Ovarian Sex Cord–Stromal Tumors

Reflections on a 40-Year Experience With a Fascinating Group of Tumors, Including Comments on the Seminal Observations of Robert E. Scully, MD

Robert H. Young, MD, FRCPath

• ***Context.***—**This year being the 60th anniversary of the publication of the excellent book *Endocrine Pathology of the Ovary* by John McLean Morris, MD, and Robert E. Scully, MD, the writer reflects on that work and in particular the remarkable contributions of its second author to our knowledge in this area.**

Objective.—**To review ovarian sex cord–stromal tumors.**

Data Sources.—**Literature and personal experience.**

Conclusions.—**The essay begins with remarks on the oftentimes straightforward stromal tumors of the ovary because the commonest of them, the fibroma, dominates from the viewpoint of case numbers. Then, the sclerosing stromal tumor and the peculiar so-called luteinized thecomas of the type associated with sclerosing peritonitis are discussed in greater detail and their wide spectrum is illustrated. Brief mention is made of 2 rare neoplasms: the ovarian myxoma and signet-ring stromal tumor. Discussion then turns to the more recently recognized intriguing tumor tentatively designated *microcystic stromal tumor* and the commonest malignant tumor in this entire family, the so-called adult granulosa cell tumor, which despite its name may occasionally be seen in young individuals. The second variant of granulosa cell tumor—that which usually, but not always, occurs in the young—the so-called juvenile granulosa cell tumor, is then discussed. In the section of Sertoli-Leydig cell tumors, particular attention is focused on unusual tumors with heterologous elements and the remarkable so-called retiform tumors, which have a predilection for the young, often have distinctive gross features, and exhibit slitlike spaces and papillae. The essay concludes with consideration of the sex cord tumor with annular tubules.**

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I am delighted to contribute an essay to this symposium based on a meeting that was a most pleasant experience, and furthermore it is always enjoyable to write on a group of neoplasms surely as morphologically intriguing as any. As the meeting was held in New Jersey, it brought back memories of the late 1970s when my association with Robert E. Scully, MD,[1] was just beginning and I remember him preparing a seminar, the 29th annual seminar of the New Jersey Society of Pathologists, in November 1979. I could not find a record of the specific diagnoses for the cases he presented but as the seminar was on ovarian tumors, doubtless he included 1 or more from the sex cord–stromal group, always among his favorites for reasons noted below. Working on these tumors always happily reminds me of my early years under Dr Scully's tutelage when I had the honor and privilege of not only studying with that master of diagnostic pathology but also "plundering" for academic purposes his group of sex cord–stromal tumors, which had been not greatly used for publications as of that time. The latter is perhaps surprising because relatively early in his career he had coauthored with John McLean (Jack) Morris, MD, a textbook titled *Endocrine Pathology of the Ovary*,[2] which had focused very largely on these neoplasms and resulted in his being sent many in consultation. He was, however, not of the "publish or perish" school and enjoyed studying the cases, contributing to the care of individual patients, and waiting for significant numbers to accumulate such that he could make meaningful observations concerning both overall morphology and the prognostic implications that they might have. Dr Morris, a gynecologist, had his own distinguished career.[3] He trained at the Massachusetts General Hospital (MGH) in the late 1940s and in the early 1950s served as assistant in surgery under the chief of gynecology, Dr Joe V. Meigs, during which time his liaison with Dr Scully likely began, although it may have been after Dr Morris was recruited to join the faculty of Yale University Medical School in 1952; he ultimately served there as chief of gynecology for several decades. During his MGH years he worked on the material that resulted in a major article published in 1953, the first definitive description of testicular feminization.[4] Dr Scully assisted with the pathology in that article. Appropriately, many years later Dr Scully coauthored, based largely on his referral material, what is as of today still the definitive article[5] on the pathology seen in

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From the James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

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Corresponding author: Robert H. Young, MD, FRCPath, James Homer Wright Pathology Laboratories, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA 02114 (email: rhyoung@partners.org).

cases with that disorder, and it reflected his interest in and complete mastery of the pathology affecting patients with disorders of sexual development.

As this essay appears on the 60th anniversary of the book Dr Scully coauthored (which I will refer to from here on as "Morris and Scully" as Dr Scully did himself[2]), I endeavor to make this contribution different from others by making it a somewhat personal recounting of my own experience with these tumors and also, to a degree, his, based on my awareness of how his knowledge of certain entities developed. As the title of this essay indicates, and being cognizant of the contributions of others, we are all greatly indebted to him for what we know about these neoplasms. One of them actually provided an initial link between us. Towards the end of my initial rewarding experience in pathology at Trinity College Dublin, a case of sex cord tumor with annular tubules came my way and when I moved to the MGH in early January 1977, I brought it with me to share with Dr Scully. Of course to me the case was remarkably unusual, but he had seen so many by that time that when I shared the case with him I remember being struck by his somewhat matter-of-fact attitude. When I became closer to him during my subsequent fellowship with him, and later years, it became obvious to me why that was; he had seen such a stunning number of unusual cases, often in great number, that it took something truly remarkable for him to be particularly excited. Nonetheless, my encountering that case provided a fortuitous opportunity for an interchange with him early in my training and indeed later an article on that entity with him ensued, as will be noted.

By the late 1970s the number of cases of sex cord–stromal tumors in Dr Scully's collection was many hundred and I was fortunate enough to have them made available to me when a fellowship with him in gynecologic pathology began in July 1979. My first article related to these neoplasms was not on them as such but rather on an aspect of their differential diagnosis, which comes about when Krukenberg tumors with a tubular pattern mimic Sertoli-Leydig cell tumors.[6] That was followed the next year by an article in which I played a greater role, one emphasizing the now very well-known propensity for endometrioid carcinomas to mimic sex cord–stromal tumors.[7] The first 2 articles focusing specifically on sex cord–stromal tumors were worked on and published at around the same time, 2 on the remarkable phenomenon whereby Sertoli-Leydig cell tumors are associated with heterologous elements of various types.[8,9] That entity, and indeed Sertoli-Leydig cell tumors overall, link Dr Scully with another giant of pathology, Dr Robert Meyer,[10] who several decades earlier had written on tumors with heterologous elements and additionally proposed the first subclassification of Sertoli-Leydig cell tumors that had prognostic relevance. Although others have contributed significantly to the field of gynecologic pathology,[11,12] I am confident no other workers have authored more papers of substance than the 2 great investigators just noted.

Although I have written about these tumors extensively before, both in peer-reviewed articles and various chapters in books, given their diversity one continually sees examples that cause further reflection on their vast array of microscopic features and ability to overlap with the appearance of other neoplasms.[13] This also sometimes causes one to reevaluate previously held reflections about these neoplasms. One of many facets that makes them further intriguing is their occasional association with hormonal manifestations and even rarely, other interesting clinical aspects, which will be noted when appropriate. Furthermore, inasmuch as many of them occur in the young, they open up for our consideration, to a degree here, a topic considered in greater detail elsewhere, namely, ovarian tumors in the young,[14] which for the most part elicit different differential diagnostic considerations than tumors in the older patient.

I begin with the tumors that, in some cases at least, are the most simple in this overall category, the stromal tumors (Figure 1), before addressing issues related to those of pure sex cord and then mixed sex cord and stromal type, a more microscopically heterogeneous group of neoplasms. However, stromal tumors themselves, including one of the best known ovarian tumors, the thecoma, have their own intriguing aspects, some of which have prompted recent contributions to the literature. I will be sparing, because of space constraints, with referencing here for 2 reasons. First of all, the topic is thoroughly referenced, up to the time of its publication in Dr Scully's fascicle[15] and older references are easily obtainable there. Newer references can be found using so-called search engines. When writing on this topic, space constraints often restrict the number of pictures that can be used, more than the writer would wish. On this occasion I am fortunate that the editor has allowed me a significant amount of space for illustrations, which I appreciate, as it enables one to do better justice to the appearances encountered and to a lesser degree, the differential considerations that arise, than is sometimes the case.

FIBROMA, INCLUDING CELLULAR FIBROMA

In most cases fibromas are a mundane diagnosis and the usual example needs little comment. The typical firm white cut surface is well known but variations are seen. Edema may result in a soft consistency, and microscopic examination in these cases shows prominent intercellular edema, which sometimes erroneously results in the diagnosis of thecoma. Edema, when conspicuous, may be associated with the well-known Meigs syndrome, named after the eminent surgeon-gynecologist who was chief of gynecology at the MGH in Dr Scully's early years at the hospital and the individual to whom "Morris and Scully" was dedicated.[2] A less common clinical association is with the basal cell nevus syndrome (Gorlin syndrome). The pathologist may occasionally earn plaudits by being the one who causes the syndrome to be unearthed by encountering bilateral calcified fibromas, particularly in a young person, before the clinical features of the syndrome are evident, and prompting evaluation that discloses 1 or more other manifestations of the syndrome. Occasional fibromas undergo cystic degeneration. This may suggest a surface epithelial stromal tumor until microscopic examination shows that the cysts are not lined by epithelial cells. Hyaline plaques, generally considered more typical of thecomas, are occasionally conspicuous in fibromas. Rare fibromas contain peculiar, often cytoplasmic, hyaline globules.[16]

Although most fibromas have a relatively uniform pattern throughout, occasional examples have a more heterogeneous morphology with normocellular and edematous or hypercellular areas alternating with each other. When vascularity is prominent, as it occasionally is, the misdiagnosis of sclerosing stromal tumor may result owing to the perception that the varied appearance is the pseudolobular pattern so typical of sclerosing stromal tumor. Although

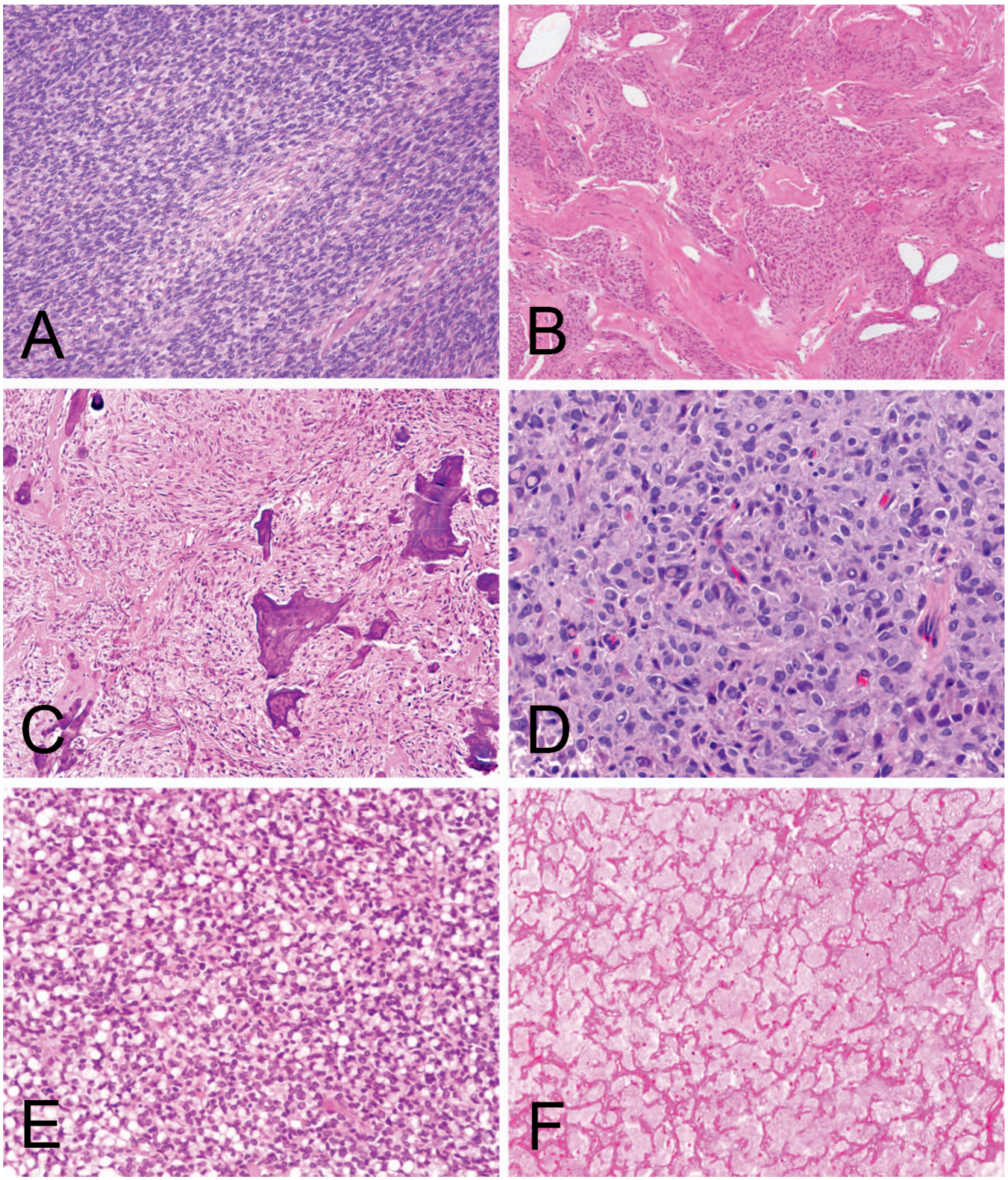

Figure 1. *Stromal tumors. A, Cellular fibroma. Typical fascicles of spindle cells. B, Thecoma. Low-power view showing classic hyaline plaques. C, Thecoma with calcification from a young patient. D, Thecoma. Typical appearance of cytoplasm. Ill-defined cytoplasmic membranes and pale gray cytoplasm. E, Signet-ring stromal tumor. Numerous signet-ring cells whose cytoplasm is empty punctuate a cellular neoplasm. F, Myxoma. Note conspicuous myxoid matrix.*

some fibromas may contain luteinized cells, they do not have the particular association with fibroblasts so characteristic of the sclerosing stromal tumor and do not show the vacuolization typical of the lutein cells in the sclerosing lesion. Fibromas with lutein cells were formally referred to as *luteinized thecomas*[17] but that term has fallen out of favor. The ubiquitous presence of lutein cells in so many ovarian tumors requires only a brief comment particularly if it correlates with some clinical finding of note such as androgenic manifestations.[18]

Problems in the differential diagnosis related to a fibroma mimicking another neoplasm are relatively limited and more often one has a circumstance in which a neoplasm of a completely different sort may mimic a fibroma and potentially be misdiagnosed as such, particularly if the notorious sampling hazard of ovarian tumor evaluation contributes to the issue. Granulosa cell tumors may be in the differential of standard fibromas, as the former may have prominent fibromatous areas, and it would be possible at the time of frozen section of a granulosa cell tumor to sample a zone that morphologically would be entirely appropriate to characterize as fibroma. In such cases one of the most important aspects of ovarian tumor evaluation, awareness of gross characteristics, can be important because most granulosa cell tumors look somewhat different from the usual fibroma and that should always be reflected upon. A historically interesting issue is of course the potential for the Krukenberg tumor to mimic a fibroma, including the cellular variant, and such was the cause of Krukenberg's initial misinterpretation of the tumors as mucinous fibrosarcomas. After his misinterpretation had been corrected, cases were still occasionally encountered in which zones of a Krukenberg tumor were so fibroma-like that a misdiagnosis of fibroma was made, and this hazard is particularly notorious at the time of frozen section. The clinical background and again gross characteristics, such as frequent bilaterality of Krukenberg tumors, should be considered in conjunction with the mere morphology. Another metastatic tumor, endometrial stromal sarcoma, may also have significant zones with a fibromatous morphology when the sarcoma is one of the recently emphasized variants with a fibrous character. This contributed to some of the issues in differential diagnosis in a series of endometrial stromal sarcomas metastatic to the ovary that we reported some years ago, in conjunction with an overall study of sarcomas of various types that had spread to the ovaries.[19] Other esoteric issues in the differential diagnosis of fibroma occasionally come up. For example, I recently saw a microcystic stromal tumor that was much more fibromatous than the usual example, and sizeable regions in isolation would have been interpreted as a fibroma, but scattered microcystic zones of course altered the interpretation. Occasional fibromas are quite vascular, which prompts brief mention of the potential differential diagnosis with solitary fibrous tumor, rare examples of which have been primary in the ovary.[20] The classic features of solitary fibrous tumor, particularly dilated, branching, so-called staghorn-like blood vessels, should bring that neoplasm to mind and prompt staining for STAT6, which should be discriminatory in most cases although it should be noted that in the study just cited, 5% of tumors in the fibroma-thecoma category (evaluated for comparison) showed some weak focal staining for STAT6.

