Journal of Cellular Biochemistry, Supplement 23:208-218 (1995)

Pathology of Ovarian Cancer Precursors

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Abstract Ninety percent of ovarian cancers in the Western world are epithelial cancers derived from the surface epithelium of the ovary and its inclusion cysts. The so-called surface epithelium is mesothelium that comes to resemble epithelium as it is reflected over the surfaces of the ovaries. At various ages, but particularly in women in the reproductive, menopausal, and postmenopausal age groups, this epithelium migrates into the ovarian stroma to form inclusion cysts. These cysts probably result from a dynamic interplay of surface epithelium and underlying ovarian stroma, but can also develop as a result of periovarian adhesions. There is abundant evidence that their formation is not related to repair of ovulation. It is generally accepted that benign and malignant ovarian epithelial tumors arise from surface epithelium and its cystic derivatives because they both, but particularly the latter, have a potential to differentiate into epithelia similar to those of normal müllerian derivation (tubal, endometrial, and endocervical epithelia) and their tumors resemble those of the fallopian tube, endometrium, and endocervix. Also, both intraepithelial carcinomas and precarcinomatous lesions can be observed in the surface epithelium and its cystic derivatives. These carcinomas may arise *de novo* or as a transformation of pre-existing benign tumors and non-neoplastic lesions of similar derivation. Surface epithelial inclusion cysts have a greater propensity to undergo neoplasia than does the surface epithelium itself. This difference has been recognized for many years because most epithelial ovarian tumors are intraparenchymal, rather than being located on the ovarian surface. More recent evidence includes the immunohistochemical demonstration of various ovarian carcinoma antigens far more frequently in inclusion cyst epithelium than in surface epithelium; and the much more frequent presence of tubal metaplasia in the cyst epithelium than in the surface epithelium. Tubal metaplasia is encountered in non-neoplastic ovaries contralateral to ovarian carcinomas two to three times as frequently as in control ovaries, suggesting that the metaplastic epithelium is more prone to the development of carcinoma that non-metaplastic epithelium. Carcinoma precursors occur in the ovary, as in the cervix and endometrium, but have been reported only rarely because they are easily overlooked and have not been searched for by pathologists.

Key words: Carcinoma, ovary, pathology, precursor lesions, surface epithelium

Surface epithelial carcinomas account for approximately 90% of ovarian cancers in the Western world. These tumors are thought to arise either directly from the surface epithelium of the ovary and its intraparenchymal inclusion cysts or indirectly from benign ovarian lesions of similar derivation. The surface epithelium of the ovary is composed of peritoneal mesothelial cells that come to resemble epithelial cells as they cover the surfaces of the ovaries. Normally these cells appear cuboidal, columnar, or pseudostratified and are separated from the underlying ovarian stroma by a basement membrane (Fig. 1). They are very fragile and, being easily detached by handling the ovary or allowing it to dry, are

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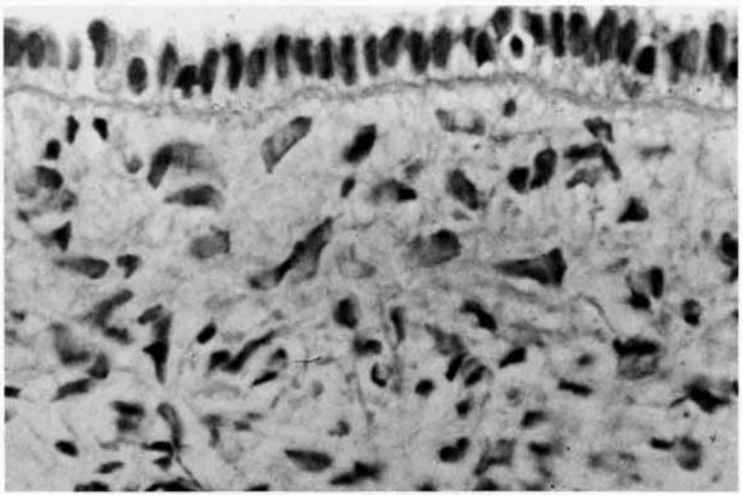

Fig. 1. *Columnar surface epithelial cells separated from underlying stroma by a basement membrane.*

