A D D E N D A

TO THE

CALIFORNIA TUMOR TISSUE REGISTRY

FORTY-FIRST SEMI-ANNUAL SLIDE CONFERENCE

ON

OVARIAN TUMORS

MODERATOR:

ROBERT E. SCULLY, M. D.
CLINICAL ASSOCIATE IN PATHOLOGY, HARVARD MEDICAL SCHOOL
ASSOCIATE PATHOLOGIST, MASSACHUSETTS GENERAL HOSPITAL
BOSTON, MASSACHUSETTS

February 26, 1966

ORDER OF DISCUSSION OF CASES

(Note: Slides with the lower Accession number are the "A" sections; the higher number, "B" sections. The only exception is case number 1 - Accession Nos. 11708A and 10804B).

Order of discussion of cases - 2

FEBRUARY 26, 1966

ACCESSION NO. 12955
(10A)

ACCESSION NO. 14051
(10B)

MODERATOR'S DIAGNOSES: Proliferating serous papillary cystadenomas without stromal invasion (possibly malignant).

Both tumors are similar in that they are papillary neoplasms in which both blunt and fine papillae are lined by cells which are ciliated in the well differentiated portions and elsewhere are proliferating more actively with nuclear atypicality, loss of polarity and occasional mitoses. Each shows the breaking off of tiny buds of tumor cells into the lumens of the cysts. Case No. 10B, at least in some of the sections, appears somewhat more malignant than Case No. 10A in that the epithelial budding is more exuberant. Both tumors are secreting mucus; the mucus in Case No. 10A is quite thick and as a result the fluid that was observed on gross examination was described as being thick and cloudy. This case illustrates the difficulty that is sometimes encountered in distinguishing serous and mucinous cystic tumors by inspection of the fluid. The serous tumors can produce mucus, which is sometimes quite concentrated; on the other hand, occasional mucinous cystic tumors produce a very thin, almost watery, mucus that simulates serous fluid. Other ovarian tumors such as the endometrioid group, the clear cell carcinomas and the metastatic carcinomas, can also produce mucus.

These two tumors, characterized by stratification of nuclei, some atypicality and solid epithelial budding belong in a category that has been called by various names in the literature, including "cystadenoma of borderline malignancy" and "papillary serous cystadenocarcinoma, Grade I or low grade." Recently an expert committee of the International Federation of Obstetrics and Gynecology (Stockholm, 1961) has coined the term "proliferating serous papillary cystadenoma without stromal invasion (possibly malignant)" to emphasize the epithelial proliferation and the fact that although these neoplasms may implant on the peritoneal surfaces, they have little or no invasive or metastatic potential. Although there have been few large series reported, the 5-year salvage for these tumors appears to be in the 80 - 90% range. They have a tendency to implant on the peritoneum, may have a prolonged course over a period of years when they do implant with late clinical recurrences, and on rare occasions undergo spontaneous regression. It is important for reporting purposes to separate these tumors from the frankly invasive papillary carcinomas, which have a more malignant clinical course.

FEBRUARY 26, 1966

ACCESSION NO. 12955
(10A)

ACCESSION NO. 14051
(10B)

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FEBRUARY 26, 1966 ACCESSION NO. 11708
(1A)

MODERATOR'S DIAGNOSIS: Serous adenofibroma with epithelial atypicality.

This tumor is composed of glands of irregular shape distributed in a fibroma-like proliferation of ovarian stromal cells. The epithelial cells exhibit some piling up and occasional mitoses, but the changes are insufficient for a diagnosis of malignancy. The glands bear some resemblance to endometrial glands, but the prevalence of ciliated cells suggests a greater kinship to fallopian tube epithelium. The mesenchymal component of the tumor is for the most part densely fibrous; often in the vicinity of the neoplastic acini, it is more cellular and the cells resemble theca externa cells. The tumor cells are secreting mucin, and special stains show that the mucin is located along the free borders of the cells and in some instances in the portion of the cytoplasm bordering on the gland lumen. Epithelial tumors of the ovary with a prominent fibrous component derived from the ovarian stroma are often referred to as adenofibromas or cystadenofibromas. Since almost all of the common epithelial tumors have some "stromal" component, the borderline between a cystadenoma and an adenofibroma is necessarily an arbitrary one; some authorities feel that the solid component should comprise at least half of the volume of the tumor in order for it to qualify as an adenofibroma. An adenofibroma may have serous, mucinous, endometrial or clear cell (so-called mesonephric) epithelium.

FEBRUARY 26, 1966

ACCESSION NO. 12437
(2B)

ACCESSION NO. 9382
(2A)

ACCESSION NO. 11154
(14A)

MODERATOR'S DIAGNOSES: Primary mucinous tumors.

Case No. 2B is a neoplasm composed of cysts and glands lined by epithelium resembling that of the large intestine and of a connective tissue component similar to that of a fibroma. The cells lining the acini are piled up with some loss of polarity and occasional mitoses. We consider this degree of atypicality sufficient to place the tumor in the borderline or possibly malignant category. Because relatively benign appearing mucinous tumors of the ovary can be associated with peritoneal implantation the criteria for malignancy based on clinico-pathological correlation are not as clearcut as they are for most other types of neoplasms, and controversy has resulted. Thus, figures for malignancy among mucinous tumors of the ovary vary from about 12 to 45% in the literature. The presence of typical goblet cells in mucinous tumors, as seen in this case, is one of the pieces of evidence suggesting an endodermal nature and teratomatous origin of at least some of these neoplasms. The presence of argentaffin granules in the basal portions of some of the tumor cells is further evidence because argentaffin granules are not found in the normal female genital tract. However, an adenocarcinoma of the cervix that contained argentaffin cells has recently been reported, suggesting the possibility that cells of mesodermal origin may under certain circumstances be able to form argentaffin granules.

Case No. 2A is one of a mucinous cystadenocarcinoma in which there are a few areas of well differentiated epithelium with mucus uniformly distributed in the cytoplasm of the cells, but in many regions the cells are proliferating forming cellular papillae and glands with a cribriform pattern. Mitoses are frequent and occasionally atypical. In some areas goblet cells are prominent, and again argentaffin granules can be demonstrated in some of the tumor cells.

Case No. 14A is a tumor composed of closely packed small cysts and acini lined by signet cells that are jumbled up and characterized by nuclei that vary in size and shape, and show occasional mitotic activity. The material in the tumor cells has a granular appearance, suggesting mucus, and its presence is confirmed by special stains. This type of carcinoma is non-specific and is an unusual form of primary tumor of the ovary; similar tumors can be seen in

the pancreas and elsewhere, so that when one encounters this type of carcinoma in the ovary he has to consider the possibility of a metastasis. Apparently, although the pancreas was embedded in tumor at autopsy in this case, the prosector thought that the site of origin of the tumor was the ovary, and not the pancreas.

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FEBRUARY 26, 1966 ACCESSION NO. 14295
(19B)

MODERATOR'S DIAGNOSIS: Mucinous cystadenoma with luteinization of stroma.