The facet of fibromas that most often results in a request for a second opinion is intense cellularity (Figure 1, A), and the topic of cellular fibromas has been the subject of some interest in the literature during the past few decades dating back to an important article by Prat and Scully[21] on the distinction of cellular fibromas from fibrosarcomas. In that series, a mitotic rate cutoff of 3 mitotic figures per 10 high-power fields aided in separation of cellular fibromas from fibrosarcoma. Subsequently, the pathology community, to a large degree, emphasized too much the mitotic activity aspect of that article and overlooked somewhat that of the 6 fibrosarcomas, 2 had moderate and 4 marked nuclear pleomorphism, in contrast to, on average, much less cytologic atypia in the cellular fibromas. A subsequent report of a larger experience pointed out that if one focused only on mitotic activity in these cases one would erroneously place tumors likely to have a benign outcome in the fibrosarcoma category.[22] Tumors with 4 or more mitotic figures per 10 high-power fields were generally clinically benign and were accordingly categorized as "mitotically active cellular fibromas." The diagnosis of fibrosarcoma should be made cautiously in part because most cellular fibromatous tumors do not have the overall characteristics of fibrosarcoma by standard histologic criteria. Cellular fibromas, even those that are intensely cellular, usually have alternating cellularity in contrast to uniform intense cellularity of most fibrosarcomas and as noted above, less atypia. Although one should, of course, endeavor to place a tumor appropriately in either the cellular fibroma or fibrosarcoma category, it is also worth pointing out that an occasional tumor that is histologically deemed only a cellular fibroma can be associated with local recurrence or even implantation, particularly if the tumor is associated with adhesions, is large, ruptured, or combinations thereof.

The differential diagnosis of cellular fibroma versus adult granulosa cell tumor may be problematic, as some granulosa cell tumors have a diffuse growth of cells that are somewhat spindled (so-called sarcomatoid granulosa cell tumor), and only focal hints of epithelial differentiation may be a subtle clue to the diagnosis. Of course, other regions of well-sampled tumors may show more overt epithelial features, but in some tumors this is relatively limited. This is one area in which a reticulin stain may be particularly helpful. We return to this "old fashioned" but still exceedingly helpful stain later when granulosa cell tumors are considered.

THECOMA

This is one of the best known ovarian tumors and has taken its place in their classification system for decades now but ironically, at least in my opinion, is a rare tumor that has received perhaps disproportionate interest in the literature in part because of its being 1 of the 2 often estrogenic neoplasms of the ovary, the other being the granulosa cell tumor. If one is stringent in diagnosing thecoma, it will be much less often encountered than the adult granulosa cell tumor. I return to this when the latter neoplasm is discussed. Of course, their frequency is entirely dependent upon the criteria used for the diagnosis and, in my opinion, if the thecoma diagnosis is to have any consistent application it should be diagnosed by using strict criteria, and focal somewhat plump cells in what is essentially a fibroma should not lead to a thecoma diagnosis. The term *fibrothecoma* has often been used for years and there is of course no harm in the term but I personally prefer to avoid it.

Thecomas occur at a slightly older age on average than the granulosa cell tumor and do not have as wide a gross spectrum, being typically smaller with a more exquisitely yellow solid sectioned surface, but exceptions occur. On microscopic examination the tumors typically have a generally diffuse growth, often interrupted by much emphasized hyaline plaques (Figure 1, B). It is worth noting that the latter may be seen in various other tumors such as fibromas and granulosa cell tumors and even occasionally in tumors that are not in the sex cord–stromal group. Occasional thecomas may be extensively sclerotic but this is also a feature of other sex cord–stromal tumors. The neoplastic cells have often been described as having an abundant lipid-rich character. Although staining for lipid is certainly usually positive, they are not lipid-rich in the way that the steroid cell tumor of the ovary occasionally is, but rather they typically have cytoplasm with a pale gray appearance (Figure 1, D).[23] Some tumors, most often those in the young, may be markedly calcified (Figure 1, C).[24] Cytologic atypia of any measurable degree is almost always absent but a rare tumor, like other sex cord–stromal tumors, may have bizarre nuclear atypia, which may cause initial consternation if the phenomenon is not known to the observer.

The differential diagnosis of a thecoma, assuming a strict definition used, is relatively narrow. As noted earlier, edema in fibromas may result in a thecoma diagnosis. Recently we have emphasized, as discussed in detail later, that occasional granulosa cell tumors have thecoma-like foci and if those areas are not evaluated by a reticulin stain, a thecoma misdiagnosis is quite possible.[25] The differential diagnosis with granulosa cell tumor of more standard type should be straightforward because of the obvious epithelial formations of most such tumors and the scant cytoplasm of most of them. An exotic differential, the subject of 1 case report, came to pass when the presence of plaques in an endometrial stromal sarcoma, and other features overlapping with thecoma, resulted in a metastatic sarcoma of that type in the ovary being initially misdiagnosed as a thecoma.[26]

SCLEROSING STROMAL TUMOR

About a decade after he had worked on "Morris and Scully,"[2] Dr Scully encountered in consultation the first case seen in that manner of what he ultimately designated *sclerosing stromal tumor* (Figure 2).[27] He commented in his letter of opinion that "there are several features about the tumor that are atypical for the usual tumor in the fibroma-thecoma group." The neoplasm, from a 46-year-old patient, was amongst other things particularly vascular, and that has remained one of the cardinal features of this tumor, but it is only one of several that make it unique, and only when they are encountered in aggregate. The next 4 cases he saw were all from patients in the second or third decade of life, which further made him realize there was a rather distinct clinical and pathologic profile to this neoplasm. Interestingly, an example of Dr Scully's excellent memory was the fact that he must have remembered an old MGH case that was in this category because reference to Table 1 in the initial description of the entity includes a 1951 MGH case, one he must have seen very soon after joining the hospital staff. As his experience with this neoplasm increased, he recognized that in contrast to thecomas (sometimes suggested by a yellow gross appearance), it was typically nonfunctioning. Low-power microscopic examination also often showed a pseudolobular appearance (Figure 2, B), the lobules typically containing a jumbled admixture of fibroblasts and luteinized cells (sometimes with eccentric nuclei and somewhat signet ring–like) and separated by a prominent stroma that varied from collagenous to edematous, the latter sometimes giving a watery gross appearance occasionally associated with cystic degeneration. The latter gross appearance represented a further difference from most fibromas or thecomas.

Dr Scully's wish to solidify his thoughts on any entity before publishing them is witnessed by his waiting until 1973 before he put together a series for publication. When we last looked at the age distribution for our available cases, the average age was 27 years. The tumors are usually incidental findings but a rare neoplasm, particularly if the patient is pregnant, does have hormonal manifestations including hyperandrogenism. They are usually not particularly large and range from uniformly solid or solid and cystic (Figure 2, A) to, rarely, mostly cystic. The solid component typically is yellow because of the content, presumptively, of weakly luteinized cells. It was the lack of robust luteinization of the cells that Dr Scully used to explain the usual lack of function of these tumors; a more typical luteinized nature with abundant eosinophilic cytoplasm is usually seen in pregnancy.[28] Other neoplasms such as steroid cell tumor are more likely to factor in the differential diagnosis in this situation, but minor foci of typical morphology can usually still be appreciated. An additional feature of the neoplasms worthy of mentioning, as it can cause diagnostic confusion with other tumors, is the presence of ectatic blood vessels (Figure 2, C), but they are only of diagnostic significance when associated with other typical features of the neoplasm. A tumor only falls in this category when the definitional admixture of fibroblasts and lutein cells is present. The vascularity can be so striking that a hemangiopericytoma is occasionally mimicked (Figure 2, E). In occasional cases the edematous regions of the sclerosing stromal tumor undergo myxoid change (Figure 2, D), which some have postulated may explain some cases of myxoma,[29] but we are not convinced by their arguments, although it may explain an occasional case. A final feature of the sclerosing stromal tumor worth brief mentioning is that some may exhibit appreciable mitotic activity. I found a recent article on this aspect[30] of interest, because when reviewing Dr Scully's 2 first examples of this entity seen in consultation, he commented on mitotic activity in both. He even thought at that time it might portend a possibility of at least local recurrence, but follow-up has not shown mitotic rate meaningful in his experience or that in the article just cited.

LUTEINIZED THECOMAS OF THE TYPE ASSOCIATED WITH SCLEROSING PERITONITIS

This is the second entity in the stromal category that Dr Scully characterized when he gradually became aware of a remarkable association between typically bilateral, often mitotically active, ovarian masses and sclerosing peritonitis. The entity (Figure 3) was described in an original report[31] in which the senior author, my great friend and collaborator of many years, Dr Philip B. Clement, wrote a characteristically scholarly treatise on sclerosing peritonitis, which I cannot improve upon and is not further considered here although it has its own fascinating aspects. The nature of the ovarian pathology in these cases is somewhat controversial, some

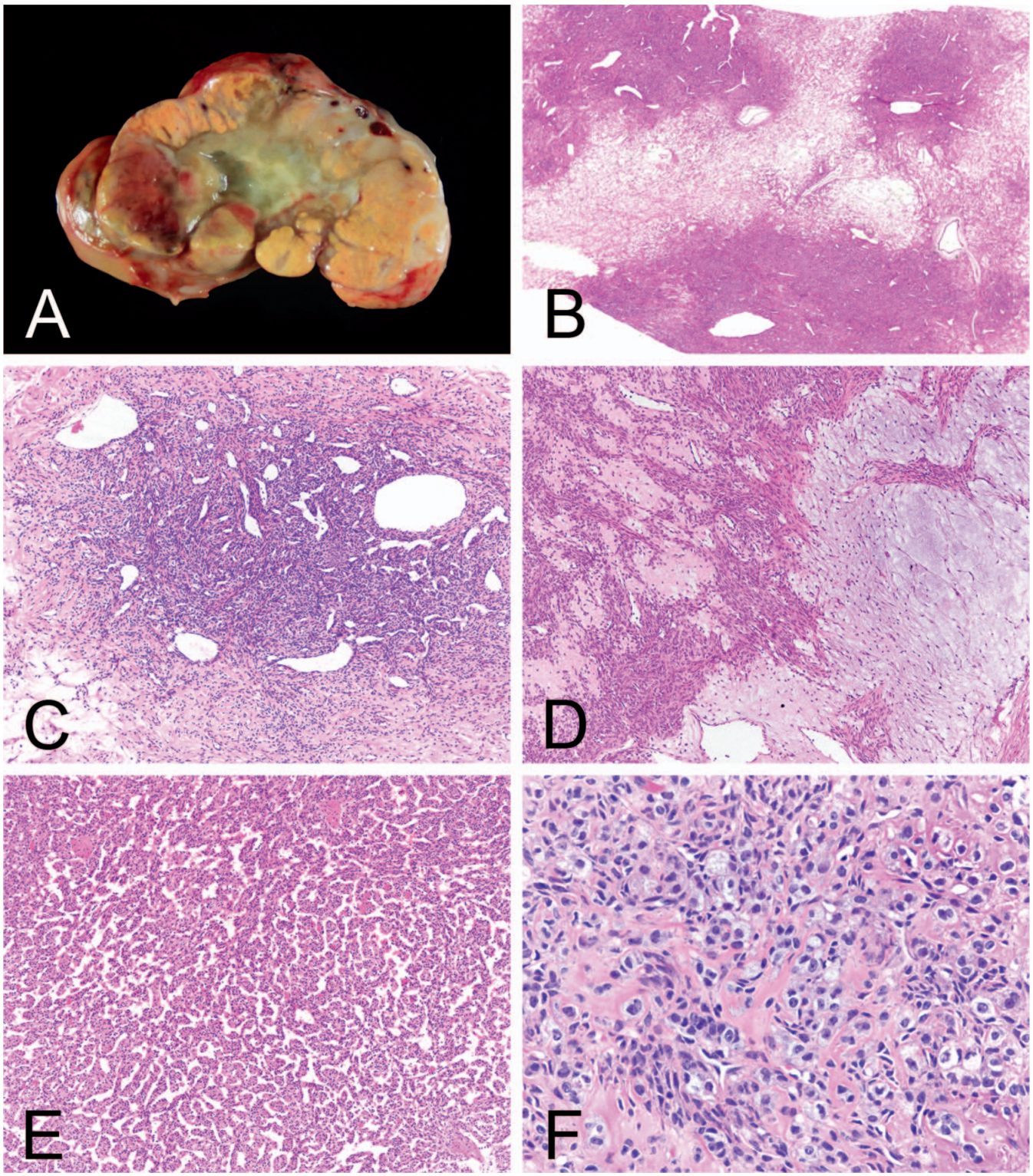

Figure 2. *Sclerosing stromal tumor. A, Characteristic solid and cystic sectioned surface with a yellow color to the solid regions. B, Classic pseudolobular appearance. Notice prominent vascularity and edematous stroma. C, Lobule showing numerous blood vessels, many of them ectatic. D, The stroma of this neoplasm was focally conspicuously myxoid. E, Striking hemangiopericytoma-like appearance. F, Typical appearance of cellular lobules showing prominent lutein cells, a few of which have eccentric nuclei and are signet ring–like. A few fibroblasts are also present.*

authorities believing it is a nonneoplastic proliferation related in some way to massive edema and ovarian fibromatosis (an entity different from the soft tissue process). We have discussed this issue in detail in a relatively recent contribution on the peculiar thecomas being considered here and will not repeat what is presented there.[32] I will, however, note that in preparation for this essay I reviewed the slides of all cases of this entity available to me, almost 30 cases, and was struck not only by their remarkable morphology but also by the failure to identify