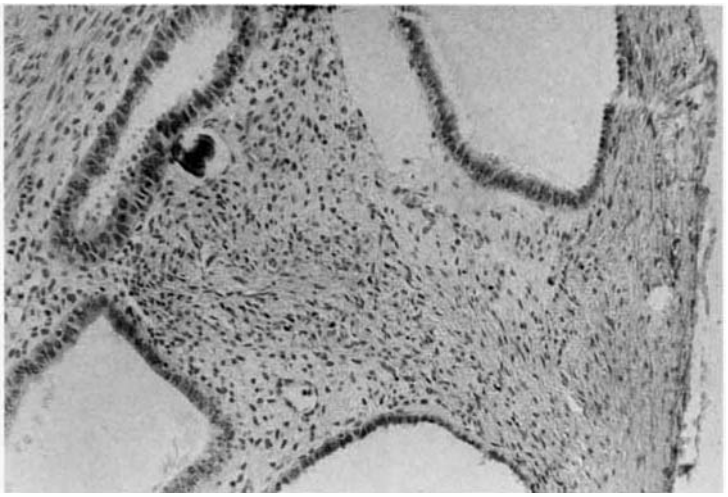

Fig. 2. Four surface epithelial inclusion cysts, one of which lies adjacent to a psammoma body. The surface epithelium has disappeared from the specimen.

commonly absent in human surgical specimens, accounting in part for our scanty knowledge about these cells in relation to the development of epithelial cancers.

In females of all ages, including fetuses [1], but particularly in older women, surface epithelial inclusion cysts are commonly found within the ovarian parenchyma (Fig. 2). The mechanism of their formation is not entirely clear. Some investigators who espouse the incessant ovulation theory of ovarian cancer development believe that these cysts form when surface epithelium grows down into the stigmas of follicles that have undergone ovulation to help repair the ovulatory defect on the ovarian surface [2]. There is strong evidence, however, that this

mechanism is not important in humans. Downgrowth of surface epithelium into ruptured follicles is rarely observed in the human ovary. Also, in one unpublished study of almost 1,000 surgically removed ovaries, we [Tozi-Cruz A, Barriola V, Scully RE, Robboy SJ, unpublished results] found surface epithelial cysts 0.3 cm or greater in diameter one and a half times more often in the ovaries of multiparous than in those of nulliparous women. Such a finding would not be expected if ovulation was important in the formation of these cysts. Also, surface epithelial inclusion cysts have been found almost five times as often in the ovaries of women with polycystic ovarian disease, a disorder characterized by anovulation or infrequent ovulation, as in nonpolycystic ovaries [3]. Two other mechanisms have been proposed for the genesis of inclusion cysts [4]. One is the formation of inflammatory adhesions involving the ovarian surface, when fibrous tissue creates surface epithelial lined spaces between the original ovarian surface and the peritoneal cavity; in some cases, ovarian stroma extends into these adhesions, resulting in the appearance of intraparenchymal inclusion cysts. The second alternative mechanism is an interplay of stromal and epithelial proliferation pinching off portions of surface epithelium to form small cysts. Ovarian stroma is a dynamic tissue that commonly proliferates, particularly in older women; also, the surface epithelium can secrete proteolytic enzymes, which may enable it to penetrate the underlying stroma [2].

What is the evidence that surface epithelium and its inclusions are the sites of origin of surface epithelial carcinomas of the ovary? First, surface epithelium and, to a greater extent, its inclusion cysts, can differentiate into epithelium similar to that of müllerian duct derivatives, that is, the fallopian tube, the uterine corpus, and the uterine cervix; surface epithelial carcinomas of the ovary exhibit the same types of differentiation. Secondly, small carcinomas of the ovary can arise in the surface epithelium (Fig. 3) and its inclusion cysts (Fig. 4) [5]. Thirdly, dysplastic alterations that appear precancerous can arise in those locations as well.