This tumor is composed of glands and cysts lined by mucus-secreting epithelium that is generally well differentiated, but in a few areas shows piling up and hyperchromatism of its nuclei with occasional mitoses. The stroma of the tumor is edematous and is composed of spindle cells that exhibit diffuse differentiation into luteinized cells characterized by abundant granular eosinophilic cytoplasm and round nuclei containing single nucleoli. This neoplasm falls into the category of ovarian tumors with functioning stroma. Such tumors may be benign or malignant, and primary or metastatic. They are characterized morphologically in most cases by a differentiation of their stroma, which is derived from the ovarian stroma, into luteinized cells having the appearance of luteinized stromal or thecal cells. They may be associated with estrogenic, androgenic or progestational effects. When they are accompanied by endometrial hyperplasia it may be difficult to prove a cause and effect relationship between the tumor and the endometrial change. However, the cases that have been accompanied by virilism have often shown regression of the androgenic manifestations after the removal of the tumor. In this case the 17-ketosteroid level dropped to 5.6 mg. per 24 hr. eight days after the operation. Subsequently, the hirsutism decreased markedly and there was some improvement in the voice and a slight decrease in the size of the clitoris; the acne disappeared and normal menstrual cycles were resumed 6 weeks after the removal of the tumor. Two years and eight months after the operation, the patient had a normal delivery; at that time she still had a somewhat deep voice, an excess of hair and some enlargement of the clitoris. Recent biochemical studies support the concept that a variety of tumors may stimulate the ovarian stroma to differentiate into functioning tumor stroma and produce steroid hormones. Androgens, estrogens, progesterone and other steroids have been recovered directly from a virilizing Krukenberg tumor of a pregnant woman. A masculinizing Brenner tumor that occurred during pregnancy formed testosterone in vitro from radioactive precursors, but only in the presence of human chorionic gonadotropin. The latter finding correlates well with the increased incidence of virilizing tumors with functioning stroma in pregnant women, presumably due to stimulation of the tumor stroma by chorionic gonadotropin.

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FEBRUARY 26, 1966

ACCESSION NO. 14432
(25A)

ACCESSION NO. 11217
(14B)

ACCESSION NO. 13615
(12B)

MODERATOR'S DIAGNOSES: Endometrioid carcinomas.

The term endometrioid carcinoma is one that has been recently accepted by the International Federation of Obstetrics & Gynecology expert committee on ovarian tumors as a name for primary carcinomas of the ovary that are indistinguishable microscopically from the classic carcinoma of the corpus uteri, whether or not an origin from benign endometriosis can be demonstrated.

Case No. 25A is a composite of 3 cases of endometrioid carcinoma that vary in grade from I to III. One of these tumors arose from the epithelium lining an endometrial cyst. There is a variation from one case to another; some of the slides show a stimulation of the stroma of the tumor that has caused it to differentiate in the direction of cells resembling theca externa cells and luteinized theca interna cells characterized by a rounded shape, abundant cytoplasm and a round nucleus containing a prominent nucleolus. This type of stimulation of the stroma is sometimes associated with steroid hormone production and this aspect of ovarian tumors has been discussed. Some of the slides may also show occasional foci of squamous differentiation in the glands, constituting focal adenoacanthoma.

Case No. 14B is a rather poorly differentiated ovarian carcinoma, which was partly solid and partly cystic. Much of the tumor has a solid architecture microscopically, but glands that are indistinguishable from those of low grade endometrial carcinoma can also be identified, establishing the diagnosis of endometrioid carcinoma. It is possible that the solid type of growth represents a poorly differentiated acanthomatous element, but it is difficult to be certain of this.

Case No. 12B is a bilateral adenoacanthoma of the ovary associated with and presumably arising in benign endometriosis. This tumor is secreting mucus, but like the cells of the serous tumors and unlike those of the mucinous tumors, the neoplastic cells contain mucus only along their free borders or at most in the uppermost portion of the cytoplasm.

FEBRUARY 26, 1966

ACCESSION NO. 14432
(25A)

ACCESSION NO. 11217
(14B)

ACCESSION NO. 13615
(12B)

Endometrioid tumors of the ovary may be benign, of borderline malignancy or frankly malignant. Endometriosis, itself, is not a neoplastic process, but benign forms of endometrioid tumors are occasionally observed. An adenofibroma may have glands that resemble those of the endometrium rather than being lined by typical serous epithelium; these glands may show squamous metaplasia. Occasionally one sees an endometrioid adenomyoma or a tumorous mass in the ovary that resembles an endometrial polyp. The endometrioid carcinomas probably comprise between 10 and 20% of all ovarian carcinomas. They may be cystic or solid; the cysts may be degenerative or may be benign endometrial cysts, from the epithelium of which the carcinoma arose. An origin from endometriosis has been reported in only a small proportion of the cases, but undoubtedly could be demonstrated with much greater frequency if a special effort was made to do so. Not infrequently, the pathologist is confronted by cancer that involves the uterus as well as one or both ovaries and it is often difficult to decide then whether the ovarian or the uterine tumor is primary. Occasionally the neoplasms of the two organs are of a different microscopic structure and are obviously independent primary tumors, but in the great majority of the cases both are adenocarcinomas or adenoacanthomas of the endometrial type. In the literature on coexistent ovarian and uterine cancers most of the attention has been focused on the adenoacanthomatous varieties. Among 40 adenoacanthomas of the ovary observed at the Mayo Clinic, two-thirds were definitely or possibly accompanied by a similar appearing tumor in the uterine corpus, which was less than 2 cm. in diameter in approximately half of the cases. The 5-year survival rate among the 27 patients with tumors of both organs who survived the operation and were followed thereafter was 50%, a higher salvage than one might expect if a cancer of one organ had metastasized to the other, suggesting that in many cases the neoplasms were independent primaries. We diagnose endometrioid carcinoma of the ovary even in the presence of carcinoma of the endometrium, if the latter is small, of low grade and noninvasive or minimally invasive of the myometrium. It is important to recognize endometrioid carcinomas of the ovary because there is little statistical information in the literature as yet on their behavior and guidelines for treatment are not as well established as they are for other varieties of ovarian cancer. It is very possible that the well differentiated forms of endometrioid carcinoma will respond to the progestational drugs in a manner similar to that of the well differentiated carcinomas of the corpus uteri. The microscopic diagnosis is made solely on

the resemblance of the tumor to the classic carcinoma of the endometrium. In some cases it may be impossible to decide whether the tumor is primary or a metastasis from an endometrial cancer, and in others, the differentiation between an endometrioid carcinoma and the mucinous carcinoma of the type that resembles bowel cancer may be most difficult. The presence of squamous differentiation indicates that the tumor almost certainly belongs in the endometrioid category. In some instances one may encounter patterns suggesting an admixture of endometrioid and serous, or endometrioid and mucinous carcinomas. Finally, it must be mentioned that endometrioid carcinomas can arise in extrovarian endometriosis and forms of cancer other than that resembling the classic carcinoma of the endometrium can originate in endometriosis of the ovary and elsewhere.

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FEBRUARY 26, 1966 ACCESSION NO. 14558 (25B); ACCESSION NO. 12931 (3A); ACCESSION NO. 14223 (24A); ACCESSION NO. 13304 (3B); ACCESSION NO. 10804 (1B); ACCESSION NO. 14362 (23B).

MODERATOR'S DIAGNOSES: Clear cell tumors, so-called mesonephromas.