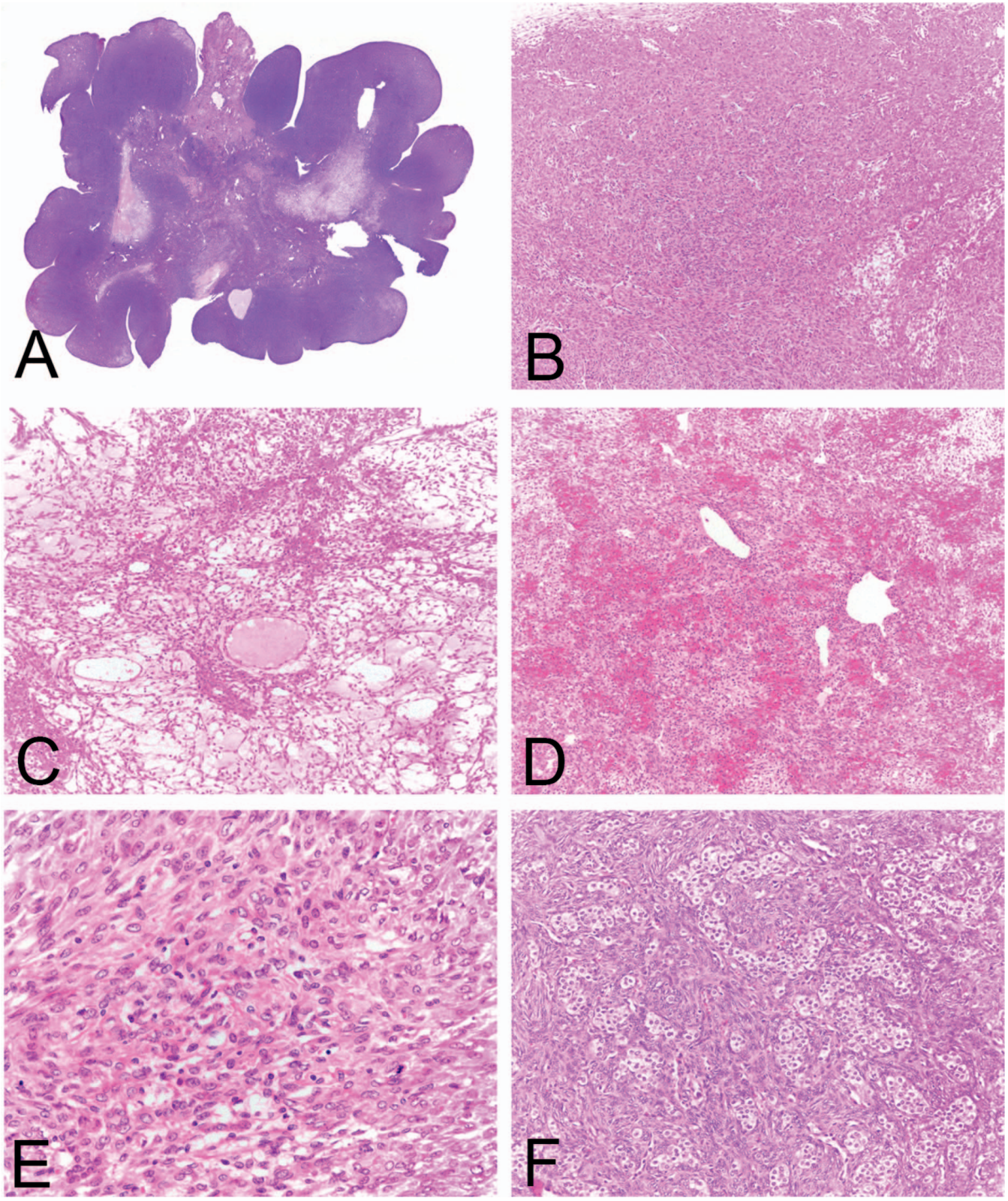

Figure 3. *Luteinized thecoma of the type associated with sclerosing peritonitis. A, Striking cerebriform pattern sometimes seen on low power. B, Densely cellular neoplasm. C, Microcystic appearance. D, Prominent hemorrhage. E, Conspicuous mitoses. F, Numerous nests of lutein cells.*

any area that resembled to my eye either typical massive edema (although there is often edema in these cases) or fibromatosis, so my own opinion that this is an odd neoplasm remains.

The process may be seen at any age but peaks at about 27 years. Abdominal pain is common, sometimes associated with ascites, and bowel obstruction due to the peritoneal process can be fatal. The typically bilateral abnormal ovaries range from normal in size but abnormal in appearance, owing to a hypercerebriform contour (Figure 3, A), to sizeable, often beefy masses. On microscopic examination, 7 aspects are seen to variable extents: a prominent cerebriform contour, intense hypercellularity, microcysts that variably punctuate the hypercellular background, hemorrhage, conspicuous mitoses, luteinized cells, and entrapped normal ovarian structures (Figure 3, B through F).

Although only seen in a minority of the cases, the cerebriform pattern can be remarkable. The contrast with an unremarkable medullary zone is striking. The hypercellular regions are characterized by very closely packed, relatively small cells that are fusiform to slightly spindled. Enigmatically, these neoplasms are either intensely hypercellular or hypocellular with an edematous to microcystic pattern within the edematous regions, normocellular fibroma-like foci being almost never seen. The edema can be banal edema or more typically has a microcystic pattern (Figure 3, C) but one that differs from what one sees in the microcystic stromal tumor considered below. Sometimes the edema can form polypoid, botryoid-like projections off the ovarian surface. In accord with the often beefy gross appearance is the relatively frequent presence, admittedly often to minor degrees, of hemorrhage sometimes having a somewhat streaky arrangement.

Dr Scully elected to consider this tumor in the family of luteinized thecomas owing to the presence of rounded cells with pale to occasionally lightly eosinophilic cytoplasm consistent with a luteinized nature (Figure 3, F). When abundant, these can stand out sharply but they are often ill defined and rarely are they the robust luteinized cells of entities such as stromal hyperthecosis or as seen in the stroma of diverse neoplasms. The neoplastic cells in the hypercellular regions often show abundant mitotic figures. A final feature of this process, which has led some to consider it nonneoplastic, is the presence within the abnormal proliferation of entrapped normal ovarian structures of various types, but in my experience they are generally not as striking as is seen in cases of massive edema and fibromatosis.

Strange as it may seem the differential diagnosis of this process is actually quite limited. The observer either knows the entity and immediately realizes what he/she is looking at or is simply confused. An important potential error is to misdiagnose it as fibrosarcoma. The presence of an unusual clinical background, bilaterality, and entrapment of background normal ovarian elements can be a clue to what the observer is looking at. The reason for the sclerosing peritonitis remains unknown and although it may cause morbidity or even mortality, most patients have an uneventful future once the lesions are resected.

SIGNET-RING STROMAL TUMOR

Credit for the recognition of this rare entity belongs to Dr Ibrahim Ramzy[33] who first described, in 1976, the occurrence in a cellular stromal neoplasm of signet ring–like cells (Figure 1, E) but which lacked the mucin of such cells in a Krukenberg tumor or the lipid of the signet ring–like cells seen in the sclerosing stromal tumor. That Dr Scully's vast archives only enabled him to subsequently report a series of 3 cases[34] speaks to the rarity of this neoplasm, and still only a small number have been reported, the largest collection being 3 cases.[35] These neoplasms have no special clinical or gross characteristics, specifically not being associated with any endocrine function. The distinctive feature microscopically is the presence of the signet ring–like cells with large vacuoles seen on ultrastructural examination that come about because of edema of the cytoplasmic matrix in some cases, in others from swelling of mitochondria, and yet in other cases apparently from cytoplasmic pseudoinclusions of edematous extracellular matrix. The background cellular neoplasm looks more like a cellular fibroma than anything else but in my admittedly still somewhat limited experience, they look slightly different. Although the unusual signet-ring change seems largely to occur in neoplasms that are purely mesenchymal, rarely a similar change is encountered in granulosa cell tumors.

Simple awareness of this phenomenon should aid in its distinction from a Krukenberg tumor, and the more variegated architecture of Krukenberg tumors is not a feature of the signet- ring stromal tumor. A mucin stain can be of crucial diagnostic aid. It should be noted that in rare cases the signet-ring stromal tumor has shown some immunostaining for cytokeratins, a potential pitfall.

MYXOMA

This rare neoplasm (Figure 1, F) is included here for completeness sake, although it can be debated whether it is truly related to standard neoplasms of unequivocal ovarian stromal origin in the fibroma-thecoma category. In 1991 Dr Scully reported, with the late Dr John H. Eichhorn as senior author, 5 cases and considered the 3 present in the literature.[36] The tumors in Dr Scully's collection occurred in relatively young individuals, the oldest being 45 years and the youngest 16 (mean, 33 years). No evidence of endocrine function has been present in any case and there are no unique clinical features. As expected, given the microscopic features, these tumors are often soft on microscopic examination, sometimes exhibiting cystic degeneration. The microscopic features are the well-known ones seen in the tumor of this name encountered in the soft tissues. Care should be taken not to "undercall" a low-grade myxoid sarcoma as myxoma, so any putative myxoma should be rigorously evaluated to make sure there is not focal cytologic atypia or mitotic activity of note to cause concern for a neoplasm with a malignant potential. The differential diagnosis with other ovarian tumors is very limited. As noted above, the sclerosing stromal tumor can be very myxoid but in our experience it does not have the particular very delicate vascularity of the myxoma. As in so many areas of ovarian tumor pathology, thorough sampling is mandated before the diagnosis of myxoma is made with confidence.

MICROCYSTIC STROMAL TUMOR

Shortly after Dr Scully retired, this writer began to see occasional examples of an unusual ovarian tumor characterized by microcysts, which seemed to represent a distinct entity.[37] When I undertook the paper describing this process I was not aware that he had seen any cases, although I always thought it strange that he had not, unless it really

was a "new entity" to the family of ovarian neoplasms, which seemed unlikely. I never remembered seeing one case with him over many years examining most of the cases sent to him. Just recently, through a chance occurrence, I came across a case in his files from decades ago, which is a very good example of this process, but unfortunately the paperwork giving his reflections on it cannot be found at this time.

This rare but fascinating tumor occurs in adults who have presented with a nonfunctioning stage 1 ovarian mass usually of modest size. Occasional examples have occurred in patients with familial adenomatous polyposis.[38] The tumor is typically solid and cystic but may be predominantly solid and tan to white to rarely yellow or cystic. They typically do not have an overtly malignant appearance. Microscopically, there are 3 components: (1) microcysts (dominant in 60% of cases), (2) solid cellular areas, and (3) hyalinized stroma (Figure 4, A through F). Rare tumors are entirely solid and can be recognized by their distinctive features and confirmatory immunohistochemical findings. No tumor is known to have recurred or spread. Like the myxoma, this tumor may not be truly related to definitive tumors of ovarian stromal origin but is, for now, placed in the stromal family as the "best fit."

The small round to oval cysts focally coalesce to form irregular channels; intracytoplasmic vacuoles are also common. The cellular areas are usually intersected by fibrous bands and hyaline plaques; the stromal component exceptionally dominates. The cells have lightly eosinophilic cytoplasm and usually bland nuclei, but bizarre nuclei are present in 60% of the cases. The tumors are positive for CD10 in contrast to tumors in the differential and there are other immunohistochemical differences with them. Nuclear staining for FOXL2, WT-1, cyclin D1, and SF-1 is typical.[38] It has been demonstrated by several groups now that most, but not all, tumors of this type have point mutations in β-catenin (*CTNNB1*), and almost all exhibit diffuse nuclear and cytoplasmic immunoreactivity with β-catenin even when the mutation is absent. Many ovarian tumors may have cysts that at least in regions are similar to those of the microcystic stromal tumor and accordingly the differential diagnosis of this entity is broad. However, thorough sampling will almost always show features that direct alternative diagnoses to surface. Most likely issues in differential diagnosis are now very briefly considered.

The coalescing cystic pattern typical of this neoplasm may suggest yolk sac tumor. The latter, however, usually occurs in a somewhat younger age group, although there is overlap, and characteristically has a more worrisome gross appearance. On microscopic examination there is greater uniformity to the cystic pattern in the microcystic stromal tumor than in the reticular-microcystic pattern of yolk sac tumor, and the cells of the latter have a more immature primitive appearance with brisker mitotic activity. Should any doubt remain, immunohistochemical stains for standard markers of yolk sac tumor will aid. The solid areas of these neoplasms may suggest a steroid cell tumor. However, steroid cell tumor would not be associated with even a minor component of the typical microcystic morphology of the microcystic neoplasm. Additionally, the steroid cell tumor is characterized by cells with more lush eosinophilic cytoplasm than the cells of the microcystic entity, and most steroid cell tumors have at least a minor component of lipid-rich cells not seen in the microcystic tumor. Hyaline bands/plaques similar to those of thecoma are one of the typical features of the microcystic neoplasm but again even minor classic microcystic foci rule out thecoma, and inhibin shows negativity in the microcystic neoplasm and positivity in thecoma (and steroid cell tumor) should any doubt exist after review of standard slides.

GRANULOSA CELL TUMORS

In **"**Morris and Scully" these neoplasms were the first to be discussed in detail after 3 chapters, one introductory, one on nonneoplastic lesions, and one on the classification of functioning ovarian tumors.[2] In accord with the approach at that time the tumors were referred to as "granulosa-theca cell tumors." Subsequently the tumors became referred to as *granulosa cell tumors*, as the thecomatous stromal component was not felt to be of any great consequence and many tumors do not have an appreciable stromal component. Of interest concerning remarks earlier on the rarity of the thecoma is inclusion in the granulosa cell section in "Morris and Scully" of some figures on the incidence of those 2 neoplasms.[2] They noted that as of that time 1000 granulosa cell tumors had been recorded compared to 300 "theca cell tumors" (thecomas) and the MGH experience was represented by 16 granulosa cell tumors and only 6 thecomas. This more or less 3:1 balance in favor of granulosa cell tumors accords to my own experience both in referral and hospital material in recent years.

The major contribution Dr Scully made to knowledge concerning granulosa cell tumors was his later appreciation that tumors from young individuals often had microscopic features different from those seen in tumors from the somewhat older patients. When I recently reviewed paperwork of the first case he saw, which he subsequently designated *juvenile granulosa cell tumor* (and the oldest case included in our 1984 study), I found that it was, interestingly, submitted by Dr Morris. In his consultation letter, Dr Scully commented that the tumor was "rather malignant looking with numerous mitoses." By the time he saw the fifth case in this category he had formed the opinion that they "differ from the usual granulosa-theca cell tumor of the adult in histological appearance." I do not know exactly when he first used the "juvenile" designation. It is not used in his 1970 review in *Human Pathology*.[39] I suspect he began to use it in the early to mid-1970s because, by the time of his first fascicle on ovarian tumors published in 1979 (worked on in the mid-1970s), his thoughts had crystalized to the extent that he was using the term *juvenile granulosa cell tumor*, and he did in that work include 3 illustrations of characteristic examples. He was using the term when showing cases at a weekly conference he conducted, showing his consultation cases, when I joined the MGH in 1977. The first detailed study of these tumors (which credited Dr Scully for recognizing the entity) was an excellent article by Zaloudek and Norris[40] published in 1982.