The evidence suggests that surface epithelial inclusion cysts are more prone to the development of carcinoma than the surface epithelium itself. Most early carcinomas of the ovary appear to be confined within the organ without involvement of its surface. Tubal metaplasia (Fig. 5), which Mittal *et al.* [6] and Bell and Scully [unpublished data] found two to three times as often in surface epithelial inclusion cysts of ovaries contralateral to ovaries containing carcinomas as in control ovaries, suggesting that this change

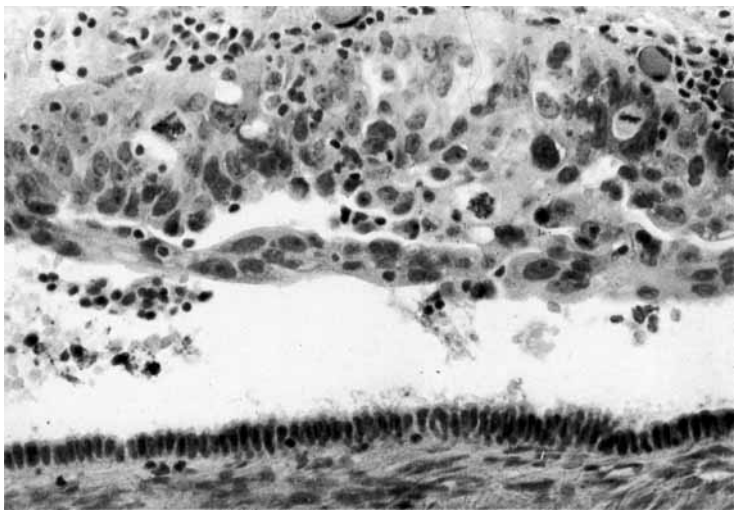

Fig. 3. Microscopic carcinoma replacing surface epithelium lining one surface of a crevice on the external surface of the ovary. The opposite surface of the crevice is lined by normal-appearing epithelium [4, Fig. 15-3, reprinted with permission].

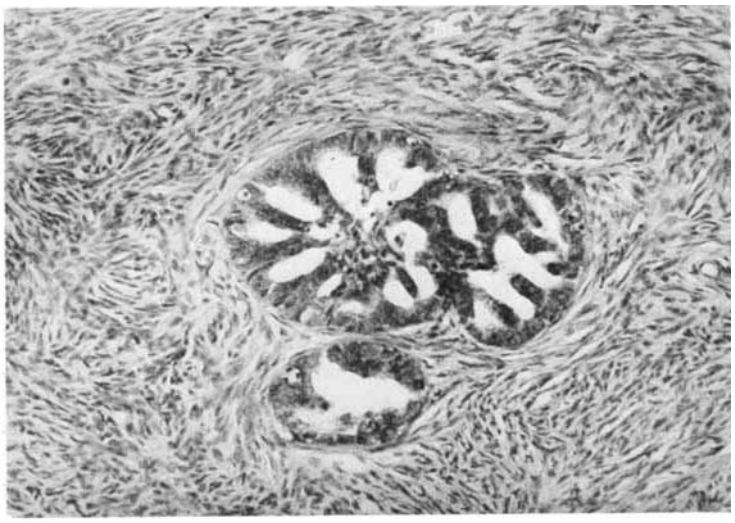

Fig. 4. Carcinoma arising in surface epithelial inclusion cysts [4, Fig. 15-5, reprinted with permission].

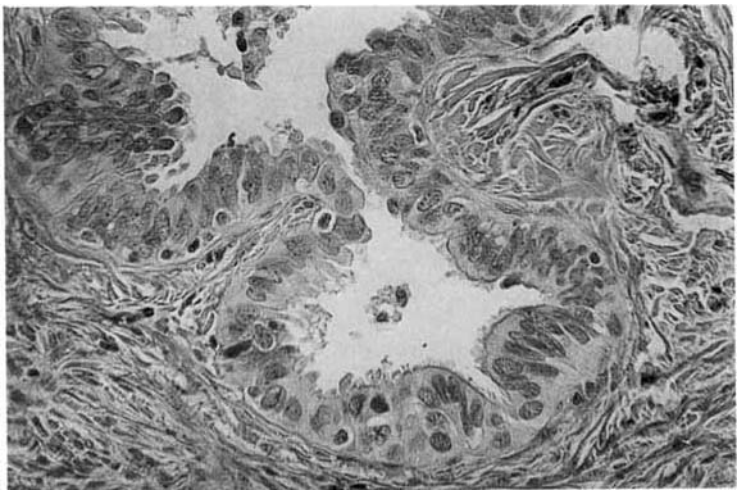

Fig. 5. Tubal metaplasia in a surface epithelial inclusion cyst. The ciliated epithelium is mildly dysplastic.