Schiller introduced the concept of mesonephroma of the ovary in 1939. His original report contained what are now considered by most aurthorities to be two distinct types of tumor, (1) a germ cell tumor composed of embryonal cells forming a network of spaces into some of which protrude single papillary projections containing a capillary and lined by tumor cells, and (2) a tumor containing cells of a more adult appearance characterized by a hobnail shape or an abundant clear cytoplasm full of glycogen. In the current literature the first type of tumor is now generally believed to be of germ cell origin and is called either embryonal carcinoma or endodermal sinus tumor. This tumor will be discussed subsequently (See 20B). It is the second type of tumor with which we are concerned that was later termed parvilocular cystoma by Schiller, but is more frequently referred to as mesonephroma, mesometanephroma, mesonephric carcinoma or clear cell carcinoma. Several detailed articles on the mesonephroma have stressed its microscopic variability. The diagnostic criteria stressed by most authors have included: (1) the presence of tubules and cysts; (2) cells with a hobnail or peg-shape; (3) cells with clear cytoplasm full of glycogen resembling those of a renal cell carcinoma; (4) cells with abundant granular eosinophilic cytoplasm; (5) the presence of mucin in the lumens of the tubules and cysts; (6) multiple papillary projections into the tubules and cysts; (7) intracystic proliferations of tumor cells and stroma creating a resemblance to glomeruli; (8) round coalescent vacuoles similar to those of the adenomatoid tumor; and (9) in some cases, a cellular proliferation of the ovarian stroma. Most authors have discussed only the carcinomatous form of this tumor, but Wade-Evans and Langley, and Schiller have described a benign form. In view of the fact that many ovarian tumors have certain of the features that are described as characteristic for the mesonephroma, and various authorities have somewhat different concepts of what the category should include, it is not surprising that there is considerable difference of opinion as to whether tumors that display only a few of the described characteristic features should be called mesonephromas. Cases 3A, 3B, 24A and 25B are malignant tumors that show a number of the so-called diagnostic features of this tumor and would most probably be accepted as mesonephromas by the authors who have discussed this type of tumor in the literature. Case 24A is of particular interest in that there are many small cysts filled with deeply staining eosinophilic fluid, which has a superficial resemblance to colloid; this tumor could easily be mistaken for a malignant struma ovarii. Case 1A is a tubular papillary carcinoma that has some of the features of the so-called mesonephroma; its tubular architecture and the

presence of a moderate amount of glycogen in the cytoplasm of the tumor cells are in favor of this interpretation, but one would prefer to examine additional material on this case before arriving at a definite diagnosis. Case 23B, which presented grossly as a firm fibrous tumor with multiple small cysts, is in general a benign-appearing tumor with occasional foci of atypical small acini. This neoplasm might be classified as a form of adenofibroma, but it is more specifically what Schiller called a parvilocular cystoma and what Wade-Evans and Langley include among the better differentiated mesonephric tumors. It is characterized by small cysts lined by cells that are flattened in some areas and hobnail in shape in the more actively proliferating regions. There is a very cellular stroma, which shows occasional mitoses, contains a few small foci of luteinized cells and in areas has hyalin plaques similar to those seen in tumors of the thecoma-fibroma group. The material in the lumens of the cysts stains weakly with mucicarmine.

The main evidence for considering the above tumors as mesonephric or metanephric is: the occurrence of tumors showing these characteristics along the course of the mesonephric ductal system, the frequent presence of clear cells resembling those of the renal cell carcinoma and the resemblance of the better differentiated tubular structures to normal tubules of mesonephric origin in man. This circumstantial evidence has not been convincing to us and other pathologists, and for that reason we have chosen to call these neoplasms clear cell tumors rather than giving them a specific name. One reason for being very skeptical about their mesonephric nature is that tumors indistinguishable from them can be seen arising directly from the uterine endometrium in which no mesonephric derivatives exist. Secondly, we have now seen about 10 of these tumors that have arisen in the wall of an endometrial cyst. Thirdly, we have encountered transitions between these tumors and adenoacanthomas in the ovary. And finally, in 13 cases of these tumors in which an origin in endometriosis could not be demonstrated, pelvic endometriosis at a distance from the tumor was definitely present in 5 and possibly present in 2 others; the coexistence of endometriosis with other ovarian carcinomas, with the exception of the endometrioid carcinoma, is in contrast, rare (8 per cent of all ovarian cancers - Corner, G. W., Jr.,quoted in Ovarian and Fallopian Tube Tumor Fascicle). It is of interest that among the 6 cases that are being discussed here, 2 (24A and 25B) were associated with endometriosis despite the fact that no particular search was apparently made for its presence. Grossly, the clear cell carcinomas of the ovary vary in appearance; the most characteristic is that of a cyst, sometimes filled with chocolate fluid, into which cauliflower-like brownish-yellow or buff-colored nodules protrude.

FEBRUARY 26, 1966 ACCESSION NO. 14558 (25B); ACCESSION NO. 12931 (3A); ACCESSION NO. 14223 (24A); ACCESSION NO. 13304 (3B); ACCESSION NO. 10804 (1B); ACCESSION NO. 14362 (23B).

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FEBRUARY 26, 1966

ACCESSION NO. 12771 (18A)
ACCESSION NO. 14027 (18B)
ACCESSION NO. 14448 (22B)

MODERATOR'S DIAGNOSES: Carcinosarcoma.

All of these tumors contain an admixture of adenocarcinoma, which in case 18A particularly, resembles endometrioid adenocarcinoma, and a sarcoma characterized by the presence of strap cells and occasional flask-shaped cells suggesting rhabdomyoblasts. We were able to identify cross striations in the strap cells in the 2 almost identical tumors that are labeled 22B. In case 18A some of the mesenchymal tumor cells contain hyalin droplets similar to those that have been described in the spindle cells of the so-called pseudosarcoma of the upper respiratory tract.

There are only a few tumors in the literature that have been diagnosed as carcinosarcoma or mixed mesodermal tumor of the ovary, although this type of neoplasm is probably much more common than the paucity of cases in the literature suggests. These tumors, which resemble the carcinosarcomas and mixed mesodermal tumors of the uterus, are seen in the great majority of cases in post-menopausal women. They are probably misdiagnosed as malignant solid teratomas in some instances, but there are clinical and pathological differences between these two varieties of tumors. To the best of our knowledge, a true malignant solid teratoma has never been observed after the menopause. The solid teratomas contain elements derived from all three germ layers and neural elements are often a prominent feature; on the other hand, the mixed mesodermal tumors are composed of tissues that can all be derived from mesoderm and the carcinomatous elements resemble those of carcinomas of the Mullerian tract rather than the embryonal forms that are found in the solid teratomas. Also, the cartilaginous elements of the mixed mesodermal tumors may be much more bizarre in appearance than in the malignant solid teratoma. It is possible that some of the carcinosarcomas of the ovary arise from endometriosis. One has been reported originating in the wall of an endometrial cyst, and a careful search for such an origin should be made in every case.

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FEBRUARY 26, 1966

ACCESSION NO. 12771 (18A)
ACCESSION NO. 14027 (18B)
ACCESSION NO. 14448 (22B)

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FEBRUARY 26, 1966

ACCESSION NO. 12745 (17A)
ACCESSION NO. 14098 (17B)

MODERATOR'S DIAGNOSES: Brenner tumors, benign and malignant.

