulum filled with fine granular material of moderate electron density are found in some cells (Fig. 4A). Lipid droplets and lysosomes are scant as well as lipofuchsin granules (Fig. 4B). Mitochondria are often numerous, generally round or oval, seldom elongated. They present mostly sparse and short cristae, predominantly lamellar in type. Occasional myelin-figures are found. Centrioles are found in many cells.

A conspicuous finding in practically all tumor cells, including the luteinized

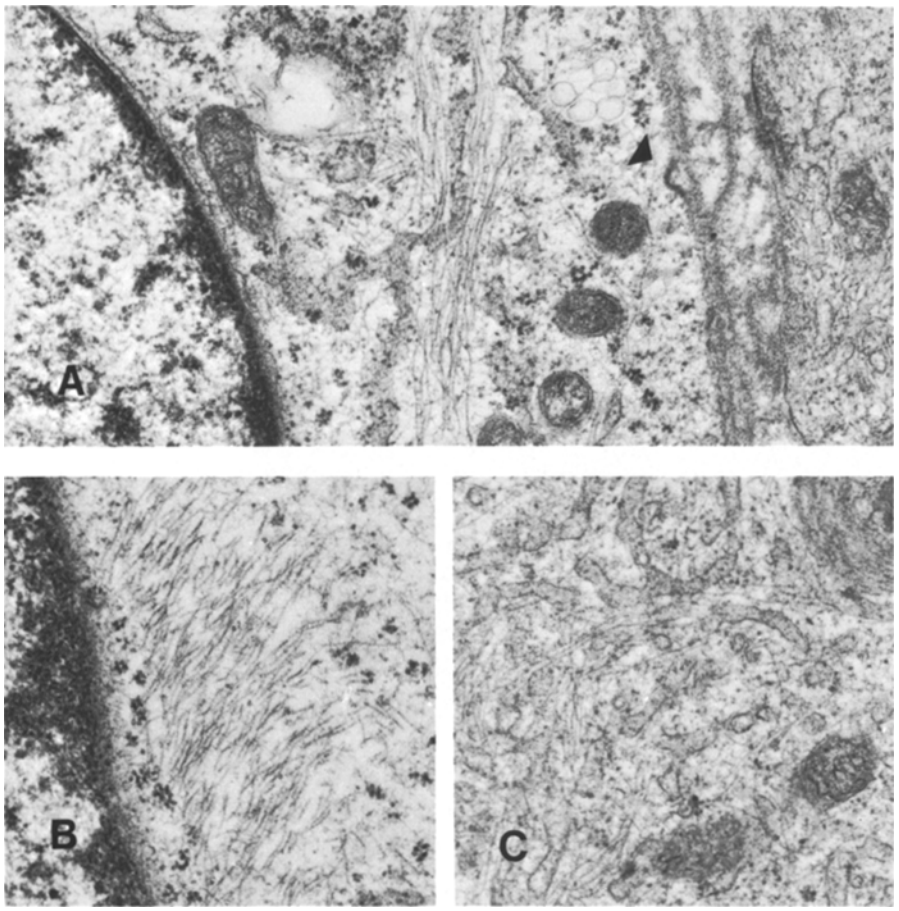

Fig. 5. A Detail of a neoplastic granulosa cell displaying intracytoplasmic bundles of microfibrils, some mitochondria and polysomes. Note the pinocytic activity at the cell membrane (▶) that is resting on a multilayered basement membrane. ×26,100. **B** Numerous microfibrils in a perinuclear location. In the cytoplasm there are some polysomes. ×26,100. **C** Some bundles of fibrillar material in the cytoplasm of a luteinized tumor cell. Note the abundant tubular and vesicular agranular endoplasmic reticulum and the small mitochondria with tubular cristae. ×26,100

type, is the presence of abundant fibrillar material in the perinuclear area as well as randomly distributed throughout the cytoplasm (Fig. 5).

The cytoplasm of the luteinized cells is characterized by a strongly developed tubular and vesicular agranular endoplasmic reticulum as found in steroid producing cells (Fig. 6). In these cells one finds only few strands of granular endoplasmic reticulum, free ribosomes being moderately numerous. The well-preserved mitochondria display mostly tubular cristae showing considerable variation in number and length (Fig. 7). Some mitochondria are swollen and disrupted.