may be a remote precursor of ovarian cancer, is observed in surface epithelial inclusion cysts approximately 10 times as frequently as in surface epithelium itself [3]. Finally, several ovarian carcinoma tumor markers (CA-125, CA19-9, placental-like alkaline phosphatase, human milk fat globule protein) can be identified immunohistochemically significantly more often in the epithelium of surface epithelial inclusion cysts than in the surface epithelium itself [7–10].

The extensive literature on precancerous lesions of the female genital tract in general does not extend to precarcinomatous lesions of the ovary [11,12]. Such lesions are not absent, but the above-mentioned fragility of the surface epithelium causes it to disappear from surgical speci-

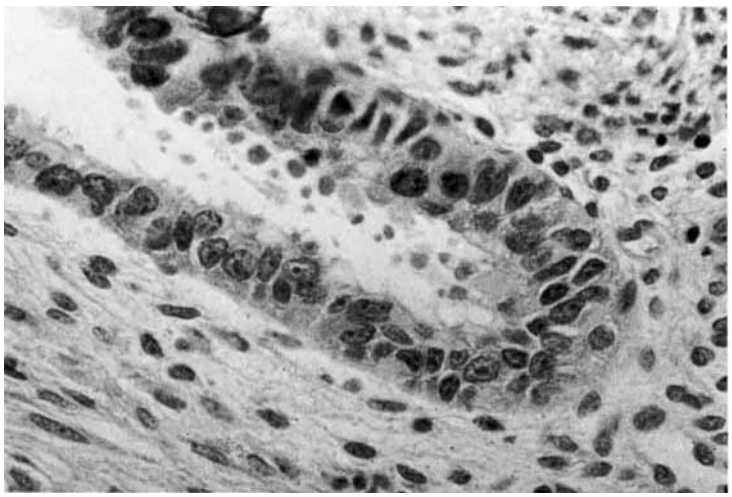

Fig. 6. Marked dysplasia of one of the surface epithelial inclusion cysts shown in Figure 2.

Fig. 7. Surface epithelium of ovary pinched off by thick, dense fibrous adhesion (closed arrow). A focus of epithelial atypicality is indicated by open arrow.

mens of ovary. Also, pathologists fail to examine surface epithelial inclusion cysts with care. Precancerous lesions can occasionally be identified by meticulous scrutiny of ovarian epithelium. A study of 14 cases of early ovarian cancer by Bell and Scully [5] found atypia of uninvolved surface epithelium or its inclusion cysts in 11 of the 13 cases in which such epithelium could be identified in the available slides. We have also found abnormalities of the surface epithelium and its inclusion cysts in ovaries that contained no carcinomas. In those cases where the abnormality was confined to an intraparenchymal inclusion cyst (Fig. 6), the lesion had been removed by oophorectomy with no possibility of evaluating its biological potential. In one case, however, tubal

metaplasia with severe dysplasia was present on the surface of the ovary in a tiny area covered by fibrous adhesions that had been overlooked by the examining pathologist (Figs. 7 and 8). The patient returned to the hospital five years later with a disseminated serous carcinoma involving the peritoneum, presumably having arisen from residual dysplastic epithelium or undetected carcinoma on the ovarian surface. Obviously, much more investigation of the surface epithelium and its inclusion cysts, using both routine and emerging techniques, will be necessary to better understand the evolution of surface epithelial carcinomas.