Pursuant to the above observations of Dr Scully, granulosa cell tumors are now divided into adult (AGCTs) and juvenile (JGCTs) forms, the latter accounting for no more than 5% of them. These terms connote a spectrum of appearances typically seen in adults or juveniles and conveniently designate the 2 variants rather than potentially unwieldy designations needed to try and capture their differing microscopic features. It should be noted that each variant may occur at an age more typical of the other, but uncommonly. For example 3 of 32 tumors in patients 16 years or younger in the series of Zaloudek and Norris[40] were

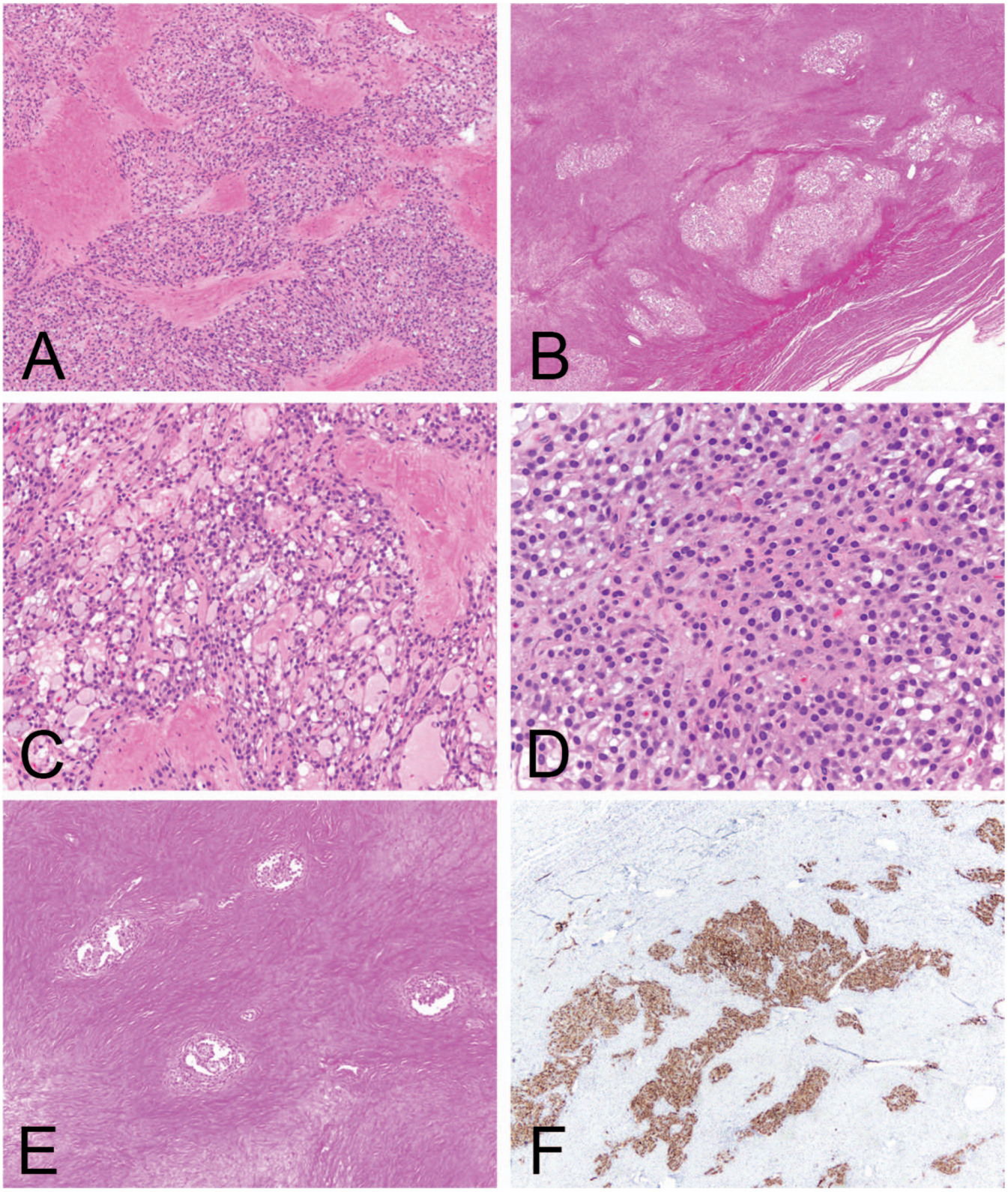

Figure 4. *Microcystic stromal tumor. A, Low-power view showing conspicuous hyaline plaques separating cellular elements of the neoplasm. B, Lobules separated by conspicuous fibrous stroma. Notice microcystic foci within several of the lobules. C, Classic microcystic morphology. D, Solid region of the tumor showing cells with eosinophilic cytoplasm, which can reasonably suggest a steroid cell tumor if microcysts are inconspicuous. E, Very conspicuous fibrous stroma that dominated over the microcystic elements in this example. F, Striking CD10 immunoreactivity.*

of the adult type. Conversely, in our large analysis of 125 cases, 3% of juvenile examples occurred in patients older than 30 years.[41] Tumors of each type are usually pure but rarely there are significant components of each. AGCTs peak between 50 and 55 years of age but as noted can occur at any age, including rarely in children, so age does not drive the designations. The usual presentation is abdominal pain and swelling, but endocrine manifestations may be striking particularly when a granulosa cell tumor of either type occurs in prepubertal girls and causes isosexual pseudoprecocity. Acute abdominal symptoms from tumor rupture and hemoperitoneum occur in 10% of cases, again in both categories.

Granulosa cell tumors of either form are usually between 5 and 15 cm and more than 95% are unilateral. The cut surfaces are typically solid and cystic. The cysts are often blood filled. The solid tissue varies from solid to friable and white to tan or yellow; some tumors are markedly hemorrhagic. They are not infrequently entirely solid or, less often, entirely cystic, so many tumors in other categories can be mimicked. Friable tissue lining cysts can, for example, suggest a surface epithelial carcinoma.

ADULT GRANULOSA CELL TUMOR

Microscopic Features

These tumors have many patterns (Figure 5, A through F), the most emphasized being microfollicular, owing to the famous eponym Call-Exner bodies, which refers to small round regular spaces that may contain eosinophilic fluid, degenerating nuclei, hyalinized basement membrane material, or even basophilic fluid. These may be diagnostically helpful but are present in no more than 10% of the tumors, and neoplasms in which they dominate are rare. A macrofollicular pattern is even less common and almost never dominates. Small hollow or solid tubules occasionally are seen to a limited degree and rarely are more conspicuous. They generally indicate Sertoli or Sertoli-Leydig cell tumor when the tumor is clearly in the sex cord–stromal family, but when overall features fit best for AGCT they are acceptable for that diagnosis. Rarely the tubules appear glandlike.

A diffuse pattern is actually most common (Figure 5, A), being characterized by sheets of cells with scant cytoplasm imparting a "small round cell tumor" appearance. An interesting anecdote relates to this comment. When I drafted the list of tumors to be considered when Dr Scully and I, late in his career, wrote an essay on the patterns and cell types of ovarian tumors, I was at first surprised when he gently chastised me for not listing granulosa cell tumors[13] in the category of small round cell tumors. He commented that most granulosa cell tumors at first encountering came across as a neoplasm with a diffuse growth of small cells with scant cytoplasm, so indeed did fit in the category, and of course they were added to those discussed under the heading just noted. In these cases it is helpful that careful scrutiny, almost always, shows focal epithelial patterns. In some tumors these dominate and are mainly as below.

An insular pattern, discrete nests usually surrounded by a conspicuous stroma, is relatively common. Trabeculae are often seen at least in minor amount. Photogenic delicate cords often referred to as gyriform or moire-silk arrangements are occasionally seen. A nodular pattern, generally smoothly contoured rounded aggregates, with a largely diffuse arrangement of cells within the nodules, is seen in a minority of cases. In some tumors there is a prominent spindle cell pattern. Even more morphologically intriguing is the much less common tumor that shows a focal to prominent pseudopapillary pattern.[42] A morphologic aspect of the AGCT, shared with the Sertoli-Leydig cell tumor, is alterations in its appearance when excised in the last trimester of pregnancy. In these cases prominent edema or luteinization may alter the appearance.[43]

The granulosa cells usually have scant cytoplasm and pale, uniform, angular to oval, often grooved nuclei that are often arranged haphazardly in relation to one another. In some tumors, particularly those with a nodular pattern, cells with appreciable pale cytoplasm and tinctorial properties reminiscent of the cells in many thecomas are seen.[25] In some tumors the cells have moderate to abundant eosinophilic cytoplasm and in these so-called luteinized AGCTs, nuclear grooves tend to be less conspicuous and nucleoli more prominent than in other neoplasms.[44,45] It should be noted, however, from the converse perspective, that other sex cord–stromal tumors may have sporadic nuclear grooves. Even more treacherously perhaps, from the viewpoint of placing a neoplasm in a completely opposite category, is the fact that some endometrioid carcinomas have cells with nuclear grooves every bit as picturesque as those seen in many AGCTs. The prominence of nuclear grooves in AGCTs is overemphasized to a degree in writings on this tumor but certainly the diagnosis should be made cautiously in their absence. The mitotic rate of the AGCT is generally low but in some tumors it may be brisk; caution is required in these cases also. The cytologic features in most tumors are low grade but an occasional tumor has features that are more worrisome than average. In such cases a notation is warranted. Otherwise typical AGCTs have, in about 2% of cases, pleomorphic so-called bizarre nuclei, which do not appear to impact prognosis.[46] They are usually focal but may be conspicuous and efface typical foci of neoplasia over wide areas. It is helpful that the mitotic rate in these areas is usually not increased.

The stroma of AGCTs varies from scanty in tumors with a diffuse pattern to abundant in those with overt epithelial patterns. It may be richly vascular and ranges from paucicellular, resembling a typical fibroma, to cellular, and commonly contains theca externa-like cells with scant cytoplasm. Luteinized cells with abundant eosinophilic or more often pale lipid-rich cytoplasm may be seen but are generally not as striking as the Leydig cells in a Sertoli-Leydig cell tumor. Rarely the stroma of the AGCT contains Leydig cells or cells with hepatocytic features.[47] Stromal fibrosis, old or recent hemorrhage, hemosiderin, and nonspecific cysts are often present and may complicate the appearance of the tumor and are more frequent than in Sertoli-Leydig cell tumors.

Differential Diagnosis

As with most categories of neoplasia, issues may relate to the neoplasm under consideration mimicking a tumor of another sort or conversely, other neoplasms mimicking the AGCT. As it is a topic of recent interest to us I will first consider the AGCT mimicking a thecoma. In recent years we have noted that a subset of AGCTs, often having a striking nodular pattern, may have within the nodules a component of cells with relatively conspicuous pale cytoplasm tinctorially resembling the cells of thecoma.[25] A reticulin stain, which of course has traditionally been of great help in delineating neoplastic granulosa cells from

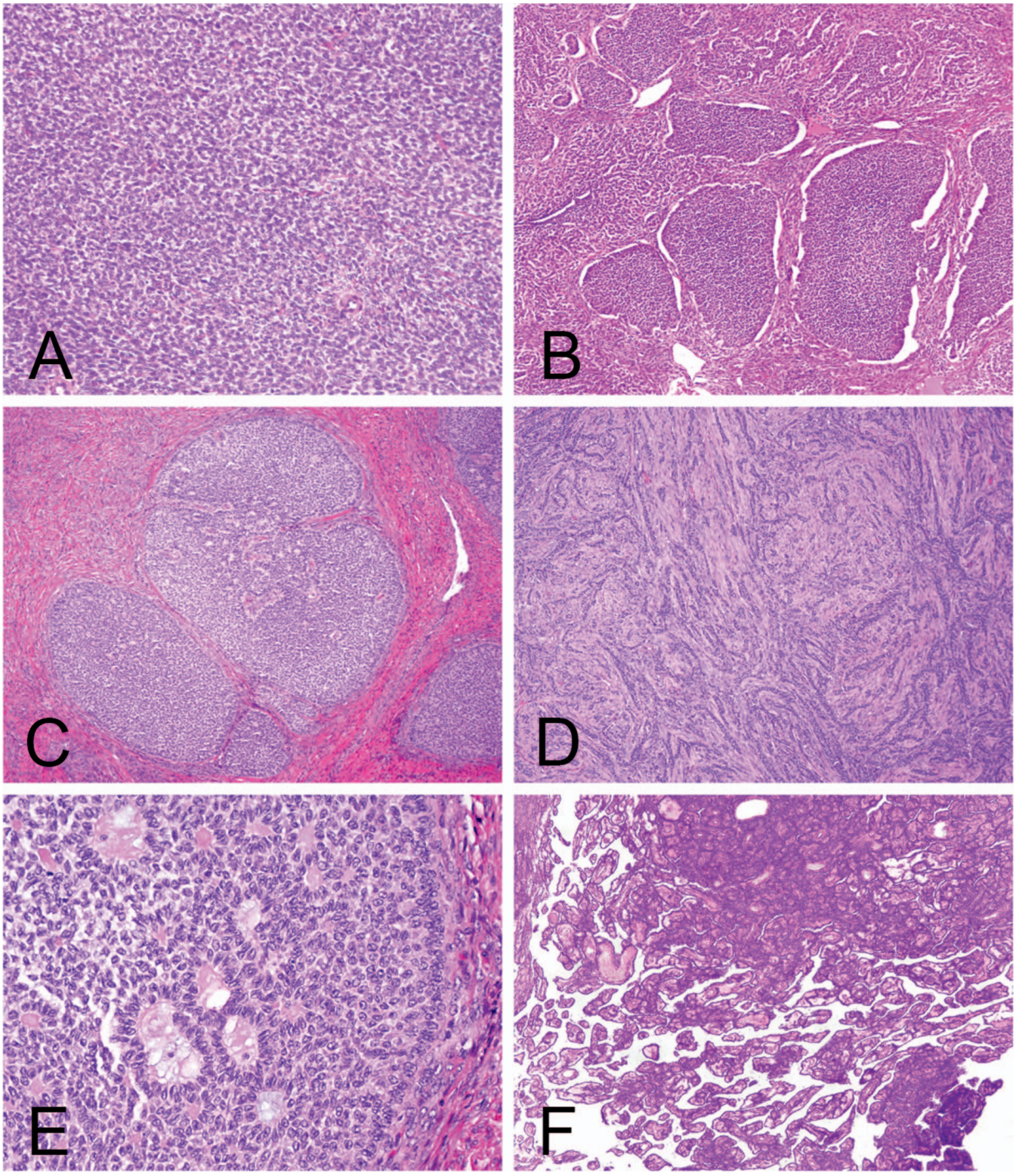

Figure 5. *Adult granulosa cell tumor. A, Typical diffuse pattern. B, Nests separated by foci that show prominent cords. C, Nodular pattern. D, Typical trabecular-corded pattern. E, Classic Call-Exner bodies. F, Prominent pseudopapillary pattern.*

pure stromal cells, is particularly helpful in enabling categorization of most cells within the nodules in these cases as falling in the granulosa cell family by displaying a dearth of reticulum. In our experience to date these neoplasms for some strange reason often have been rather small and uniformly solid and yellow, and of course that results in a gross appearance perfectly consistent with thecoma, so we have concluded that almost certainly in the past some of these neoplasms have been misdiagnosed as thecoma. This is likely not an error with great clinical

consequence given the neoplasms are small but it is nonetheless of academic interest.

Confusion of the AGCT with other sex cord–stromal tumors should be relatively limited. There is of course some overlap in what one may see in Sertoli-Leydig cell tumors but the overall features of the 2 neoplasms are markedly different. The stroma in the Sertoli-Leydig cell tumor generally does not have a cellular fibrothecomatous character as is so typical of the AGCT, and on low power a lobulated pattern different from the nodular pattern of the AGCT just noted is very common. Also, the scattering of Leydig cells between the lobules of a Sertoli-Leydig cell tumor is relatively distinctive and unlike the more even scattering of usually singly dispersed lutein cells in the stroma of the AGCT. Distinction from the juvenile granulosa cell tumor is considered under the latter heading.