Both cell types present occasional well-developed cilia (Fig. 8). This is a consistent finding in all three tumors and, to our knowledge, has not yet been reported in human granulosa cell tumors.

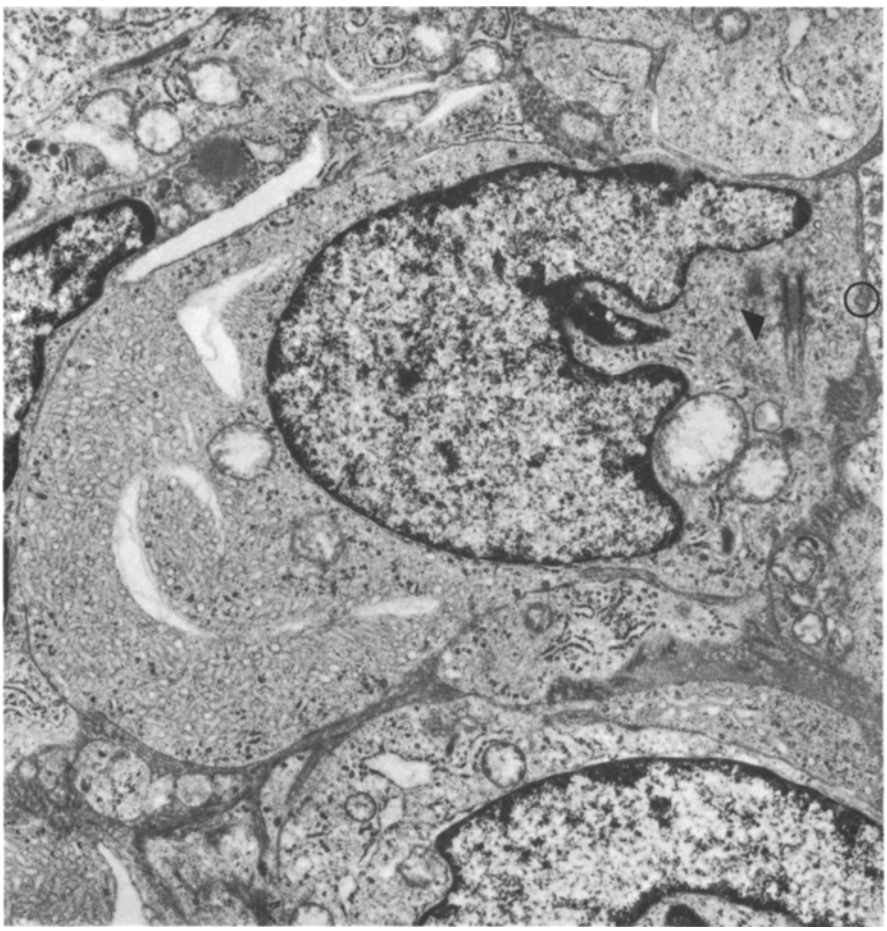

Fig. 6. Low magnification electron micrograph of a luteinized neoplastic granulosa cell with its deeply indented nucleus. Note the great amount of tubular and vesicular agranular endoplasmic reticulum. A cilium (▶) and a micropinocytic vesicle are also present (○). ×9,600

Call-Exner bodies appear mostly as round or slightly angular cavities containing clumps of amorphous material of moderate electron density. Scanty fibrillar structures and cellular detritus are commonly found (Fig. 9). At higher magnification the cell membrane limiting the cavity seems to be thickened in some areas and interrupted at other sites but this could represent an artefact. A few micropinocytic vesicles and some coated vesicles are found but no other specialization of the cytoplasm or cell membrane seems to exist in this apical part of the cell (Fig. 10). The cavity itself is outlined by an obvious basement membrane.