Case 17A is a typical Brenner tumor composed of nests of transitional-type epithelium containing glycogen and embedded in a proliferation of ovarian stroma that resembles a tumor of the fibroma-thecoma group. The stroma is quite cellular in some areas especially in relation to the epithelial nests; it contains occasional hyalin plaques, a few of which are partially calcified; also present in the mesenchymal element of the tumor are nests of cells with eosinophilic cytoplasm and round nuclei, cells that are referred to as luteinized because of their morphologic resemblance to the cells of the corpus luteum. The unusual history of regular bleeding beginning at the age of 60 and the finding of active-appearing adenomyosis in the uterus suggest the possibility of abnormal estrogen levels in this patient, which were confirmed by biochemical studies of the tumor tissue. The luteinized cells of the stroma would appear to be the most likely site of formation of the estrogens. There is evidence from the literature of an association between Brenner tumors of the ovary and hyperplasia or carcinoma of the endometrium. This association has probably been exaggerated because many of the cases are not well documented and often the term endometrial hyperplasia has been used in case reports to describe a senile cystic endometrium instead of true hyperplasia; the relationship to carcinoma of the endometrium is also probably suspect because undoubtedly many of the cases of such an association were examples of incidentally found Brenner tumors in patients whose ovaries were removed because of uterine cancer; also, such cases tend to be reported, in contrast to uncomplicated Brenner tumors. Nevertheless, there have been some cases in which a cause and effect relationship may well have existed between a Brenner tumor and hyperplasia of the endometrium; also there have been two cases in which a Brenner tumor has been associated with the development of virilism. In one of these there was strong evidence from the clinical history and from in vitro studies of the tumor tissue that the neoplasm was producing androgens. So, in certain instances, the Brenner tumor appears to fall into the category of neoplasms that we have called ovarian tumors with functioning stroma and case 17A may well be an example of this phenomenon.

Case 17B is composed of solid and cystic nests and masses of epithelial cells of varying sizes and shapes, lying in a stroma that resembles ovarian stroma. Some of the nests are typical of those found in a benign Brenner tumor, but many others are large, closely packed and often cystic. In such nests the cells are sizeable and have abundant clear cytoplasm and malignant-appearing nuclei with frequent mitoses, some of them atypical. The larger nests are often of irregular shape with buds protruding into the surrounding stroma. Some of the cysts are lined by layers of cells that recall the

appearance of a papillary carcinoma of the urinary bladder. The cells with clear cytoplasm contain glycogen, occasional cells lining the cystic spaces are filled with mucus, and mucus is also present in the lumens of the cysts. The stroma of the tumor is very cellular surrounding some of the epithelial aggregates and show scattered areas of hyalinization and calcifications. There is a minimal focal deposition of lipid in the stroma and within the tumor cells. This tumor has the cytological features of malignancy, and a cytological examination of the ascitic fluid revealed malignant cells. Nevertheless, the patient was alive and well over two years postoperatively; no radiation therapy had been administered. Between 25 and 30 neoplasms have been described in the literature as malignant Brenner tumors, but only a minority of these reports are convincing. Some of the tumors have been clinically malignant, while others have been cured by surgery. The others have not been reported with follow-up data. A few of the recorded tumors that have been associated with metastases have not, according to the published photomicrographs, differed significantly in microscopic appearance from the present case. The malignant Brenner tumors may be solid or cystic. The cystic forms are lined by atypical Brenner epithelium and resemble papillary carcinomas of the urinary bladder. Most of the tumors in the malignant category have the appearance of transitional cell or squamous cell carcinoma; in a few there has been gland formation or a mixture of glandular and squamous elements; in such cases the question arises whether the tumor should not be better classified as an endometrioid adenoacanthoma.

Another interesting aspect of tumor 17B was its accompaniment by endometrial hyperplasia and carcinoma, but such an association may have been coincidental. No luteinization was observed in this tumor and there was only a small amount of lipid, whereas most cases of Brenner tumor that have been accompanied by endometrial hyperplasia have had luteinization of the stroma or have shown the presence of large amounts of lipid in the stroma. The opposite ovary showed marked stromal proliferation with occasional foci of luteinization, but such changes, in our opinion, do not account for estrogenic stimulation of the endometrium. Also, the patient's total urinary estrogens, measured chemically, were 3 times normal preoperatively, but were also at the same level 5 weeks after the removal of the tumor. This case illustrates the danger of attributing hormonal abnormalities to ovarian tumors on the basis of insufficient evidence; the source of the high estrogen levels in this patient remains a mystery.

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FEBRUARY 26, 1966 ACCESSION NO. 7320 (7A); ACCESSION NO. 11025 (7B); ACCESSION NO. 10555 (6A); ACCESSION NO. 13328 (6B).

MODERATOR'S DIAGNOSES: Metastatic carcinomas.

Cases 7A and 7B are metastatic carcinomas having the microscopic appearance that was described by Krukenberg. Although some authors use the term "Krukenberg tumor" to indicate any metastasis to the ovary and others to signify any metastasis from the gastrointestinal tract, we feel that the term should be reserved for the signet cell carcinomas that have elicited a marked proliferation of the ovarian stroma. We prefer this use of the term not only because Krukenberg felt the tumor was distinctive because of its microscopic characteristics, but also because the tumor has distinctive clinical and pathological features that are different from those of metastatic carcinomas of other types in the ovary. The site of the primary tumor in case 7A was the stomach, where the great majority of metastases having these microscopic features originate. Case 7B has an unusual source for a Krukenberg tumor, the urinary bladder, where a primary tumor containing signet cells was removed 7 years prior to the development of the ovarian metastasis. Saphir, reviewing series of cases of signet cell carcinomas of the stomach, colon, gallbladder and breast, pointed out that there is a much higher incidence of ovarian metastases from this morphologic type of tumor than from other types of primary tumors of those organs. Subsequently, he reported 2 cases of signet cell carcinoma of the urinary bladder in males and speculated that such tumors in females might also be expected to have a higher incidence of ovarian metastasis than other types of bladder carcinoma. We have seen only 1 metastasis to the ovary from the urinary bladder; the primary tumor in that case was a low grade transitional cell carcinoma and the ovarian metastasis was very difficult to distinguish microscopically from a Brenner tumor. Rare cases of ovarian tumors having the microscopic features of the Krukenberg tumor have apparently been primary, as evidenced by a long survival after surgical extirpation. Krukenberg considered his original published cases as primary. The evolution to considering these tumors to be secondary, rather than primary, has been gradual but quite complete.