Perhaps the most common potentially clinically significant error in differential diagnosis is misdiagnosing an endometrioid carcinoma as an AGCT. When we first elaborated on the confusion of sex cord–stromal tumors and endometrioid carcinomas in 1982, it was prompted largely by the mimicry of Sertoli-Leydig cell tumor by tubules and other patterns in endometrioid carcinomas.[7] Since that time we have seen the issue as much, if not more, to be solid sheets of cells in endometrioid carcinoma and microfollicular or trabecular patterns mimicking similar patterns of the AGCT. Given how well known this issue is in ovarian tumor diagnosis today, it is interesting to reflect that as late as 1980 or thereabouts it was hardly discussed at all in the literature and I have vivid memories of cases being sent in to Dr Scully with the wrong diagnosis, which of course is why he prompted that the series he had collected as of that time be reported. The carcinomas in these cases are usually low grade and many of them are associated with endometriosis, arise out of an adenofibroma, or show squamous differentiation, features lacking except perhaps in the first 2 instances by happenstance in the case of an AGCT. Of all the microscopic findings in ovarian tumor pathology, one of the most definitive is squamous differentiation, as it is unacceptable in a sex cord–stromal tumor of any type. Although the features just noted are common and will help in most cases, this is an area in which immunohistochemistry may be helpful and indeed it is a relatively crisp situation inasmuch as inhibin and calretinin positivity is so typical of the AGCT and that neoplasm almost never stains for epithelial membrane antigen, converse findings being typical, with rare exceptions, of the endometrioid carcinoma. Although given the era in which he practiced it is no surprise that Dr Scully's primary focus was on anatomic pathology as it was practiced until the mid-1980s, namely, an emphasis on clinical, gross, and standard microscopic features, he had a very inquisitive mind and was one of the first to use immunohistochemistry in evaluating gynecologic, particularly ovarian tumors,[48] and indeed coauthored what was the first article exploring immunohistochemistry in the problematic area just considered.[49]

Cellular fibromas can occasionally be difficult to distinguish from AGCTs with a diffuse growth in which the cells are somewhat spindled, but pure or almost pure AGCTs of the type just noted are distinctly uncommon and even subtle foci of overt epithelial differentiation can lead to procurement of a reticulin stain, which will often disclose in what at first appear to be uniformly mesenchymal zones an epithelial pattern of reticulum, at least focally, indicating that more of the tumor is actually of granulosa cell type than at first glance may seem the case.

It should be noted that although in most granulosa cell tumors there is a dominant population of epithelial cells, in occasional examples the stroma predominates. Unless the granulosa element is really minimal (in which case the diagnosis of stromal tumor with minor sex cord elements is warranted),[50] the tumors should be placed in the granulosa cell category, although when granulosa cell elements are dominated by the stromal component I remark upon it because it is logical to think that the relative dearth of epithelial cells in those cases might have some favorable prognostic significance, although it is unlikely anyone will ever procure a large enough series of cases with long follow-up to objectively make that point.

As noted above, one of the best known features of the AGCT is the famous Call-Exner body and anytime pathologists see small acini reminiscent of such a structure, that they might be Call-Exner bodies comes not unreasonably to mind, and this happens with diverse neoplasms including endometrioid carcinomas with microacini as well as monodermal teratomas such as struma ovarii and carcinoid. An association of the latter 2 neoplasms with a dermoid cyst is a helpful gross feature but in some cases it is only microscopic examination that will disclose evidence of that finding, and in some cases evidence of a background dermoid is effaced. There is 1 educational case in the literature in which a struma ovarii with a trabecular pattern mimicked an AGCT tumor and led to the tumor being misreported as an AGCT associated with a dermoid cyst. Many years later at the time of the writing up of unusual cases of struma from Dr Scully's files,[51] our curiosity about that case prompted immunohistochemical stains to be performed and they confirmed that the "AGCT" in that case was actually a trabecular pattern of struma.

Finally, a very important tumor in the differential diagnosis of the AGCT is the small cell carcinoma of hypercalcemic type,[52] which before its recognition by Dr Scully, always certainly was most often misdiagnosed as an AGCT because of the follicles that are present in 80% of cases of the hypercalcemic neoplasm. Enigmatically, the hypercalcemic tumor has cells that are not much less uniform than those of the AGCT in their general appearance one to the next but they appear much more malignant cytologically and have much brisker mitotic activity. One of the many paradoxes of ovarian tumor pathology is that if one finds bizarre nuclei in a tumor in which the differential is the highly malignant hypercalcemic neoplasm and the more indolent AGCT, those nuclei actually favor an AGCT because marked nuclear pleomorphism is uncommon in the hypercalcemic neoplasm and giant cells are almost never found. It is helpful that the AGCT usually occurs at a much older age.

Three metastatic tumors may be in the differential of the AGCT. The first is metastatic malignant melanoma when the cells have scant cytoplasm and nuclei that are pale and granulosa-like as may be the case. A history of melanoma, bilateral ovarian involvement, malignant nuclear features, melanin pigment, and positivity for melanoma markers are all variably helpful. Metastatic lobular carcinoma of the breast may simulate an AGCT to a remarkable degree from the pattern viewpoint by exhibiting diffuse growth, nodules, or delicate cords. It is treacherous that some cases of lobular carcinoma present in the ovary before the primary tumor is discovered. The cells of lobular carcinoma and the AGCT are

of roughly similar size but those of a lobular neoplasm are more uniformly rounded and lack grooves. Sometimes they show focal mucin containing intracytoplasmic vacuoles, which one does not see in the AGCT. This is an area where the standard immunohistochemical stains that label breast carcinomas may be helpful in confirming or establishing the diagnosis. An AGCT may also be mimicked by metastatic low-grade endometrial stromal sarcoma, as both tumors have cells of similar size with scant cytoplasm most of the time. The history (sometimes needing to be looked into by reviewing prior hysterectomy slides) may be crucial. I have seen some cases of metastatic stromal sarcoma with pale nuclei occasionally having grooves that in an individual zone would be acceptable for those of an AGCT. Although stromal sarcoma metastatic to the ovary typically grows in a diffuse pattern, it is very helpful that there is often extraovarian disease that typically shows the tonguelike growth so typical of endometrial stromal sarcoma. That having been noted, however, some low-grade cellular neoplasms primary in the ovary, should they extend into the paraovarian soft tissue such as the AGCT, can have a somewhat nodular almost tonguelike growth. A variety of features such as the greater frequency of bilaterality of any metastatic tumor to the ovary and immunohistochemical differences should aid.

JUVENILE GRANULOSA CELL TUMOR

Microscopic Features

Although the JGCT has a variety of differences from the AGCT, which generally pertain in an individual case, both architectural and cytologic, it is the latter that were paramount in Dr Scully's appreciating the distinctive features of a great majority of granulosa cell tumors in the young. Late in his career I reviewed this with him from the historical perspective and he emphasized to me that it was his observing a more malignant appearance of the tumors in the young that first highlighted to him that there was a difference in the tumors of children, most of the time, even though as time went by he also observed that the cytoplasm was usually more abundant and there were also architectural differences (Figures 6, A through F; and 7, A through F).

The cytologic features that are relevant in this matter are the usual lack of grooves in the JGCT, higher mitotic rate, and even greater frequency of pleomorphic, enlarged, alarming nuclei of the "bizarre type." These (seen in about 2% of AGCTs) are seen in almost 15% of JGCTs. These aggregate findings led cases in Dr Scully's collection to be submitted to him with diagnoses such as a form of primitive germ cell tumor or even sometimes simply a high-grade carcinoma, albeit the submitting pathologist was alert enough to realize that such a diagnosis was unlikely in a young person. The architectural differences observed with time were primarily a more varied follicular architecture although nodular growth also was noted to be quite common. Time also showed an additional cytologic feature, not related to the malignant appearance or otherwise of the tumor, namely, cells having more abundant eosinophilic cytoplasm, that is, being "luteinized." It should be noted, however, that the cytoplasm is not always abundant and indeed may be scant, resulting in a basophilic appearance.

Although most tumors have all the above features, except the bizarre atypia seen only in a minority, it is the immaturity of the nuclei that is, as noted, the defining feature. On low-power examination one is usually first struck by an eosinophilic appearance of the cytoplasm and punctuation of a solid cellular neoplasm by follicles of varying size and shapes. In some cases there is a striking macronodular-micronodular pattern, nodularity being somewhat more frequent in the JGCT than it is in the AGCT. Then, on high-power examination one sees the cytologic features already emphasized. One final architectural feature of the JGCT worth noting and also seen as depicted earlier in cases of AGCT is the presence of pseudopapillae, apparently the result of cystic degeneration with resultant papillary formations protruding into cyst lumens. In most cases these are only focal findings but when conspicuous, they can produce a somewhat challenging interpretation, the transitional cell pattern of serous carcinoma in particular being occasionally a challenge, albeit that would be an unlikely diagnosis to be made in a young person.

Differential Diagnosis

The above remarks on architectural and cytologic features, in aggregate, readily distinguish most cases of JGCT from AGCT. The features also are unlike those of any primitive germ cell tumor, albeit the very rare polyvesicular vitelline variant of yolk sac tumor has cysts that sometimes may be misconstrued as the follicles of the JGCT. Eccentric constrictions of the cysts of the polyvesicular neoplasm may be found focally and can be a helpful finding, as in some cases may be the very intense hypercellular stroma that characterizes some examples of that tumor. I can imagine a diagnosis at frozen section being somewhat challenging but a thoroughly sampled neoplasm of each form should readily be interpreted correctly in my opinion. Even standard yolk sac tumor not in the polyvesicular family may have cysts that can be at first glance somewhat reminiscent of the follicles of the JGCT (Figure 12, E).

One important tumor in the differential of the JGCT is the so-called large cell variant of small cell carcinoma of hypercalcemic type.[52] The "large cell variant" designation is used to characterize the cells in the hypercalcemic neoplasm that have abundant eosinophilic cytoplasm, sometimes having a rhabdoid-like appearance. Confusion can arise from the clinical perspective because of the occurrence of both neoplasms in a young patient, the hypercalcemic neoplasm peaking at 24 years of age. Both tumors are typically unilateral and both have brisk mitotic activity, albeit it is more striking in the hypercalcemic tumor. The shared follicles of the 2 neoplasms are further confusing. It is helpful that it is rare for the large cell variant to have a pure or almost pure population of large cells, most having a measurable component of the more typical small cell morphology. Enigmatically, bizarre atypia and giant cells are uncommon in the hypercalcemic neoplasm, the much more malignant of the two. The latter has in general a more varied irregular architecture than the more structured alternating follicles and solid or nodular foci seen in the JGCT. A rare issue in the differential diagnosis of the JGCT is with dysgerminoma. This can arise when the latter has spaces that may simulate follicles (Figure 12, D). This is analogous to the spaces that have been emphasized recently as an occasional finding in cases of seminoma and these may be seen in dysgerminoma, albeit less frequently in my experience. In well-fixed specimens this should not be an issue but occasional dysgerminomas are suboptimally fixed, which can provide various hazards in diagnosis, and I can

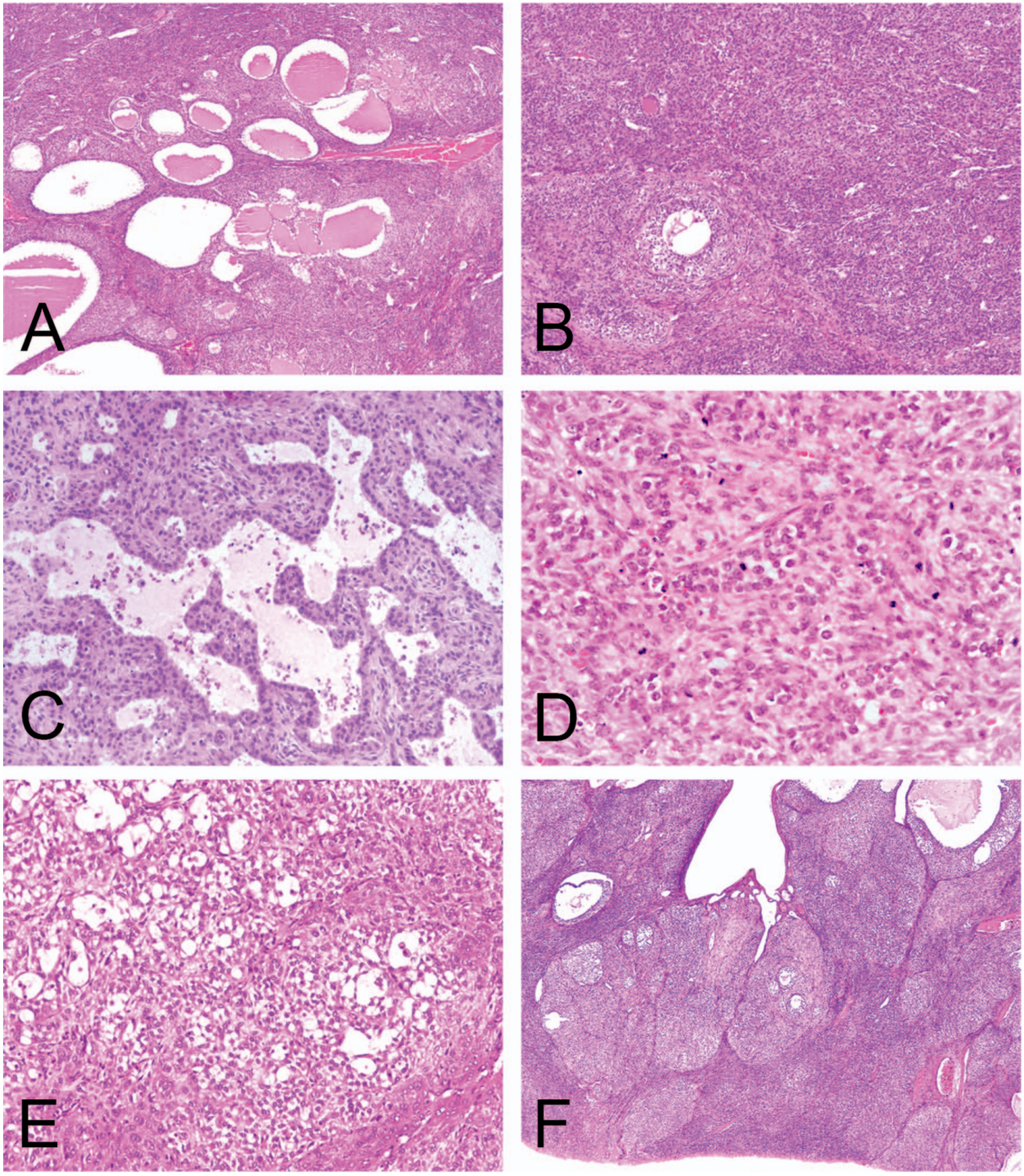

Figure 6. *Juvenile granulosa cell tumor. A, Classic low-power appearance showing numerous follicles set upon a background of more solid cellular neoplasm, which is brightly eosinophilic owing to abundant cytoplasm. B, Solid cellular neoplasm with only a single follicle. C, Irregular branching follicular pattern. D, High-power view showing immature appearance of the nuclei, lack of nuclear grooves, and conspicuous mitotic figures. E, The follicles are poorly formed and result in a microcystic, almost focally reticular pattern, that could conceivably suggest yolk sac tumor in a young person. F, Nodular pattern that dominates in an occasional neoplasm.*