Surface epithelial cancers that appear to arise directly from the surface epithelium or its inclusion cysts have been referred to as *de novo* carcinomas of the ovary [5]. The ultrasonic detection of apparently benign, thin-walled, ovarian cyst adenomas in women being screened for ovarian cancer has focused attention recently on whether some epithelial cancers arise from pre-existing benign epithelial tumors or non-neoplastic processes rather than *de novo*. There is circumstantial evidence that benign epithelial tumors may become malignant. In an epidemiologic study, Bourne *et al.* [13] found that the prevalence of benign epithelial tumors in first and second-degree relatives of patients with ovarian cancer was five times greater than in controls without relatives having ovarian cancer, suggesting a relation between the two types of tumor. Also, ovarian carcinomas occur at an average age 10–15 years earlier than benign tumors of the same cell type [4]. To address this problem more directly, investigators from the University of Kentucky [14] retrospectively examined a series of mucinous and serous carcinomas, searching for benign-appearing epithelium in the involved ovaries. They found such epithelium in 28 of 31 mucinous carcinomas (90%) and in 22 of 39 serous carcinomas (56%). A similar retrospective study by G.M. Abu-Jawdeh and me [17] in our laboratory involved 189 epithelial cancers occurring in 156 patients; we identified benign epithelium in 74% of mucinous carcinomas, 46% of endometrioid carcinomas, 39% of clear cell carcinomas, 31% of mixed serous-transitional cell carcinomas, and 15% of pure serous carcinomas (Figs. 9 and 10). The benign epithelium accounted for over 25% of the total epithelium in 48% of the mucinous carcinomas, 33% of the endometrioid carcinomas, 32% of the clear cell carcinomas, and none of the serous carcinomas and mixed serous and transitional cell carcinomas. Except for patients with endometrioid carcinoma arising in association with endometrioid adenofibroma, the patients with carcinomas of

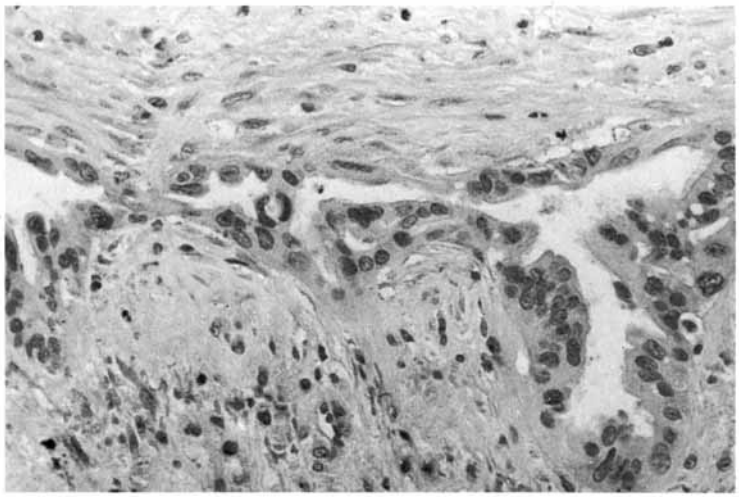

Fig. 8. Close-up view of focus of surface epithelial atypicality shown on Figure 7. The atypical epithelium is ciliated and of tubal type.

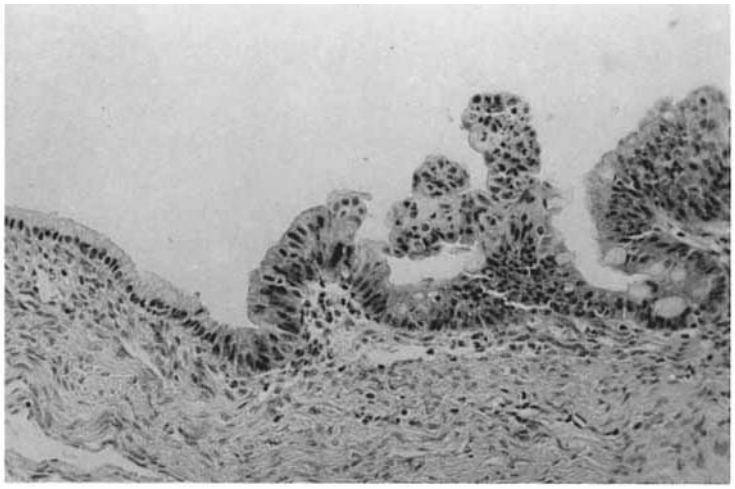

Fig. 9. Benign-appearing epithelium (left) undergoing transition to malignant epithelium (right) in mucinous cystic tumor.