A few tumor cells display conspicuous vacuolization of the cell surface (Fig. 11). The neighboring cells also present numerous micropinocytic vesicles. Another prominent finding in this particular cell type is the presence of partially

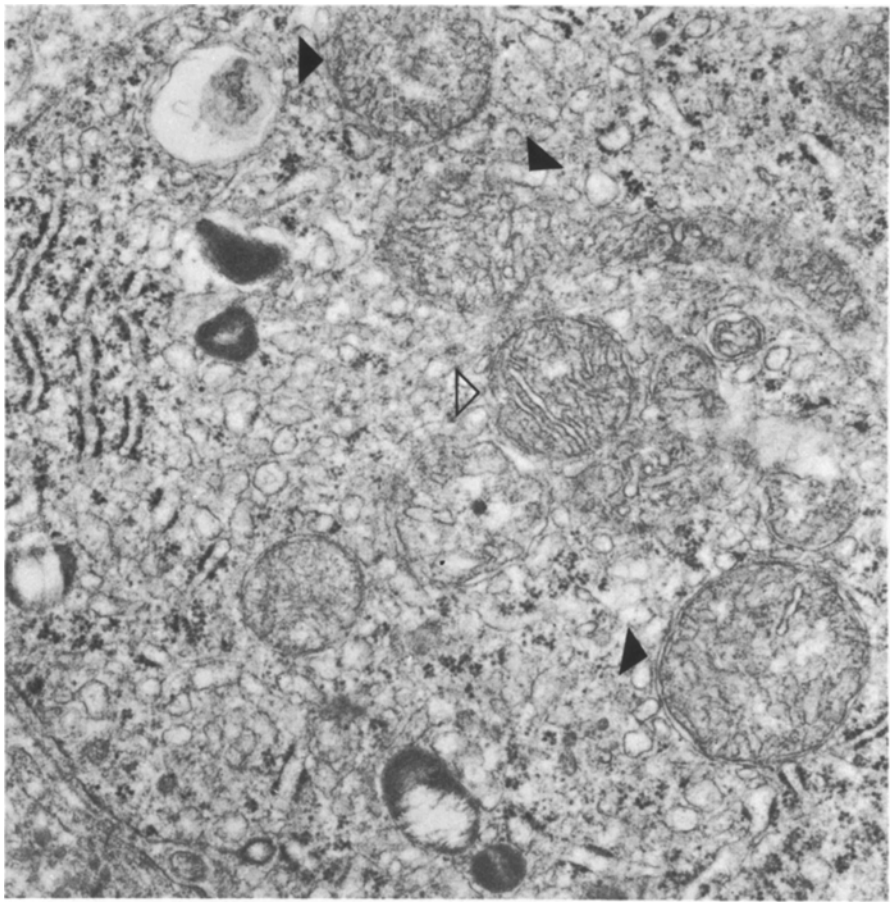

Fig. 7. Cytoplasmic detail of a luteinized tumor cell. The agranular endoplasmic reticulum is strongly developed, the mitochondria are small and mostly display tubular cristae (▶). However in one mitochondria the cristae are lamellar (▷). Some lysosomes, polysomes and short arrays of granular endoplasmic reticulum are also present. ×26,100

agranular endoplasmic reticulum arranged in whorls and broad bundles of filamentous material, the fibrils being thicker than those seen in the other tumor cells. This appearance is strongly reminiscent of immature smooth muscle cells.

A few elongated cells of smaller size are present, displaying a dark nucleus, an electron dense cytoplasm and often numerous swollen mitochondria (Fig. 12). These cells, resembling non-specialized ovarian stroma cells somewhat, may either represent thecal elements or tumor cells with regressive changes. The relation of the tumor cells to blood vessels presents no particularities.

Discussion

The present ultrastructural findings are similar in many ways to those of the previously reported cases. The main submicroscopic features of the non-lutein-