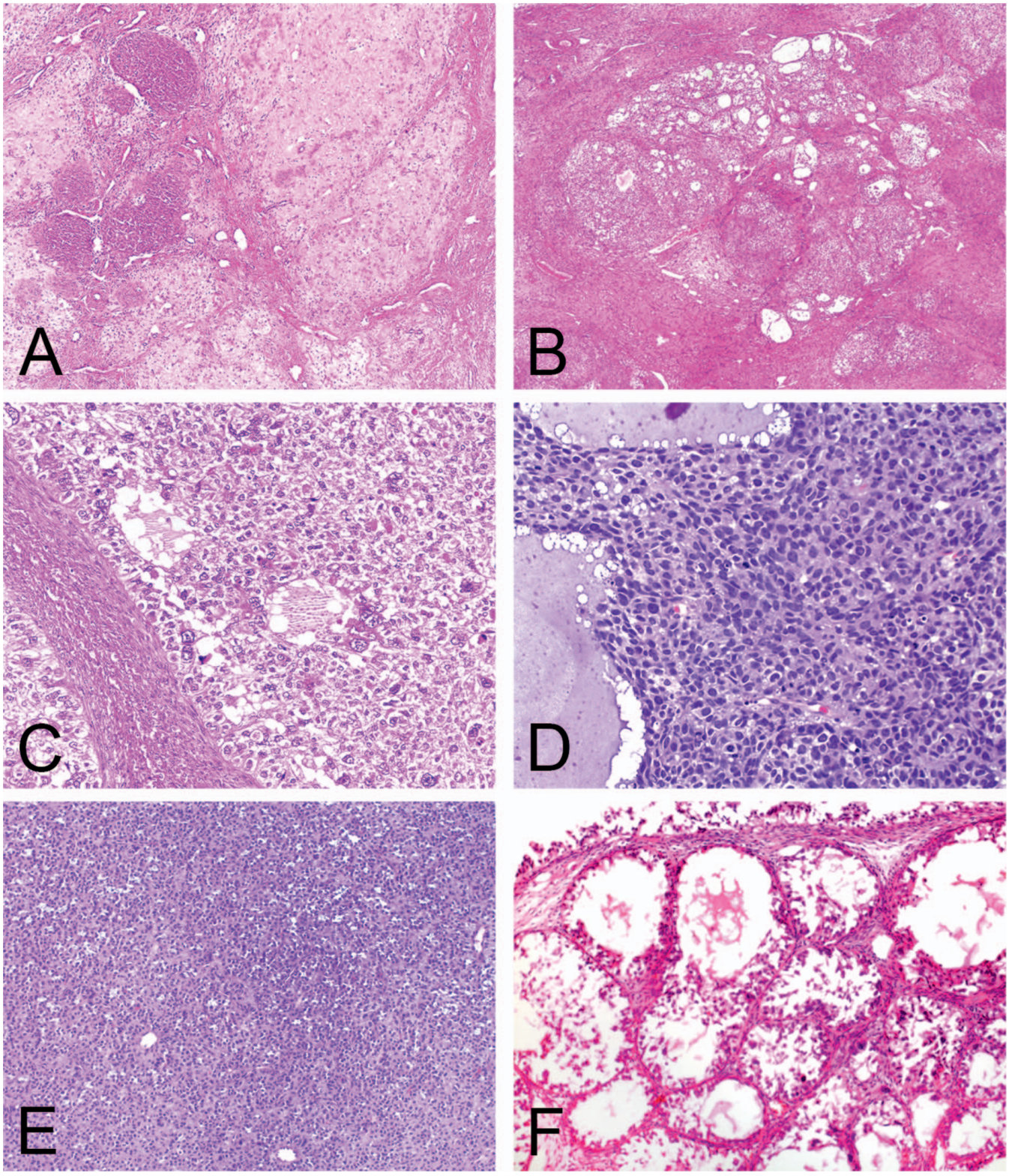

Figure 7. *Juvenile granulosa cell tumor. A, Extensive sclerosis. B, Microcystic to macrocystic pattern. C, Marked nuclear pleomorphism as is seen in 10% to 15% of these tumors. D, The neoplastic cells in this neoplasm had less cytoplasm than is characteristic, imparting a more basophilic appearance than is usual. Note 2 follicles. E, A largely solid neoplasm shows many spaces likely representing very early abortive follicular differentiation. F, Follicles, many of them dilated, result in an appearance vaguely reminiscent of tubulocystic clear cell carcinoma.*

certainly imagine the scenario just noted being an issue at the time of intraoperative evaluation by the pathologist. This is an area in which the gross findings may be helpful, as most dysgerminomas appear different from most cases of JGCT.

An occasional patient with a JGCT is pregnant, and pregnancy luteoma may rarely be in the differential because the latter may have follicle-like spaces[53] and the cells of that benign entity have abundant eosinophilic cytoplasm (Figure 12, F). They have much more homogenous patterns and cytologic features, albeit mitotic figures are not rare. In addition, the pregnancy luteoma is frequently multiple, bilateral, or both.

SERTOLI CELL TUMOR

In "Morris and Scully," Sertoli cell tumors are considered in the section on Sertoli-Leydig cell tumors and do not get their own separate heading.[2] Reference is made to the historically famous "folliculome lipidique" now usually referred to as lipid-rich Sertoli cell tumor. This is one example of a neoplasm having received disproportionate attention in the literature when one reflects on its great rarity. Indeed, Dr Scully's collection of sex cord tumors, which must be larger than any other existent that I am aware of, contains at most 2 or 3 examples of this very rare neoplasm. As we have recently reported a large series of Sertoli cell tumors,[54] and they are rare, I will not belabor the topic here other than to make a few remarks touching upon some of the more important or interesting aspects.

It should be emphasized that many tumors can mimic a Sertoli cell tumor by having acinar and tubular patterns, such that the Sertoli cell tumor is a diagnosis of exclusion and except in classic cases should be buttressed by immunohistochemical confirmation. These tumors are probably if anything less common than Sertoli-Leydig cell tumors and are characterized in most cases by a pure or predominant tubular pattern although occasional variant morphologies may be seen in tumors that are less well differentiated; the rare lipid-rich type, when it occurs in children, which it typically does, may result in isosexual pseudoprecocity and 4 among the small number of patients in this category have had Peutz-Jeghers syndrome.[55] These tumors of whatever subtype are almost invariably unilateral and stage I and typically have a lobulated, solid, yellow sectioned surface. On microscopic examination (Figure 8, A and B), most of the tubules are hollow or solid and the latter are usually elongated, sometimes resembling prepubertal testicular tubules. Rare neoplasms have a diffuse pattern of growth that on low power can be vaguely reminiscent on occasion of dysgerminoma because of an alveolar pattern (Figure 8, C; analogous to an issue described recently in testicular tumor pathology), and other less common patterns of Sertoli cell neoplasia include cords, trabecular, pseudopapillary, retiform, and spindled.[54] The tumor cells usually have relatively limited pale cytoplasm, except for the lipid-rich type, and occasional neoplasms that have abundant eosinophilic cytoplasm. A few of the latter have occurred in patients with Peutz-Jeghers syndrome. Most tumors are cytologically bland but a rare neoplasm has atypical features and may be clinically malignant. The differential diagnosis is broadly similar to that of Sertoli-Leydig cell tumors considered below.

SERTOLI-LEYDIG CELL TUMOR

These neoplasms (Figures 8, D through F; 9, A through F; and 10, A through F), arguably the most fascinating in the entire sex cord family, receive their own chapter in "Morris and Scully" and indeed, to the best of my knowledge, it was that work that popularized the descriptive designation *Sertoli-Leydig cell tumor* rather than arrhenoblastoma as was usually used in the literature as of that date.[2] The latter term was considered unsatisfactory because of its connotation of masculinization, which is a finding not always present in Sertoli-Leydig cell tumors (SLCTs) and indeed present in only 50% of the cases reported from Dr Scully's experience many years later.[56] That having been said, the clinical presentation of virilization of a young female is certainly a very dramatic one when it does arise, leading to individual cases of that phenomenon always being striking, particularly when associated with often fascinating morphologic features. These tumors overall occur at an average age of about 25 years with the well-differentiated tumors recurring on average about a decade later. The most intriguing of all, at least in my opinion, is the fact that those with a striking retiform pattern (see below) occur at a particularly young age, average age of 15 years, and indeed are the most common variant seen in the first decade of life. An unusual finding has been an elevated α-fetoprotein level but rarely as high as in cases of yolk sac tumor.

SLCTs have been associated sporadically for years with thyroid disease, embryonal rhabdomyosarcoma of the cervix, and pleuropulmonary blastoma. As each of these is now known to be associated with germline or tumor-specific mutations in *DICER1*, it is not surprising that most Sertoli-Leydig cell tumors have also been found to be *DICER1* related.[57,58] A recent analysis showed tumor-specific or germline *DICER1* mutations in 36 of 37 SLCTs.[57] In that study, half the patients were found to have predisposing germline *DICER1* mutations or mosaicism, and the documentation of this finding allowed screening of the offspring of these young women for pleuropulmonary blastoma. Notably, predisposing mutations may include deletions, thus testing of tumor tissue and germline DNA may be necessary to accurately determine if a SLCT is *DICER1* related and allow appropriate management and genetic counseling. When a germline *DICER1* mutation is identified, surveillance guidelines are available that may allow diagnosis of related conditions in their earliest, most curable form.

SLCTs typically have solid, lobulated, yellow sectioned surfaces and range from small to occasionally massive. Some tumors, especially those with heterologous or retiform components, are cystic and the former may mimic a mucinous cystic tumor. The cysts in the retiform tumors may contain papillary or polypoid excrescences and some retiform tumors have a spongy sectioned surface.[59] These 2 gross aspects can be very suggestive of the diagnosis, particularly in the first decade of life when other options are limited. Poorly differentiated tumors are usually large with frequent hemorrhage and necrosis.

Microscopic Features

Well-differentiated tumors are characterized by a predominant tubular pattern often growing in a lobular arrangement. The tubules typically have small round to oval lumens but may be cystic and can appear endometrioid-like.[60] Cells with copious eosinophilic cytoplasm, or

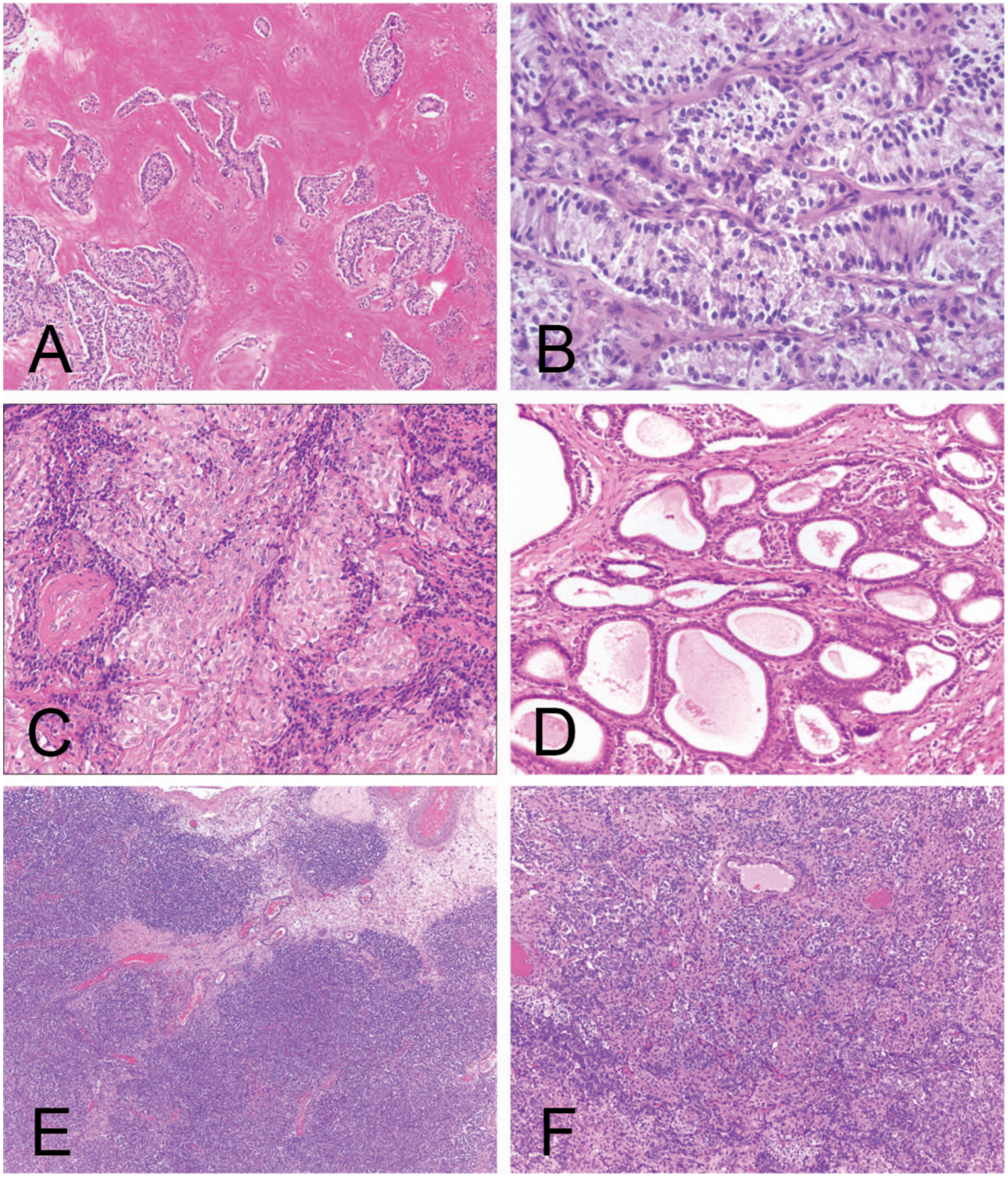

Figure 8. *Sertoli and Sertoli-Leydig cell tumors. A, Sertoli cell tumor. Typical solid tubules are separated by a prominent fibromatous-hyalinized stroma. B, Solid tubular pattern of Sertoli cell tumor. C, Sertoli cell tumor with large nested pattern. Note septal framework with inflammatory cells, resulting in an architecture reminiscent of dysgerminoma, but the cytomorphology is in marked contrast. D, Well-differentiated Sertoli-Leydig cell tumor. Numerous hollow tubules are separated by a stroma that contains focal Leydig cells. E, Sertoli-Leydig cell tumor of intermediate differentiation. Characteristic low-power view showing densely cellular lobules. F, Sertoli-Leydig cell tumor of intermediate differentiation. Ill-defined aggregates of darkly staining Sertoli cells separated by many aggregates of eosinophilic cells representing the Leydig cell component.*