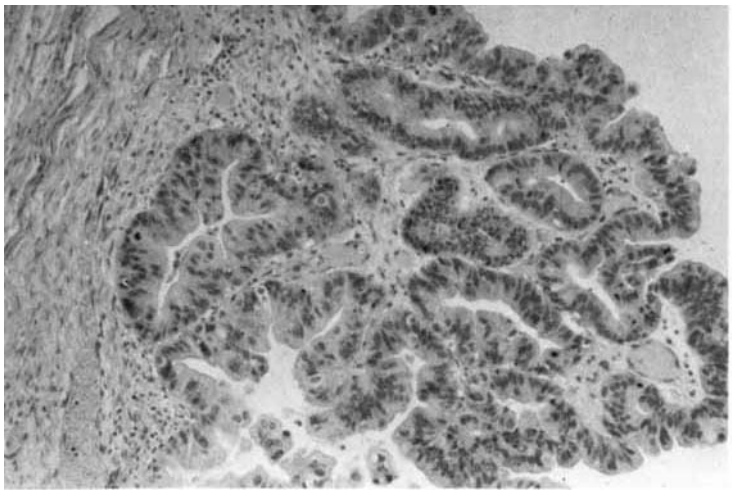

Fig. 10. Central portion of carcinoma, the edge of which is illustrated in Figure 9.

each subtype in whose slides benign-appearing epithelium was identified were 7–16 years younger on the average than patients in whose tumors benign-appearing epithelium could not be identified. This finding suggests that the epithelium of benign epithelial tumors may be more prone to the development of carcinoma than the surface epithelium and its inclusions.

There are difficulties, however, with studies of this type, particularly when they are retrospective. The problems are most obtrusive when one is evaluating the association of mucinous carcinomas with mucinous cystadenomas. What appears to be a transition from benign to malignant mucinous epithelium can be duplicated indistinguishably by metastatic mucinous adenocarci-

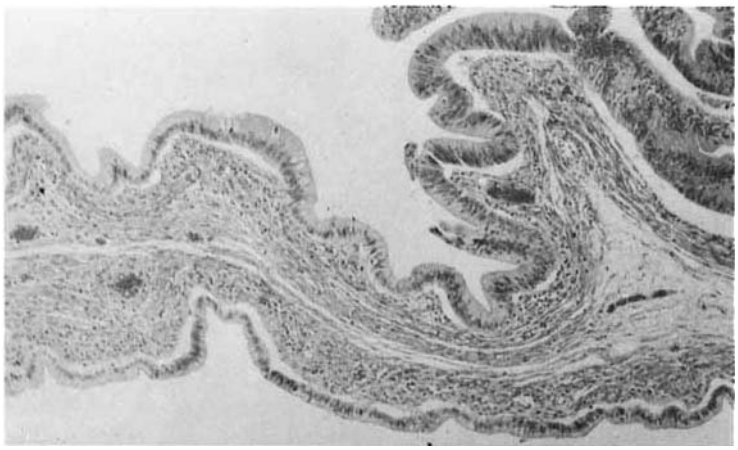

Fig. 11. Transition from benign-appearing epithelium (left) to malignant epithelium in cystic metastatic adenocarcinoma from large intestine to ovary [23].

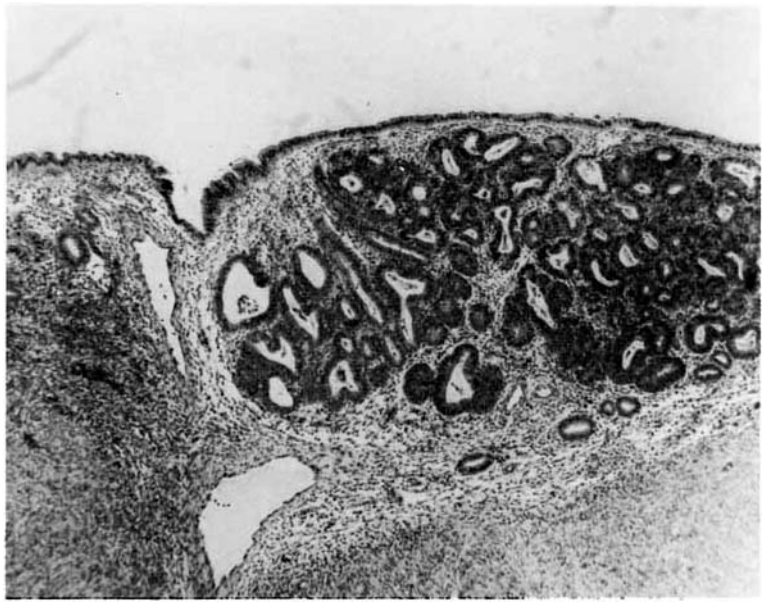

Fig. 12. Focus of severe complex atypical hyperplasia (carcinoma *in situ*) in stroma of endometriotic cyst.