Cases 6A and 6B are metastatic adenocarcinomas with a glandular pattern, which differs from that of the Krukenberg tumors. Case 6A is typical of a metastasis from the large intestine. Metastases of intestinal origin are encountered by the surgeon approximately twice as frequently as Krukenberg tumors of gastric origin. Unlike the latter, the metastases from the intestine tend to undergo cystic degeneration secondary to necrosis and often rupture either spontaneously, during examination or in the course of surgical removal. They are somewhat less frequently bilateral than Krukenberg tumors. Both cases 6A and 6B show luteinization of the stroma of the tumor. The luteinized cells in case 6A are large and rounded with spongy cytoplasm; those in case 6B are much more numerous and have eosinophilic cytoplasm

similar to that seen in the theca lutein cells of follicles during pregnancy. Metastases to the ovaries with luteinization of the stroma have been reported in association with estrogenic, androgenic and progesterone-like effects. In case 6A there was a history of postmenopausal bleeding associated with tenderness of the breasts; the uterus was enlarged measuring 11 cm. in length and polypoidhyperplasia of the endometrium was described on gross examination. It is possible, then, that the luteinized cells of the stroma of the tumor elaborated estrogens resulting in the apparent endocrine phenomena, but it would be desirable to have knowledge of the microscopic appearance of the endometrium and of the postoperative follow-up as far as the breast changes were concerned in order to evaluate the possible functioning nature of this tumor. The tumor 6B was removed during the 5th month of pregnancy. Although extensive luteinization of the stroma is present there is no evidence in the clinical abstract that the tumor was functioning. Luteinization of the stroma of ovarian tumors is more common and more extensive in general during pregnancy than during the non-pregnant state, presumably due to the high level of chorionic gonadotropin. Several types of ovarian tumors that have occurred during pregnancy and have shown luteinization of their stroma have been accompanied by virilization, and a few have been shown to contain steroid hormones or to be able to convert steroid precursors to active hormones in vitro. Because of the high levels of estrogens and progesterone during a normal pregnancy, a tumor of this type could very well be producing either of these hormones without a recognizable clinical effect and biochemical studies would be necessary to determine whether or not the tumor was functioning. Thus, it is possible that tumor 6B was also elaborating active steroid hormones.

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FEBRUARY 26, 1966 ACCESSION NO. 14100 (11)

MODERATOR'S DIAGNOSES: Carcinoid, most probably metastatic.

This bilateral ovarian neoplasm shows many typical and a few atypical features for a carcinoid tumor. The cells are arranged in nests, cords and masses. Many characteristic, small round acinar spaces are present and in some areas the basal portions of the tumor cells contain orange-red coarse granules that stain positively with the argentaffin reaction. The nuclei are round, vary slightly in size and have a coarse chromatin pattern; the cytoplasm is moderate to abundant and eosinophilic. There is a marked proliferation of the ovarian stroma to form tumor stroma, which in some areas is hyalinized. Marked hyalinization of connective tissue was also seen adjacent to the peritoneal implant and has been described a number of times in association with carcinoid tumors. At first glance, this neoplasm might be confused with a granulosa cell tumor, but the characteristic appearance of the nuclei, the presence of true glands in contradistinction to Call-Exner bodies and the identification of argentaffin granules exclude that diagnosis. An atypical feature of this tumor is the formation of large glandular structures, but there are several precedents for their occurrence in carcinoid tumors in the literature. An even more unusual finding is the presence of numerous foci of calcification, some of which have the laminated quality of psammoma bodies; they were also present in the peritoneal implant. We have found mention of calcification within carcinoid nests in only one other case in the literature.

Carcinoids of the ovary may be primary or metastatic. The primary tumors, of which approximately 30 cases have been reported, are usually found in the wall of a dermoid cyst, but may occur within a solid teratoma or in the wall of a mucinous cystadenoma, or may be apparently pure. No case has yet been reported with metastases to the best of our knowledge. About a third of the cases have been accompanied by the carcinoid syndrome, which has been relieved in several instances by the removal of the tumor. None of the reported cases have been bilateral.

In the present case the bilaterality of the tumor, the spread to the peritoneum, the impression of the surgeon that lymph nodes in the mesentery of the small bowel were involved and the absence of any teratomatous elements in many sections suggest strongly that the ovarian tumors were metastatic. On rare occasions, as in this case, a carcinoid tumor of the intestinal tract presents clinically as unilateral or bilateral ovarian masses.

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FEBRUARY 26, 1966

ACCESSION NO. 11647 (5B)
ACCESSION NO. 14004 (15B)
ACCESSION NO. 12773 (15A)
ACCESSION NO. 11491 (5A)
ACCESSION NO. 14361 (22A)

MODERATOR'S DIAGNOSES: Granulosa and granulosa-theca cell tumors, definite and probable.

Tumor 5B shows several patterns of granulosa cell tumor. The best differentiated areas are characterized by a trabecular arrangement, but for the most part the neoplastic cells are growing in either a diffuse or a moiré silk pattern. In the available sections almost all of the tumor is made up of granulosa cells and there is very little reticulum. The tumors in this group that have little intercellular tissue are prone to undergo cystic degeneration with hemorrhage into the cysts, and sometimes rupture followed by hemoperitoneum, and this tumor was described as containing blue cysts up to 9 cm. in diameter filled with blood. The multicystic appearance with hemorrhage into the cysts is one of the most characteristic gross pictures that the granulosa cell tumor may assume. This tumor was presumably non-functioning because the patient was postmenopausal and was not bleeding. However, one cannot rule out the possibility of estrogenic stimulation of the endometrium without examining it under the microscope; women with active cystic hyperplasia of the endometrium after the menopause may not have vaginal bleeding, at least initially.

Case 15B shows basically a trabecular pattern, but is atypical in that in many areas the tumor cells are forming acinus-like spaces and cysts containing eosinophilic fluid. The mesenchymal element of the tumor resembles that of a cellular fibroma. This tumor grossly contained locules filled with clear fluid; they are often seen in granulosa cell tumors and on occasion, a neoplasm of this type may be composed of single or multiple cysts filled with clear fluid. It is impossible to determine whether or not this tumor was functioning because the patient apparently was on estrogens prior to its removal.

Tumor 15A is composed of granulosa cells and mesenchymal elements. These are distinguishable in most areas, but in some regions the two types of cells appeared in a jumble. The granulosa cells are arranged in nests, some of which contain cavities filled with fluid and others of which are dilated to form cysts. The mesenchymal element is made up of spindle cells. There are mitoses in both elements of the tumor, but they are much more frequent in the spindle cells than in the granulosa cells. On the basis of our experience with a small number of cases, this tumor is a type of granulosa-theca cell tumor that is often seen prior to puberty. Both elements tend to be plumper and more active than in the familiar tumor of this variety seen in adults. Although tumors in children often look quite active microscopically, the prognosis appears to be very good.

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ACCESSION NO. 11647 (5B)
ACCESSION NO. 14004 (15B)
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ACCESSION NO. 14361 (22A)

Tumor 5A is composed to a large extent of a proliferation of stroma that resembles ovarian stroma. Scattered throughout are round and oval nests of epithelial cells in which are round hyaline bodies resembling Call-Exner bodies. Although both the epithelial and mesenchymal elements are more suggestive of a neoplasm in the granulosa-theca cell group, neither is entirely typical of that tumor and we would place the neoplasm in the less specific sex cord-mesenchyme category (what Mostofi et al call gonadal stromal tumor when it occurs in the testis) with a strong leaning toward the granulosa-theca cell type.

Tumor 22A is made up of masses of cells with irregularly rounded nuclei, moderately prominent nucleoli, occasional mitoses and lacy cytoplasm, which, with the yellow appearance of the tissue on gross examination, suggests a lipid content. Despite its cellularity, the tumor looks relatively benign with infrequent mitoses. The tumor was adherent in the pelvis at the time of operation and there is considerable chronic inflammation and fibrosis at the periphery. Although there is no response of the ovarian stroma, such as one sees in the usual granulosa cell tumor, the general appearance of the cells is suggestive of that diagnosis. A reticulum stain shows a little or no penetration of the tumor cells by the fibrils; it brings out clearly a suggestion of a tubular pattern in areas, indicating that the neoplasm could also be a Sertoli cell tumor. Our diagnosis on this unusual looking neoplasm is sex cord-mesenchyme tumor, probably granulosa cell tumor; possibly Sertoli cell tumor. In view of the history of the onset of the menarche after the removal of the tumor, it is reasonable to speculate that the neoplastic cells may have been producing a steroid hormone that was suppressing the pituitary gland.