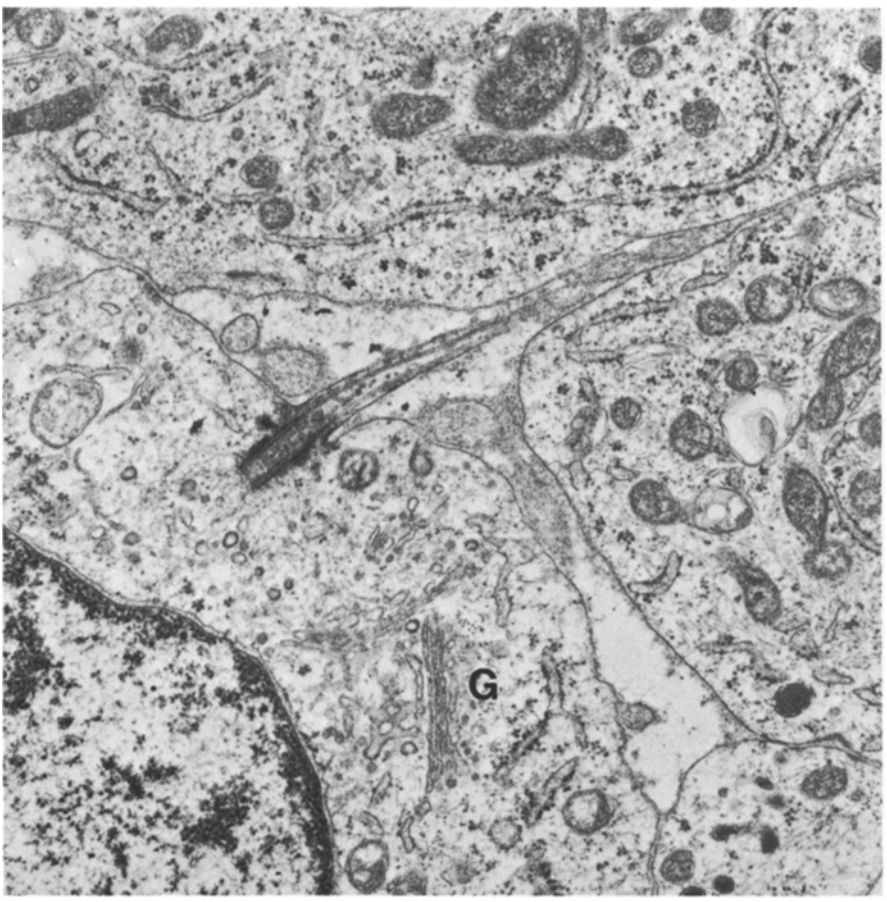

Fig. 8. Three tumor cells, one of them displaying an evident and well-developed cilium projecting in the intercellular space. The mitochondria are somewhat pleomorphic. The partly agranular endoplasmic reticulum is sparse, some microfibrils, microvesicles, a few lysosomes are also seen as well as a well-developed Golgi apparatus (*G*). ×18,800

ized neoplastic granulosa cells are deeply indented nuclei with prominent nucleoli, sparse to moderately developed predominantly granular endoplasmic reticulum, scanty lipids and lysosomes, small round mitochondria with lamellar cristae and numerous microfibrils mostly randomly distributed throughout the cytoplasm. The luteinized cells display an abundant agranular tubular endoplasmic reticulum and mitochondria with tubular cristae.

Gondos (1969) interpreted the marked irregularity of the nuclei, the deep invaginations of the nuclear membranes, the focal aggregation of the chromatin and the prominent nucleoli as morphologic alterations reflecting the malignant character of the metastasizing tumor he studied. In two reported cases of granulosa cell tumors (Gondos and Monroe 1971; Bjersing et al. 1973) the nuclei were found to be round or only occasionally slightly notched. Unfortunately it is