noma from the colon and pancreas in ovary (Fig. 1) [15]; raising the question whether the benign-appearing epithelium in primary mucinous carcinomas is truly benign, or is a malignant epithelium that has matured to the extent that it is no longer recognizable as such on routine staining. The most convincing evidence of a transition from benign epithelium to carcinoma is found in endometrioid and clear cell carcinomas with a background of endometriosis. In such cases one can be certain the the endometriotic cyst from which the carcinoma arose is benign because it is accompanied by endometriotic stroma, the presence of which cannot be explained by maturation of carcinoma cells. The very high association of endometrioid and clear

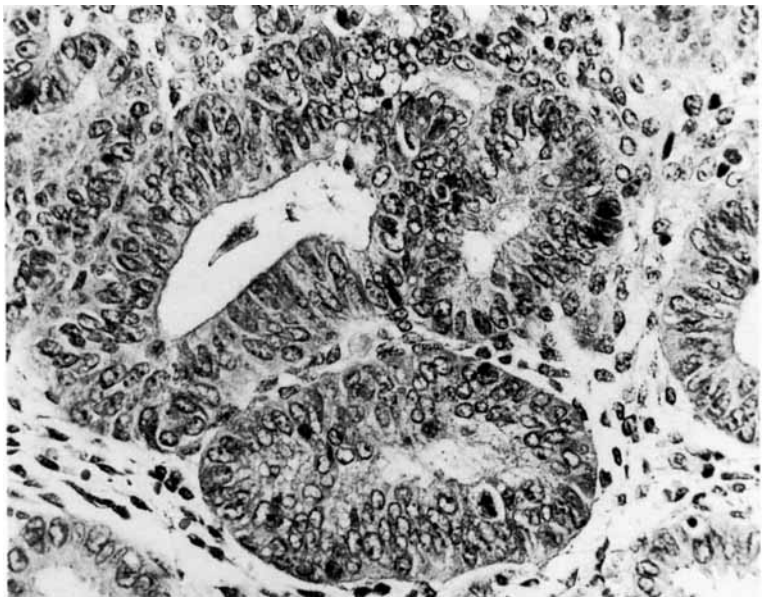

Fig. 13. High-power view of lesion shown in Figure 12. The glands are lined by malignant-appearing epithelium but are not back-to-back.

cell carcinomas with endometriosis contrasts with the very low association of serous and mucinous carcinomas with that disorder [16], indicating that endometriosis is a precancerous lesion for those two types of carcinoma. Also, the entire spectrum of precancerous hyperplastic lesions observed in the endometrium can also be encountered in endometriosis (Figs. 12 and 13).

Although the two studies referred to above [16,17] suggest that benign epithelial lesions are precancerous, much more investigation is needed to prove such an association. Prospective studies must pay particular attention to identifying benign-appearing areas in carcinomas and to studying the transitional zones between those areas and obvious malignant areas. Molecular genetic studies will probably be required to confirm whether the benign-appearing epithelium is truly benign or malignant. Recent studies by Zweizig *et al.* [17] have begun to approach this problem. Those investigators found identical allele deletions on the short arm of chromosome 11 in both benign-appearing and obviously malignant epithelium within an ovarian cancer.