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FEBRUARY 26, 1966

ACCESSION NO. 11647 (5B)
ACCESSION NO. 14004 (15B)
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FEBRUARY 26, 1966

ACCESSION NO. 14359 (21B)
ACCESSION NO. 13861 (13A)
ACCESSION NO. 10331 (21A)

MODERATOR'S DIAGNOSES: Tumors (one doubtful) and non-neoplastic proliferation of the ovarian stromal cell.

Case 21B is a typical ovarian fibroma with intersecting bands of small cells of ovarian-stromal type forming collagen. Slide 13A is a spindle cell tumor, which had apparently twisted and shows vascular thrombosis and areas of necrosis. It is composed of cells that vary in appearance from spindle elements producing collagen to rounded cells with lacy cytoplasm, which may be due to a lipid content. Some of the spindle cells are plump and resemble the cells in the theca externa while others have nuclei that are rounded, contain nucleoli and some have an occasional mitosis. Scattered among the tumor cells are occasional hyaline plaques and the most striking feature is the extensive network of sinusoidal endothelium-lined spaces throughout most of the tumor. A reticulum stain reveals fibrils individually investing the tumor cells. We find it difficult to choose between two diagnoses in this case: (1) a tumor of the fibroma-thecoma group and (2) a hemangiopericytoma. We have never seen a tumor in the fibroma-thecoma group with such a rich vascular network; on the other hand, the tumor cells are consistent with that diagnosis and the presence of hyaline plaques, which are characteristic of tumors in that group, is very suggestive of such a diagnosis. The tumor also appears to fit the criteria of Stout for a hemangiopericytoma and he has reported having seen one in the ovary. In a brief survey of the literature we have not encountered any mention in the text or any photomicrograph of hyaline plaques in hemangiopericytomas. The results of a fat stain on this tumor are now known; the presence of lipid would be very characteristic of a tumor in the fibroma-thecoma group; whether or not lipid occurs in the tumor cells of a hemangiopericytoma we have not been able to discover from the literature.

If one excludes granulosa cell tumors, which some authorities believe arise from the ovarian stroma, but which we think may be derived from the sex cords and ultimately the germinal epithelium, the ovarian stromal cell gives rise to 4 types of tumor, among which transitional forms occur. The most common is the fibroma, in which the stromal cells become spindle-shaped and form collagen. The second type is the thecoma, in which some of the neoplastic cells are plump and rounded and contain a large quantities of lipid. A third type is one that has the basic pattern of a fibroma, but has scattered discrete nests of large rounded cells with abundant eosinophilic or vacuolated cytoplasm and round nuclei with single prominent nucleoli; such cells are generally called luteinized cells, although the analogy to cells of the corpus luteum is only morphological and not physiological. That variety

of tumor is often called a thecoma, but might equally well be termed a fibroma with luteinization. The final type of ovarian stromal cell tumor is one composed entirely of luteinized cells, forming a parenchymal nodule that we have termed "stromal luteoma". This tumor can be recognized when it is situated within the ovary proper, but if it enlarges to the point where its topography is no longer identifiable, it cannot be distinguished from other tumors that are placed in the lipoid cell group. It is possible that the pregnancy luteoma to be discussed below is merely a stromal luteoma occurring during pregnancy. There is no agreement among pathologists as to where to draw the line between the so-called fibroma and thecoma; tumors that contain considerable lipid may show no evidence of function, so it is preferable to include the first three types of tumors mentioned above in the general category of tumors of the fibroma-thecoma group.

Slide 21A is an example of bilateral marked ovarian stromal proliferation or hyperplasia. Stromal proliferation can involve the medullary or central portion of the parenchyma, the cortex or both. It can be seen prior to the menopause, but is more frequent during the menopause and in the two succeeding decades; it is less often encountered in women over the age of 70 years. We prefer the term stromal proliferation to hyperplasia because the lesion is so frequent that it is not possible to draw a sharp dividing line between normal and abnormal degrees. It is interesting that the lesions in this case were grossly suggestive of neoplasia. This is sometimes the case, but microscopically the small size of the nuclei and the scarcity of collagen are characteristic of stromal proliferation and not of a tumor in the fibroma-thecoma group. Also, fibromas are bilateral in only a small percent of cases, and thecomas almost never. Some authorities believe that stromal proliferation results in the production of estrogens, endometrial hyperplasia and sometimes carcinoma. Although we do not deny the possiblity that such a sequence may occur in isolated cases, we have not been able to find any statistical correlation between the degree of ovarian stromal proliferation and changes in the endometrium. On the other hand, we do believe that women with the severe grades of stromal proliferation are more apt to show evidence of androgen overproduction, obesity, hypertension and diabetes. There is also biochemical evidence that ovarian stromal tissue can produce testosterone in vitro. In this case the hyperplasia of the endometrium is more likely related to a luteinized follicle cyst, which was present in the left ovary.

Another ovarian lesion that is closely related to stromal proliferation is variously called "hyperthecosis", "thecosis", "thecomatosis", and "luteinization of the ovarian stroma". This is characterized by the presence of nests of luteinized cells in a stroma that generally shows proliferation, which is often marked. The finding of the luteinized cells is a factor of how care-

fully one searches for them. In a postmortem study we were able to identify luteinized cells in the stroma in 28% of unselected autopsies. The significance of hyperthecosis is not entirely clear; however, in severe cases, it may be associated with obesity, menstrual abnormalities, more commonly oligomenorrhea and amenorrhea, but occasionally irregular and increased flow, hirsutism, virilism, obesity, hypertension, impairment of glucose tolerance, and the development of carcinoma of the endometrium. In the premenopausal age group, when follicle cysts may be present in the ovaries, hyperthecosis merges imperceptibly both clinically and pathologically with the polycystic ovaries of the Stein-Leventhal syndrome. Like marked stromal proliferation without luteinization, hyperthecosis may also be associated with a tumor-like enlargement of the ovaries and the term "pseudothecomas" has been used to designate such cases. We have seen one instance in which hyperthecosis resulted in ovarian enlargement to 7 cm. in diameter.

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FEBRUARY 26, 1966

ACCESSION NO. 11845 (9A)
ACCESSION NO. 14005 (13B)
ACCESSION NO. 14153 (19A)

MODERATOR'S DIAGNOSES: Lipoid cell tumors and pregnancy luteoma.

The term "lipoid cell tumor" is used for a group of neoplasms of unknown and probably diverse origins, which are composed of cells that resemble Leydig or hilus cells, luteinized stromal and thecal cells and adrenal cortical cells. If careful search reveals the presence of crystalloids of Reinke in a tumor that was initially placed in the category of lipoid cell tumor the more specific diagnosis of hilus cell tumor can be made. If the neoplasm occurs during pregnancy and especially if it occupies the parenchyma and not the hilus of the ovary, it can be put in the specific category of pregnancy luteoma. If the tumor lies in the ovarian parenchyma in a woman who is not pregnant and the stroma elsewhere contains foci of luteinized cells, the diagnosis of stromal luteoma can sometimes be made. Often one cannot establish a specific morphological diagnosis, but in such cases, findings on hormone assay and biochemical studies of the tumor tissue may contribute to highly probable and possibly in the future certain diagnoses of the cell of origin of the tumor.