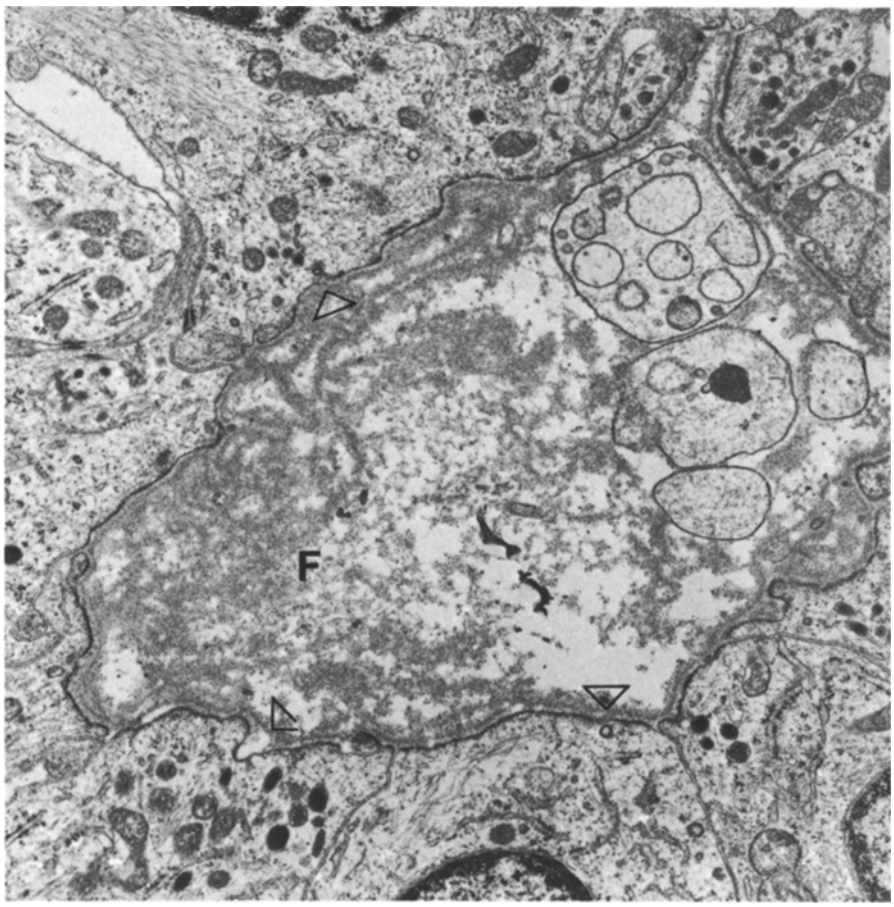

Fig. 9. Call-Exner body at low magnification. The cavity is lined by a basement membrane and contains amorphous and fibrillar material (*F*) as well as cell detritus. The cells surrounding the cavity contain abundant microfibrils, some mitochondria, a few lysosomes and sparse granular endoplasmic reticulum. Some micropinocytic vesicles are present (▷). ×13,800

uncertain whether these tumors actually showed a benign course in the long term, the recurrences appearing, characteristically, many years after removal of the primary tumor. All other authors found, as we did, polymorphic and deeply indented nuclei. Mestwerdt et al. (1977) observed similar nuclei in the normal granulosa cells of secondary follicles. It seems difficult to assign to the intensity of nuclear indentation therefore, an important role in determining the grade of malignancy of the tumor.

Gondos (1969) first observed the presence of rare intranuclear inclusions. Bjersing et al. (1973) also reported similar findings, the granules being mainly located in the nuclei of the thecal type of cell and being reminiscent of so-called perichromatin granules, but often several times larger. We also observed such rare intranuclear inclusions in one case, their significance remaining unknown.