Very little is known about precancerous lesions of sex cord-stromal and germ cell tumors. Granulosa cell tumors account for approximately 5% of ovarian cancers. A recent study [18] reports the frequent finding of apparent granulosa cell and Sertoli cell tumorlets in atretic follicles during pregnancy, possibly due to the FSH activity of chorionic gonadotropin (Fig. 14). The relation of these lesions to clinically evident granulosa cell tumors and Sertoli cell tumors is presently only speculative. We are not aware of epidemiologic investigations of these relatively rare tumors; therefore, their relation to parity and gravidity remains unknown. Because of the demonstrated role elevated gonadotropin levels play in the development of granulosa cell tumors and other sex cord tumors in animals [19], and because preliminary reports suggest that granulosa cell tumor incidence increases in women exposed to ovulation-inducing drugs without becoming pregnant [20], the tumorlets of pregnancy may possibly be early stages of clinically evident tumors. Nevertheless, the higher granulosa cell tumor incidence in postmenopausal women and the confinement of microscopic tumors of this type to the ovarian stroma suggest an origin from stromal cells rather than directly from granulosa cells in follicles. Embryologists do not

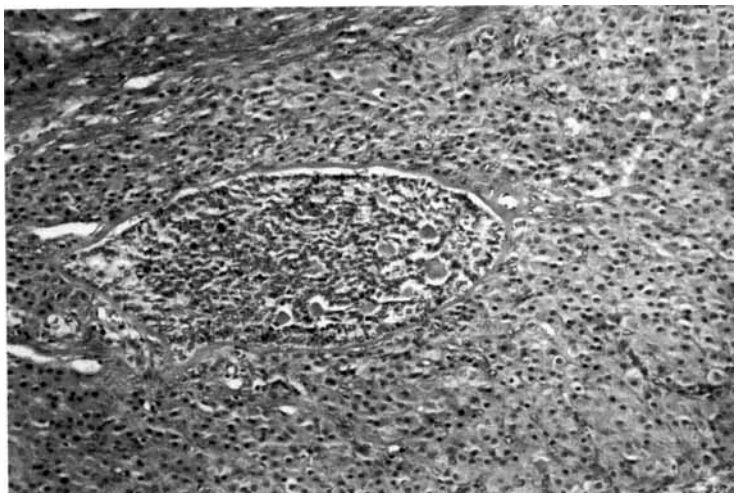

Fig. 14. Granulosa cell tumorlet containing Call-Exner bodies (small cavities filled with hyaline material) in atretic follicle, surrounded by thick layer of luteinized theca interna cells.

agree about the origin of granulosa cells in the normal ovary, complicating attempts to understand the origin of tumors of these cells.

Except for primitive germ cell tumors in phenotypically female patients with developmental abnormalities of their gonads, no precancerous lesions of the ovary have been identified [4]. In phenotypically female patients with abnormal sexual development and a karyotype containing Y chromosome material, gonadoblastomas and testicular intratubular germ cell neoplasia unclassified have been identified as precancerous lesions [4], but only a small minority of primitive germ cell tumors occur in patients with these disorders. Intratubular germ cell neoplasia unclassified has been found in a high proportion of cases of germ cell neoplasia in the testis [21]; however, intrafollicular germ cell neoplasia has not been identified in association with ovarian primitive germ cell neoplasms. When ovarian primitive germ cell tumors are encountered in microscopic form, they are characterized by the presence of small foci of tumor lying within the ovarian stroma with no clue to their site of origin—adding nothing to our understanding of their histogenesis.

Though we lack knowledge of precursor lesions in cases of primitive malignant germ cell tumors of the ovary, the dermoid cyst is known to be a benign precursor of many varieties of the relatively rare adult-type germ cell cancers, particularly squamous cell carcinoma, which accounts for approximately 80% of these tumors [4]. The age incidence of these cancers reaches its height in the fifth to seventh decades, in contrast to the age incidence of dermoid cysts from which they arise, which reaches its peak incidence in the third to fifth decades; this provides strong evidence that the latter tumors are precursors of the former. The frequency of finding a cancer in a dermoid cyst rises with age to 15% over 70 years of age [22]. The gynecologist should strongly suspect the possibility of malignant change in dermoid cysts in older women. In addition to invasive squamous cell carcinoma in a dermoid cyst, squamous cell carcinoma *in situ* has occasionally been observed, attesting to the precursor nature of this benign tumor.

In conclusion, much is known, and yet much remains to be learned, about the origin of the most common forms of ovarian cancer; even less information is available regarding the origin of granulosa cell tumors and primitive germ cell tumors of the ovary. Much greater attention must be paid by pathologists in this area to identify precancerous lesions with careful investigation of ovarian changes in regions not directly involved by cancer.

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