Case 9A is a lipoid cell tumor with a hilar location, which makes a hilus cell tumor or an adrenal cortical rest tumor the two leading possibilities. We were unable to find crystalloids of Reinke in the cytoplasm of the neoplastic cells, so we cannot make a diagnosis of hilus cell tumor. In occasional cells rounded hyaline bodies resembling those sometimes seen in hilus cell tumors can be identified, but these inclusions are not specific. The arrangement of the tumor cells in rounded nests separated by vascular sinusoids suggests the architecture of the adrenal cortex, but this is not a diagnostic feature. Biochemical studies would have been of great interest in this case. A recently reported lipoid cell tumor produced testosterone both in vivo and in vitro, but was not able to form cortisol; also, the results of stimulation with human chorionic gonadotropin and ACTH and of attempted suppression with dexamethasone were strongly suggestive that the tumor was of gonadal rather than adrenal cortical type.

Tumor 13B, an incidental finding at cesarian section, shows the typical features of a pregnancy luteoma. It is composed of large rounded cells with abundant eosinophilic cytoplasm and active appearing nuclei showing mitoses. There are numerous small cysts filled with thin eosinophilic fluid. The pregnancy luteoma was first described as an entity by Sternberg, who noted that neoplasms having this morphological appearance are relatively commonly encountered as incidental findings at the time of cesarian section, but are distinctly rare in the absence of pregnancy. He raised the question, therefore,

whether these "luteomas" may not be nodules of chorionic gonadotropin-dependent hyperplasia of luteinized cells rather than true neoplasms. Grossly, they are generally soft, fleshy and gray, brown or yellow and have varied up to 16 cm. in diameter. About half of them are multinodular and about a third, bilateral. Microscopically, nuclear pleomorphism and mitoses, including abnormal forms, may be encountered, but no case, as yet, has pursued a malignant course. Most of the tumors have not been associated with endocrine effects, but it is possible that some of the silent ones produce estrogens or progesterone, the presence of which might be difficult to detect in view of the high levels of those hormones during pregnancy. A few cases have been associated with virilization. In one recently reported case, structural degeneration and loss of androgenic function was demonstrated by hormone assays and microscopic examination of the lesions just after delivery and again six weeks later (Malinak et al.). All of the reported pregnancy luteomas have occurred either at term or in the last two months of the pregnancy.

Tumor 19A is, at least superficially, similar to 13B, being composed of large, rounded cells with abundant eosinophilic cytoplasm and central nuclei containing prominent nucleoli. However, a reticulum stain discloses a more extensive network of fibrils than we have seen in 3 typical pregnancy luteomas. In the latter, reticulum surrounds large masses of cells, whereas in the tumor under discussion the fibrils in some areas enclose small groups of cells and even individual cells. The possibilities that have to be considered in this case are a pregnancy luteoma, a hilus cell tumor and an adrenal cortical rest tumor. Except for the arrangement of the reticulum fibers there is no morphological evidence that favors or is against any of these 3 diagnoses. An elaborate investigation, as yet incomplete, of the steroid hormones and their metabolites has been carried out in this patient. The results so far have been in favor of a gonadal rather than an adrenal cortical origin of the steroids. The Porter-Silber chromogens and free cortisol in the urine were normal to borderline-elevated. The 17-OH corticoids were very high, but gonadal steroids could account for their elevation. It is interesting that the virilizing Krukenberg tumor with luteinization of its stroma that occurred during pregnancy and was reported by Spadoni et al. was also associated with a high level of ketogenic steroid (148 mg. per 24 hr.). In that case the hormones were in all probability being produced by the luteinized cells that arose from the ovarian stroma and that are probably the same type of cell as that of the pregnancy luteoma.

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ACCESSION NO. 11845 (9A)
ACCESSION NO. 14005 (13B)
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FEBRUARY 26, 1966

ACCESSION NO. 14089 (16A)
ACCESSION NO. 14090 (16B)
ACCESSION NO. 14101 (9B)
ACCESSION NO. 10332 (23A)

MODERATOR'S DIAGNOSES: Sertoli-Leydig cell tumors.

Cases 16A, 16B and 9B illustrate several of the wide variety of patterns that may be seen in Sertoli-Leydig cell tumors. The Sertoli cells may form small tubules, the lining cells of which may have a spongy cytoplasm loaded with lipid. These cells may also grow in the form of masses, solid tubular structures, trabeculae or small winding cords resembling sex cords. The Leydig cells may appear mature with abundant cytoplasm that varies from eosinophilic to spongy and loaded with lipid. Rarely crystalloids of Reinke can be identified after careful search; a few of these were found in Case 9B. The Leydig cell element may also be in the form of spindle cells, which may be immature. Sometimes, one sees an admixture of closely packed, poorly differentiated, round and spindle cells, and it may be difficult without the use of reticulum stains to separate the epithelial or Sertoli component from the mesenchymal or Leydig cell element. In some areas in Case 16A, the Sertoli cells are flattened and are lining cysts containing eosinophilic fluid; elsewhere they line a network of spaces simulating the rete. In Case 9B there are aggregates of cells containing large lipid-filled vacuoles; some of them also have lipochrome pigment in their cytoplasm. Because of the presence of the latter we believe that they are more likely to be Leydig than Sertoli cells, although this identification is difficult to establish with certainty. Such large vacuoles can be seen in the cells of both Sertoli and Leydig cell tumors and are often encountered in those neoplasms when they occur in the canine testis. Both Cases 16A and 16B contain acini lined by cells that resemble those of intestinal epithelium with a scattering of goblet cells. In Case 16A argentaffin granules are demonstrable in the basal portions of some of the cells lining these acini. The presence of mucus-secreting epithelium, argentaffin cells, skeletal muscle and cartilage in occasional cases of Sertoli-Leydig cell tumors have led some observers to speculate that these neoplasms may be of teratomatous origin. However, aside from those atypical elements, Sertoli-Leydig cell tumors resemble in no way the solid teratomas of the ovary. The cartilage and skeletal muscle can be explained as atypical manifestations of mesodermal derivation, and, as we have remarked in the discussion of the mucinous tumors, it is also possible for argentaffin cells to be formed in tumors of mesodermal origin, such as adenocarcinoma of the cervix. It is interesting that in the 3 cases the urinary 17-ketosteroid excretion levels were only slightly elevated, varying from 15.9 to 20.5 mg. per 24 hr. Only one out of three patients with this type of tumor has a value greater than 20 mg. per 24 hr., and rarely is the level markedly raised. The apparent reason for the causation of virilism by these tumors in the presence of normal

or only slightly elevated 17-ketosteroid levels is that they are able to secrete testosterone, small quantities of which can masculinize without its metabolites being detectable as an abnormal increase in the 17-ketosteroid value.