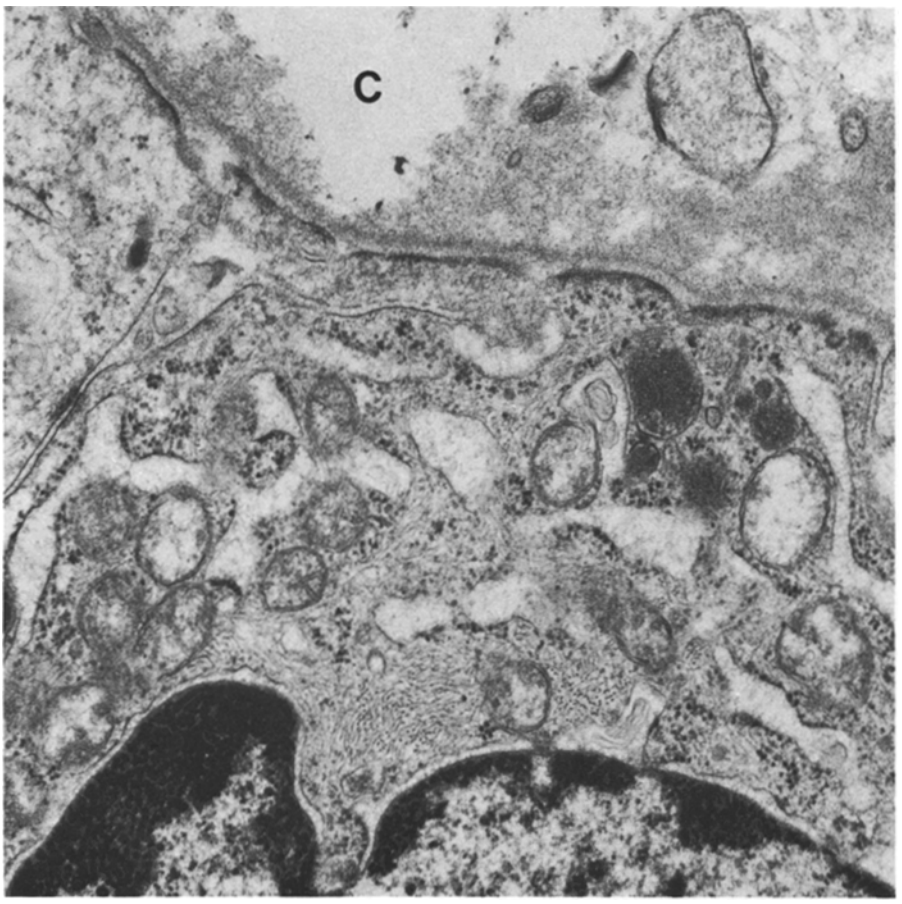

Fig. 10. High magnification electron micrograph of a tumor cell limiting the Call-Exner body. An evident basement membrane is present, the cavity (*C*) contains microfibrils, amorphous material and cellular detritus. The cell membrane seems to be thickened at some areas and interrupted at other sites, this appearance possibly being an artefact. In the cytoplasm, microfibrils, partly disrupted mitochondria and some dilated cisternae of granular endoplasmic reticulum are also seen. ×27,300

Waisman et al. (1975) observed large amounts of thick layered basement membranes. Bjersing et al. (1973) described a basement membrane associated with some collagen fibers surrounding small groups of cells. In the three reported tumors the amount of both basement membrane and collagen fibers showed considerable variation form one area to another. Pedersen and Larsen (1970) obviously found no basement membranes, the tumor cells they observed being scattered in a loose intercellular substance containing few collagen fibers. This last ultrastructural aspect is quite reminiscent of that presented by theca cell tumors (Laffargue et al. 1973).

The presence of abundant fibrillar intracytoplasmic material was a conspicuous finding in all reported cases as well as in the tumors reported here. Pedersen

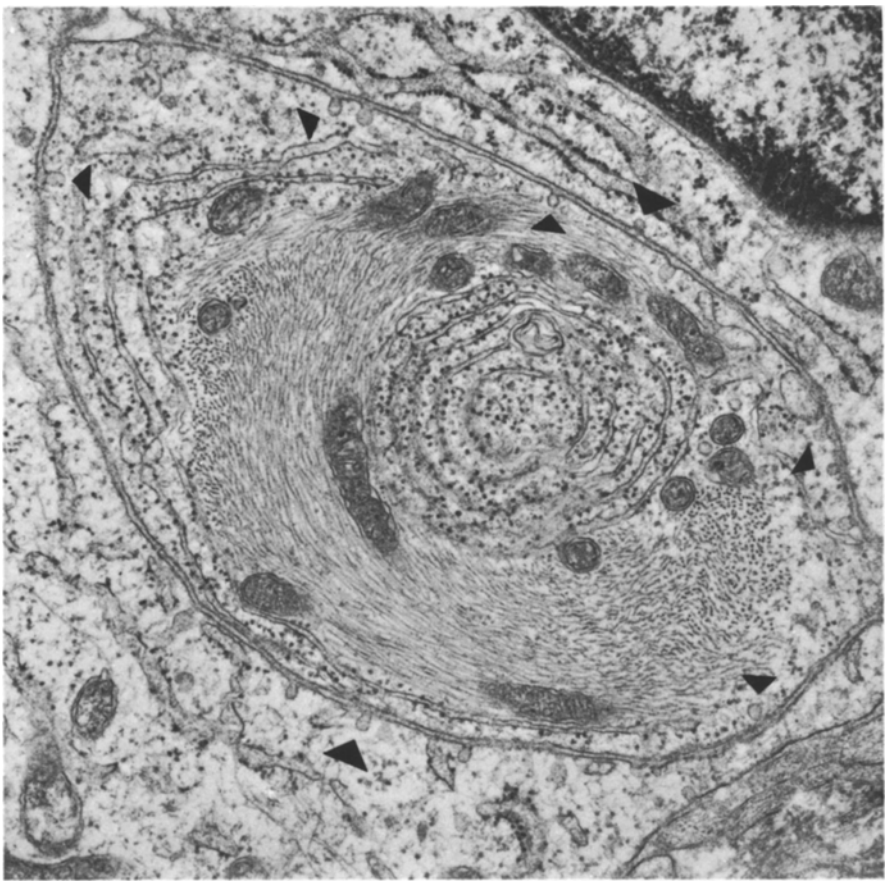

Fig. 11. Tumor cell exhibiting intense vesiculation of its cell membrane (▶), broad bindles of fibrillary material and concentric arrays of endoplasmic reticulum, quite reminiscent of a smooth muscle cell. The neighboring cells also present numerous micropinocytic vesicles (▶). ×26,100