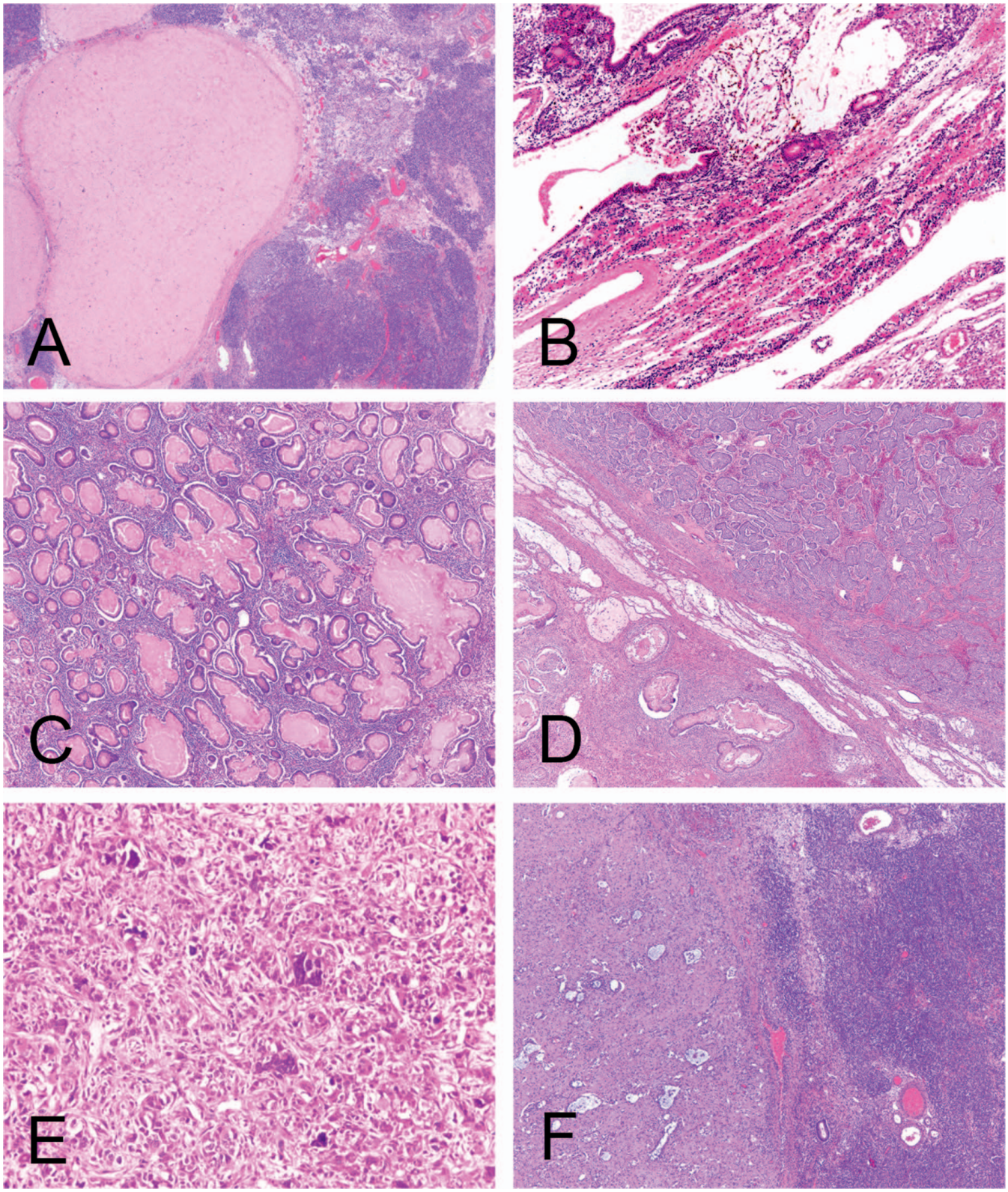

Figure 9. *Sertoli-Leydig cell tumor. A, Tumor of intermediate differentiation showing focally extensive sclerosis. B, Tumor of intermediate differentiation showing delicate cords and clusters of Leydig cells. A few heterologous tubules are also seen. C, Tumor with mucinous heterologous elements. D, Tumor with mucinous heterologous elements (bottom left) and insular carcinoid (top right). E, Tumor with bizarre nuclei. Same tumor as in (B). F, Pattern typical of juvenile granulosa cell tumor (left) occurring within Sertoli-Leydig cell tumor (right).*

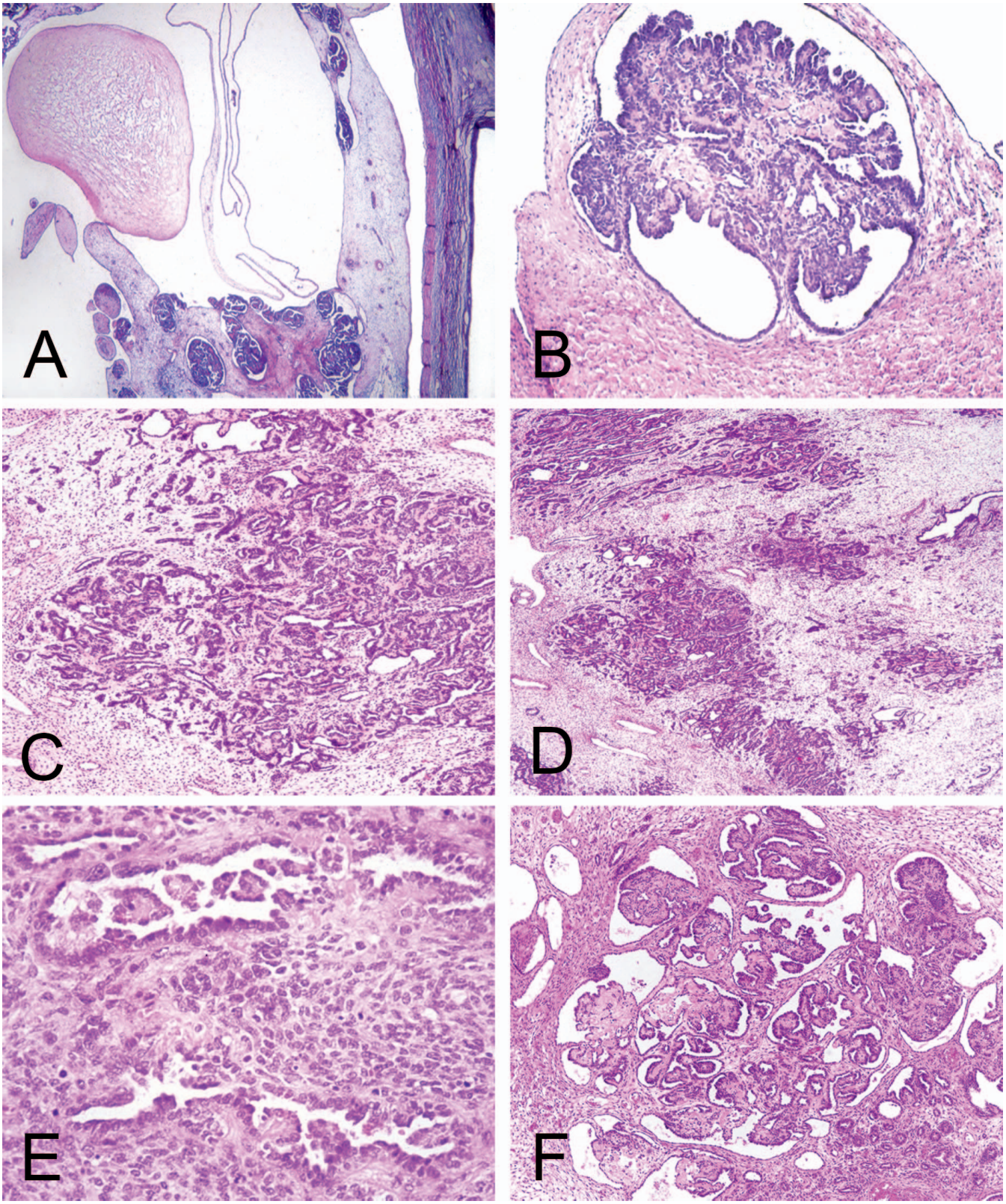

Figure 10. *Retiform Sertoli-Leydig cell tumor. A, Large edematous polypoid frond and many cellular papillae. B, Intracystic papillary pattern. C, Typical slitlike tubules. D, Cellular elements with background of prominent edematous stroma. E, Biphasic pattern. F, Complex papillary pattern.*

less often pale lipid-rich cytoplasm, consistent with Leydig cells, are usually prominent in the intervening stroma.

The typical low-power appearance of the more common tumors of intermediate differentiation is that of cellular masses, also often in a striking lobular pattern. The lobules are composed of immature Sertoli cells sometimes in an alveolar arrangement, with small, round hyperchromatic nuclei and usually scant cytoplasm admixed with Leydig cells; occasionally, the Sertoli cells have moderately abundant pale to clear cytoplasm that may be lipid rich. It may be difficult on occasion to know if such cells are epithelial or stromal in nature but it is of no consequence. Larger nests, solid and hollow tubules, thin cords, or occasionally broad columns are also frequent, the last noted seeming to be more common in tumors with a retiform component. Small or large cysts occur in some tumors, occasionally containing eosinophilic secretion, resulting in a struma-like appearance. Occasional nonspecific follicles may be seen and exceptionally they are conspicuous. Particularly intriguing are occasional SLCTs in which large nodules arise often with a rather loose basophilic aspect to the stroma and varying degrees of follicular differentiation, which when overt may produce a picture in isolation, indistinguishable from juvenile granulosa cell tumor. Some of these tumors have undoubtedly been diagnosed as gynandroblastoma in the past but the more I have seen them the more I think this is best considered just a variant differentiation within what is still fundamentally a SLCT. I would reserve the designation *gynandroblastoma*, or as Dr Scully would prefer to designate it *sex cord–stromal tumor of mixed types* for tumors in which large discrete foci in an individual neoplasm represent one variant of sex cord–stromal tumor and another sizeable component represents another. Spotty variant differentiation within what is dominantly another variant in my opinion should not result in the gynandroblastoma sex cord-stromal tumor of mixed cell types categorization. This is, one has to admit, largely a matter of personal preference. However, that the gynandroblastomas that Schultz et al[57] have studied have shown the *DICER1* mutation supports that they are fundamentally in the SLCT family. Poorly differentiated SLCTs exhibit only focally recognizable patterns of SLCT. These are usually composed extensively of solid sheets of poorly differentiated cells that range from epithelial-like to primitive mesenchymal in nature. The mitotic rate is high. Rarely the primitive epithelial appearance can mimic the picture of embryonal carcinoma. It is helpful in this regard that embryonal carcinoma, a relatively common neoplasm of the male gonad, is exceptionally rare in the female and I do not think I have seen a convincing example during a 40-year experience with numerous ovarian tumors. When seen in the ovary it is usually as a component of a mixed germ cell tumor.

The stromal component of the SLCT is most often edematous and typically contains Leydig cells. However, particularly in poorly differentiated tumors, it may consist of immature cellular mesenchyme tissue. A confusing feature of the Sertoli or Leydig component is the occasional presence of bizarre nuclei (Figure 9, E) similar to those seen slightly more often in the AGCT.

I now turn to surely one of the most intriguing of all subtypes of sex cord–stromal tumor, the so-called retiform variant of SLCT[60] (Figure 10). When I began a review of all of Dr Scully's cases of SLCT, I remember vividly coming across examples with a prominent retiform pattern and being struck by the confusion of the submitting pathologist and Dr Scully's somewhat laconic mention in his opinion letter that one could see this pattern occasionally. It became apparent to me that very few other, even expert, gynecologic pathologists had much awareness of this pattern and although he was reluctant, I was allowed to report them as a separate paper. It has ended up one of those I remember most fondly not only because of the inherent interest of the tumors but also because it clearly "put on the map" a tumor that before that delineation was often misdiagnosed as a carcinoma or even a malignant mixed mesodermal tumor. These account for 15% of SLCTs and exhibit focal to extensive patterns resembling those of the rete testis, usually occurring within otherwise typical intermediate and poorly differentiated SLCTs; heterologous elements may also be present. These patterns can, however, be the almost exclusive appearance of a tumor.

On microscopic examination, irregularly branching, elongated, narrow, often slitlike tubules and cysts with intraluminal papillae or polypoid projections are characteristic. Cysts may become markedly dilated and contain a colloid-like secretion. The tubules and cysts are lined by cells with varying degrees of stratification and nuclear atypicality. The papillae and polyps are of 3 types: small, rounded, and often with a hyalinized stroma; large and bulbous, often with edematous cores; and delicate and branching and lined by stratified cells and cellular buds, simulating the papillae of a serous tumor. The stroma varies from hyalinized (this being more common than in nonretiform tumors) or edematous (most common) to densely cellular and immature.

Heterologous elements are seen in 20% of SLCTs. It is most often mucinous epithelium but may be islands of fetal-type cartilage, rhabdomyosarcoma, or both; the latter 2 both tend to occur in poorly differentiated tumors.[8,9] The mucinous epithelium varies from benign, to borderline, to low-grade adenocarcinoma and may dominate such that rarely a pure mucinous tumor is mimicked. Insular or mucinous goblet cell carcinoids, almost always of microscopic size, occasionally arise from the mucinous epithelium. The carcinoid may take the form of scattered clusters of cells with eosinophilic cytoplasm that can mimic aggregates of Leydig cells if neuroendocrine stains are not used.

Differential Diagnosis

As my first foray into the world of sex cord–stromal tumors from the publishing viewpoint was as a participant in an article on issues related to Krukenberg tumors with a tubular pattern[6] mimicking SLCT (Figure 12, A), I begin this section with that tissue, which can embarrass pathologists if they diagnose a good prognosis lesion only to have further review or the course of disease show the opposite is true.

By circa 1980 Dr Scully had collected a series of 13 cases in which a tubular pattern in a Krukenberg tumor, often associated with stromal luteinization (responsible in some cases for androgenic manifestations), resulted in the misdiagnosis of a SLCT. The descriptive term *tubular Krukenberg tumor* was coined, as the tubules were the primary cause of the error although luteinization, hormone production, and the relative youth of many patients also contributed significantly. If one broadens the discussion point to SLCT versus Krukenberg tumor overall other occasional similarities can be mischievous. Both tumors often (SLCT) or occasionally (Krukenberg tumor) have a prominent low-power appearance of densely cellular lobules often separated in the case of each tumor by a

stroma that may exhibit conspicuous edema. A variety of features, frequent bilaterality of the Krukenberg tumor, and its various distinctive features inconsistent with SLCT, such as intestinal-type glands and signet-ring cells (only allowable in goblet cells of carcinoid foci in some heterologous SLCTs), should lead to the correct diagnosis. Immunohistochemical stains will also aid if needed, as the cells in the tubules will be inhibin negative if the tumor is a Krukenberg tumor. Of course, the stromal lutein cells of the Krukenberg tumor will be inhibin positive.

The SLCT may be confused with several neoplasms in the surface epithelial category: mucinous tumors, endometrioid tumors, serous tumors, and even malignant mixed mesodermal tumors. Confusion with serous tumors occurs in cases of the retiform variant, and a malignant mixed mesodermal tumor can be mimicked when retiform tubules are associated with primitive mesenchyme imparting a biphasic pattern. I remember well a tumor being submitted with a ''favor malignant mixed mesodermal tumor'' diagnosis but the child was 12 years old, which of course made that diagnosis unlikely, and it was a classic retiform tumor with cellular mesenchyme. Mucinous tumors can be suggested when heterologous elements dwarf the "parent" SLCT as occasionally happens, one of numerous examples one could provide of the crucial importance of thorough sampling in ovarian tumor evaluation. Confusion with endometrioid tumors of course pertains when the latter may mimic a sex cord tumor by forming small tubular glands or microacini, in particular, something considered earlier. Finally, at the outset having mentioned the contributions of both Dr Morris and Dr Scully on testicular feminization, it is worth briefly mentioning that the gonads of patients with that disorder are occasionally misdiagnosed as Sertoli-Leydig cell tumor if the bilaterality of the gonadal abnormality and an appreciation of the distinctive features of testicular feminization are not picked up.