and Larsen (1970) observed them exclusively in the non-luteinized tumor cells. In contrast such fibrils were obviously present in the luteinized cells of Case 2 (Fig. 5C). In the metastases studied by Gondos (1969), this filamentous material was often aggregated in whorls and associated with lipid deposits. It was most abundant in the tumor cells situated around blood vessels. Waisman et al. (1975) described these fibrils as being condensed near the cell borders. Intracellular fibrils are certainly not characteristic for steroid producing cells and their significance in neoplastic granulosa cells remains unknown. Mestwerdt et al. (1977) observed abundant bundles of filamentous material in the normal granulosa cells of primary and secondary follicles but such fibrils were not present in the theca cells of the same follicles. These authors postulate that this filamentous material is synthesized by the granulosa cells and contributes to the formation of the Call-Exner bodies.

The exact nature of the Call-Exner bodies remained in dispute for many

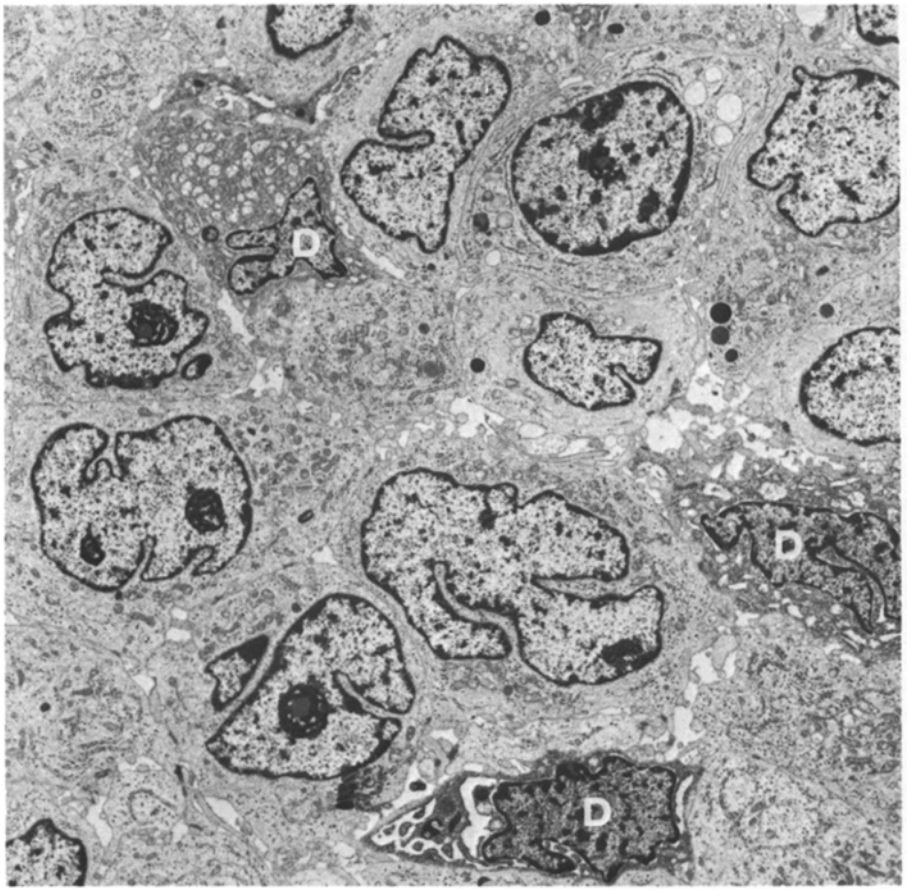

Fig. 12. Low magnification electron micrograph illustrating a few fibroblast- or theca-like cellular elements (D) with electron dense cytoplasm admixed with typical neoplastic granulosa cells. ×4,200

years. The first to describe these structures (Call and Exner 1875) thought that they represented newly formed oocytes developed from granulosa cells. Motta (1965) described the Call-Exner bodies in rabbit ovaries as small cavities filled with a characteristic material similar to the liquor folliculi.

In the Call-Exner bodies they observed, Mestwerdt et al. (1977) found filamentous material of variable density similar to basement membrane lamina and arranged in concentric whorls. These authors postulate that this material constitutes a synthetic and secretion product of the follicular granulosa cells.

MacAulay et al. (1967) and Gondos and Monroe (1971) described the Call-Exner bodies as accumulations of electron dense partly fibrillar material and of cellular fragments and degenerated organelles. Our own findings are similar and are consistent with the generally held idea that these bodies represent areas of liquefaction and sequestration of products of cell degeneration and necrosis.

Gallipi et al. (1976) are the only authors who observed intracellular cavities

into which protrude multiple short microvilli. They interpreted these structures as follicular fluid canaliculi related to the liquor folliculi secretion and associated with the formation of the Call-Exner bodies.

An unusual finding in our three cases is the presence of well-developed cilia in the luteinized and non-luteinized tumor cells. Such cilia have also been observed in Sertoli cells of ovarian androblastomas (Kalderon and Tucci 1973; Ramzy and Bos 1976; Genton 1980). In their ultrastructural study of an ovarian interstitial cell tumor, Merkow et al. (1971) also described the presence of some cilia. Such organelles have been observed in several types of endocrine cells (Bergland and Torak 1969; Dingemans 1969; Klinck et al. 1970). Their function and significance remain to be elucidated as their presence seems difficult to correlate with the endocrine activity of the cell.

The difficulty of correlating the structural appearance of a cell with its functional activity has been emphasized by many authors. In the normal ovary the source of oestrogens is generally thought to be in theca cells, because lipid stains and various other histochemical stains are typically positive in theca and negative in granulosa cells. All these methods are nonspecific. They only permit the localization of certain enzymes that play a role in the biosynthesis of steroid hormones but do not specifically identify the hormones themselves. Electron microscopy provided some evidence that abundant agranular endoplasmic reticulum and mitochondria with tubular cristae are typical for steroid producing cells. These organelles are not present in non-luteinized granulosa cells. However, in vitro studies have shown that granulosa cells are capable of oestrogen production from androgenic precursors (Dorrington et al. 1975).

The tumors in the two postmenopausal women studied here (Cases 1 and 3) obviously produced oestrogens judged by the hyperstimulation exhibited by the endometrium. In Case 2 no curetting material was available for histological examination. A few luteinized cells presenting the typical organelles known to be associated with steroid production were found in Cases 1 and 2. In contrast such cells were not observed in Case 3 although an obvious hyperoestrinism was present. The serum oestradiol level was 34 pg/ml (normal range in the post-menopause: <30 pg/ml). The FSH level was very low, <2 mIE/ml (no: 25–200 mIE/ml) as well as LH, 5.7 mIE/ml (no: 25–100 mIE/ml). It seems therefore very unlikely that only the luteinized granulosa cells are capable of oestrogen synthesis. Another possible explanation could be that luteinized cells were present in the tumor but not in the tissue samples processed either for light- or electron microscopy.

In their immuno-histochemical investigation of granulosa-theca cell tumors, Kurman et al. (1979) were able to demonstrate that both cell types are capable of synthesizing steroid hormones. In their study it appeared that oestradiol is localized mainly in granulosa cells and progesterone in theca cells. These results, however, do not prove the actual synthesis of these hormones in the respective cell types as the method used cannot distinguish biosynthesis from intracellular storage. Based on their own observations and on results of in vitro incubation studies (Fortune and Armstrong 1977), these authors propose the hypothesis that, in the normal ovary, the granulosa cells convert the testosterone produced by the theca cells into oestradiol under the influence of follicle

stimulating hormone. They conclude that the neoplastic theca and granulosa cells are capable of synthesizing a wide range of steroid hormones, thus explaining the virilizing effects of certain granulosa-theca cell tumors (Giuntoli et al. 1976).

In conclusion, there seems to be some lack of correlation between cellular function and ultrastructure. For steroid producing cells, it is possible that the classical organelles (large amounts of agranular endoplasmic reticulum and mitochondria with tubular cristae) are not always necessary. It might be that steroid synthesis is possible via different pathways, some of which possibly occur without the usual morphological expression of such an activity. Immuno-histochemical methods applied to tissues examined ultrastructurally might bring further information about this fascinating problem.

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