SEX CORD TUMOR WITH ANNULAR TUBULES

The distinctive entity (Figure 11, A through D), characterized so aptly by the above designation, is intriguing both clinically and morphologically.[61] For reasons noted at the outset of this essay, it is one for which I have special affection and indeed was the subject of my first original publication on sex cord-stromal tumors.[62] By the time I had the privilege of working on it, it was a well-established entity based on Dr Scully's seminal description of it in 1970,[61] a year that is notable for being the year of publication of another of his remarkable articles, that being his magnum opus on gonadoblastoma. Enigmatically, there is some overlap in the morphology of the 2 entities even though they are clinically so different. My review of Dr Scully's files recently disclosed that, as best I can ascertain, the first referral case of sex cord tumor with annular tubules that he included in either his 1970 or 1982 articles was sent to him by Dr Hazel Gore in 1962 (case 7 of the 1982 article). In his letter of consultation he mentions having seen the pattern twice before and I surmise that one of those cases must be a very old MGH case from 1938, which was also included in the 1982 article, but the other case remains a mystery with regard to its origins. During the 1960s he obviously became progressively interested in this fascinating lesion such that late in that decade he undertook a thorough investigation of the reported ovarian neoplasms in patients with Peutz-Jeghers syndrome and found that 3 of the 12 cases were further examples of the sex cord tumor with annular tubules. By the time of my arrival with a case in my suitcase, he had seen yet further cases such that when they and those in the literature were combined in 1982, we had 27 cases of the process occurring in patients with Peutz-Jeghers syndrome, the remainder being nonsyndrome associated, the total series amounting to 74 cases. By that time an association with adenoma malignum of the cervix had also become apparent and 4 of the patients with Peutz-Jeghers syndrome had that cancer also. In contrast to the ominous implications of the cervical process, the sex cord tumor with annular tubules in patients with Peutz-Jeghers syndrome is usually clinically benign, but there are rare exceptions in which the process has evolved into a malignant lesion and in yet other cases it has evolved into a Sertoli cell tumor. A recent tabulation of the literature on ovarian sex cord–stromal tumors other than typical sex cord tumors with annular tubules occurring in Peutz-Jeghers syndrome found that there were 6 Sertoli cell tumors, 4 of the lipid-rich type and 2 of the oxyphilic type.[55] There were 2 sex cord–stromal tumors with their own unique features that we described,[63] 2 examples of malignant sex cord tumor with annular tubules, a granulosa cell tumor, 2 Sertoli-Leydig cell tumors, and miscellaneous others.

The typical sex cord tumor with annular tubules in the Peutz-Jeghers cases is usually an incidental microscopic finding but a small nodule up to 3 cm is occasionally observed. The process is typically bilateral and multifocal and often focally calcified.

Lesions of the same name found in patients without Peutz-Jeghers syndrome contrast with those that are syndrome associated by almost always being larger, unilateral, and not calcified. They may be associated with progesterone production and more frequently exhibit lymph node spread than other sex cord tumors. Grossly, they are usually solid and yellow but occasional examples are markedly cystic.

This lesion is typified by sharply circumscribed rounded nests containing ring-shaped tubules typically encircling hyalinized basement membrane–like material (Figure 11, A and B). The nests may contain simple tubules encircling a central rounded hyaline mass or may be more complex with communicating tubules encircling multiple hyaline masses. The hyaline material may connect with similar material surrounding the tubules. The centers of the tubules are filled with pale cytoplasm and the nuclei are characteristically located antipodally at the periphery of the tubules. Calcification typically occurs within the center of the tubules and may focally efface the epithelial component. Occasionally, within aggregates of the tubular formations there is a proliferation of cells with a solid pattern that may occasionally be composed of lipid-rich cells. We have seen one remarkable case in which this central confluent zone within an aggregate of tubules was characterized by a striking microcystic morphology. In other cases, as is alluded to above, the sex cord tumor with annular tubules evolves into a confluent overgrowth of cells with Sertoli characteristics (Figure 11, C) having a diffuse growth of oxyphil cells or in some cases, tubules typical of the so-called lipid-rich Sertoli cell tumor.

The morphology of this lesion is so distinctive that its differential diagnosis is limited but it must be acknowledged that some authorities believe it overlaps sufficiently with, at least in some cases, Sertoli cell tumor, or in other cases, granulosa cell tumor, that it is not necessarily a distinctive

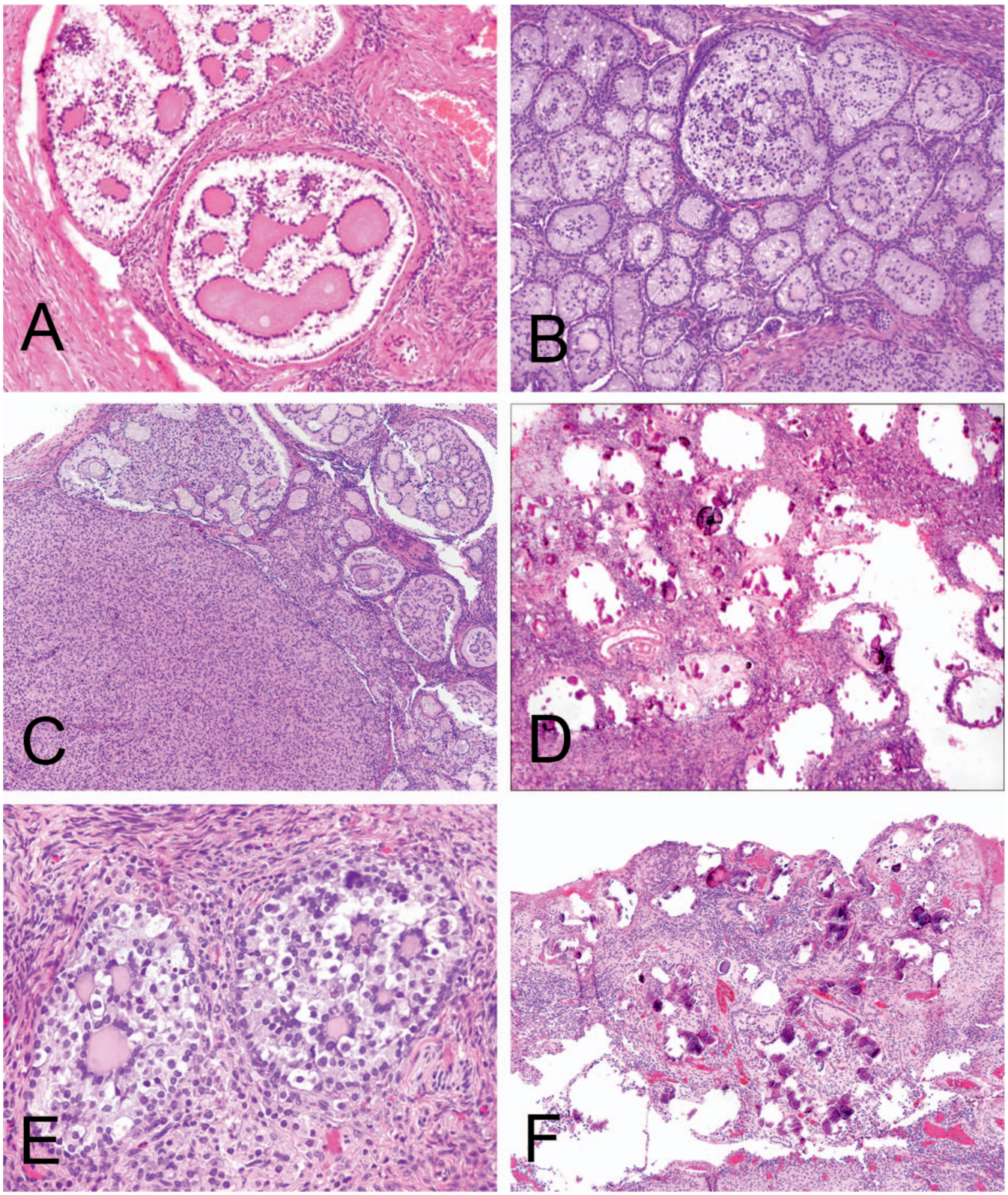

Figure 11. *Sex cord tumor with annular tubules (A through D) and gonadoblastoma (E and F). A, Classic tubules of SCTAT. Patient had Peutz-Jeghers syndrome. B, Classic pattern of SCTAT, nonsyndrome associated. C, SCTAT from patient with Peutz-Jeghers syndrome merging with solid pattern of Sertoli cell tumor. D, SCTAT with calcification in patient with Peutz-Jeghers syndrome. E, Gonadoblastoma. The pattern is SCTAT-like but rare germ cells are also present. F, Calcification in gonadoblastoma. Note similarity to appearance in D.*

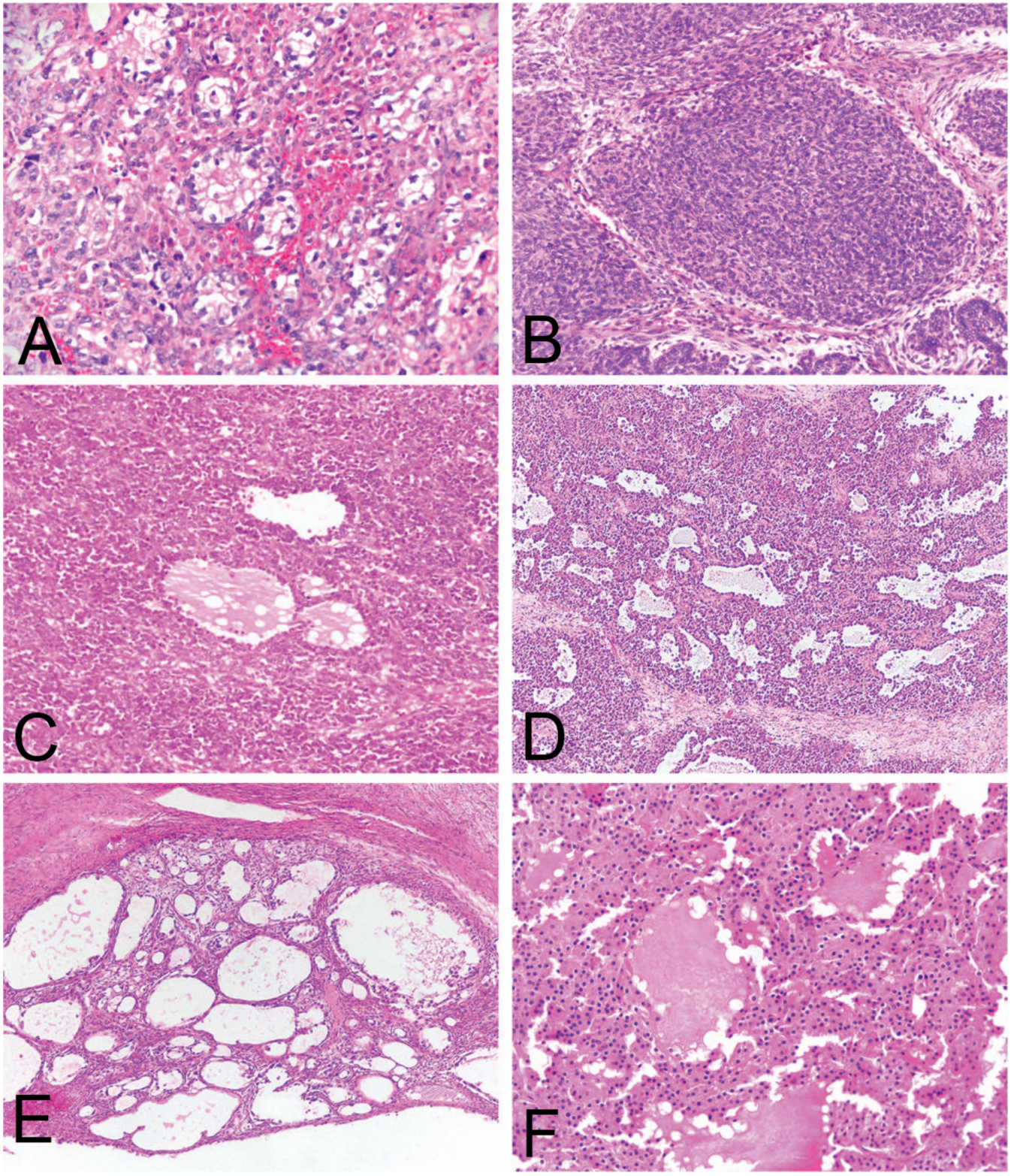

Figure 12. *Selected mimics of sex cord–stromal tumors. A, Tubular Krukenberg tumor. The tubules may be misconstrued as Sertoli tubules and luteinized stromal cells as Leydig cells. B, Endometrioid carcinoma. An insular pattern with uniform cells may suggest insular granulosa cell tumor. C, Small cell carcinoma of hypercalcemic type. Follicles may suggest a granulosa cell tumor. D, Dysgerminoma. Rarely follicle-like spaces are conspicuous and may suggest a follicle-forming tumor such as granulosa cell tumor. E, Yolk sac tumor. Cysts may suggest the follicles of a granulosa cell tumor. F, Pregnancy luteoma. Follicle-like spaces and typical abundant eosinophilic cytoplasm may suggest a juvenile granulosa cell tumor.*

neoplastic proliferation, but I feel strongly otherwise as Dr Scully did. It really does have a particularly distinctive pattern, which is unlike anything one sees for the most part in other sex cord–stromal tumors, albeit one has to acknowledge overlap to a degree in various formations seen in sex cord–stromal tumors. That does not detract from the fact that typical forms represent unequivocal distinct entities. There is a superficial resemblance between the annular tubules pattern and the formations seen in the nests of gonadoblastoma (Figure 11, E), but the latter almost always contains germ cells, at least in most of them, and that entity more typically is calcified even though the calcification that occurs in each can look similar (Figure 11, D and F). Also, of course, the clinical setting is markedly different in most cases.

Concluding Remarks

I have presented some reflections on the morphology and resultant diagnostic issues that arise in association with the remarkable family of sex cord–stromal tumors of the ovary. They may be mimicked by many neoplasms (Figure 12, A through E), even tumor-like lesions (Figure 12, F), and the converse can happen. It has not been possible to consider everything; for example, some interesting tumors that fall in the unclassified category did not receive comment.[64] I have also not considered neoplasms that contain sex cord as well as germ cell elements, so-called mixed germ cell sex cord–stromal tumors of which the gonadoblastoma is the most remarkable example, although I have briefly noted it above in the differential diagnosis of the sex cord tumor with annular tubules. Both these entities and many others are known to us exclusively or mostly due to the remarkably astute eye and awareness for associated clinical manifestations that was one of many hallmarks of my mentor, the late Dr Robert E. Scully, a truly great morphologist and practitioner of medicine. We are all indebted to him for his many insights not only in this area of gynecologic pathology but in many others. His name will be mentioned as long as the neoplasms, both common and uncommon in this and other families of gonadal neoplasia, are evaluated by the light microscope, and his observations will stand the test of time.

ACKNOWLEDGMENTS

As is apparent from the title and tenor of other remarks, my greatest debt is to my mentor, Robert E. Scully, MD, with whom I had the privilege of working for more than 3 decades. His example at the microscope and personal qualities will always be treasured.

Many of the cases illustrated and reflections formed were based on review of many cases in Dr Scully's collection with Dr Jennifer N. Stall (now with Hospital Pathology Associates, Minneapolis, Minnesota) when she served for a year as the surgical pathology fellow for the Robert E. Scully Collection. I am grateful to her for unearthing from his collection many interesting cases and for her own insights when studying them with her. Dr Kris Ann Schultz of Children's Hospital, Minneapolis, Minnesota, kindly provided advice on the section pertaining to the *DICER1* mutation.

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