Case 23A is a tumor composed of solid tubular structures, for the most part separated by a cellular stroma rich in collagen, but in a few areas lying back to back. Some of the tubules have ill-defined cavities, but they appear to be due to degeneration of the neoplastic cells and not to be true tubules. Most of the solid tubules are filled with epithelial cells containing small to moderate-sized oval and round nuclei and ill-defined threadbare cytoplasm occasionally forming large vacuoles. The cytoplasm is said to contain finely dispersed lipid droplets. In the areas where the solid tubules are back to back, there is almost no recognizable cytoplasm and the nuclei are larger, more hyperchromatic and irregular; occasional mitoses, some of them atypical, can be identified. The pseudotubular architecture of this neoplasm is indistinguishable from that of the less well differentiated Sertoli cell tumors of the canine testis, which are often estrogenic. The functioning tumors of the canine testis contain large quantities of lipid in the form of large vacuoles; the absence of any significant vacuolization of the neoplastic cells in the present case is consistent with its lack of function clinically. Teilum was the first to point out that occasional estrogenic tumors of the human ovary and testis show striking morphologic similarity to the estrogenic Sertoli cell tumor of the canine testis. He used the term "androblastoma tubulare lipoides" to refer to human Sertoli cell tumors that are estrogenic. We prefer to avoid the terms "arrhenoblastoma" and "androblastoma" because they have a connotation of masculinization, even though the authors who coined them did not so imply. Also, it is more in keeping with the accepted nomenclature for the female tumors of the ovary to name the male neoplasms by their cell types. The feminizing tumors that are now placed in the Sertoli-Leydig cell group by many authors may be associated with estrogenic phenomena before puberty, during the reproductive years and after the menopause. They include neoplasms that previously had been diagnosed as "tubular granulosa cell tumor" and "folliculome lipidique". The evidence that the Sertoli cells appear to be estrogenic in occasional gonadal tumors does not exclude the possiblity that the Leydig cell element may be the source of estrogens in other cases.

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ACCESSION NO. 14089 (16A)
ACCESSION NO. 14090 (16B)
ACCESSION NO. 14101 (9B)
ACCESSION NO. 10332 (23A)

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FEBRUARY 26, 1966 ACCESSION NO. 13914 (4B)

MODERATOR'S DIAGNOSES: Dysgerminoma.

This is a typical dysgerminoma with lymphocytes and granulomas in the stroma. PAS staining reveals considerable glycogen in the cytoplasm of the neoplastic cells. Although a congenital anomaly of the lower Mullerian tract was observed at operation, examination of many sections of the neoplasm revealed a residual graafian follicle, and the opposite ovary appeared normal with a regressing corpus luteum. Therefore, this patient did not have evidence of an underlying gonadal abnormality, which is sometimes seen in association with dysgerminomas. The treatment of unilateral dysgerminomas is controversial. There have been many cures with conservative surgery, but because of the relatively high incidence of bilaterality of this tumor (15-20 percent), conservation must be practiced with the knowledge that there is a risk of recurrence involved; often such recurrences can be successfully treated. This case is also interesting in that metastasis to a para-aortic lymph node was detected at the time of operation and radiation therapy was administered subsequently. The dysgerminoma, like the seminoma, is a type of tumor that can occasionally be cured by radiation therapy even though metastases have occurred.

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ACCESSION NO. 13863 (20A)
ACCESSION NO. 11616 (4A)

MODERATOR'S DIAGNOSES: Dysgerminomas arising in gonadoblastomas.

Both tumors consist largely of dysgerminoma, but a careful search of many of the sections reveals discrete nests, cords and masses characteristic of an underlying gonadoblastoma from which the dysgerminomas probably arose. The nests are characterized by the presence of two types of cells: (1) germ cells showing mitotic activity and indistinguishable from the dysgerminoma cells and (2) small oval epithelial cells, which may be either Sertoli or granulosa cells, arranged around the germ cells much as follicular epithelium surrounds an ovum or along the periphery of the nests. Another feature is the presence within the nests of round hyaline bodies that have a resemblance to Call-Exner bodies. In Case 20A, in which the gonadoblastoma elements are more conspicuous, but may not be present in all the slides, there are a few foci where psammoma bodies have formed within the nests, still another characteristic feature of the gonadoblastoma. Whenever one encounters calcification in a germinoma, he should always search further for the presence of gonadoblastomatous elements. The great majority of the gonadoblastomas that have been reported in the literature have occurred in intersexual individuals. The neoplasm appears to arise most often in a streak gonad and less frequently in an abnormal testis. Almost all the patients who have this type of tumor are chromatin-negative and most of them are phenotypic females. Occasional examples have been found in the testis or ovary of apparently normal individuals, but such individuals have not been studied carefully from a chromosomal viewpoint. In Case 20A there is no indication from the clinical history that any gonadal abnormality existed. However, we were unable to indentify sex chromatin bodies in the smooth muscle nuclei of arterial media or the walls of mesonephric tubules that happened to be in the sections we examined. It would be interesting to have the results of a buccal smear on this patient.

In Case 4A the gonadoblastoma occurred in an individual with a gonadal anomaly. The patient apparently did not have the stigmata of Turner's syndrome, but she did have a streak gonad on the side opposite the tumor. We have no idea in what type of gonad the neoplasm arose. It could have been a streak gonad, indicating that the patient had so-called pure gonadal dysgenesis without the various congenital anomalies associated with Turner's syndrome, or it could have been a testis, in which case a diagnosis of mixed gonadal dysgenesis or asymmetrical gonadal differentiation could be made. Since the apparent lack of masculinization of the external genitalia, the positive buccal smear and the finding of Barr bodies in the nuclei of the fallopian tube masculature are against the latter diagnosis, the patient probably had pure gonadal dysgenesis with bilateral streak gonads. The presence of sex chromatin indicates that the patient may have been an XX or possibly a mosaic. The sex chromatin bodies appeared somewhat small in the smooth muscle nuclei, indicating that possibly a deletion of a portion of an X chromosome may have taken place.

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The gonadoblastoma may present as a large tumor or as an incidental microscopic nodule generally in an abnormal gonad. The smaller nodules are often passed off as abnormalities of development or hamartomas, but we believe that they are true neoplasms. They are indistinguishable microscopically from the larger tumors, mitotic activity is often present in their germ cell element and they may show evidence of pressure on surrounding structures. The gonadoblastoma has not been reported to metastasize as yet. Its chief importance seems to be that the germ cell element may overgrow to form a dysgerminoma or seminoma, as the case may be. A very careful study of germinomas, especially in individuals with abnormal gonads, often shows islands of gonadoblastoma, particularly along the periphery of the tumor.

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FEBRUARY 26, 1966 ACCESSION NO. 14099 (20B)

MODERATOR'S DIAGNOSES: Embryonal carcinoma (endodermal sinus tumor) and dysgerminoma, mixed.

This neoplasm is composed of a typical dysgerminoma, with lymphocytes and granulomas in its stroma, sharply demarcated from a more highly malignant form of germ cell tumor, the embryonal carcinoma (endodermal sinus tumor). The latter is characterized by a network of spaces lined in part by somewhat pale cells that do not have a typical epithelial appearance, as well as more columnar frankly epithelial cells. In some of the spaces single papillary projections containing a central capillary and lined by tumor cells are encountered. Another typical feature, which is not too prominent in the present case, is the occurrence of round eosinophilic hyaline bodies resembling Russell bodies within the neoplastic cells and extracellularly. The embryonal carcinoma also exhibits a granulomatous reaction and shows extensive necrosis. The sharp demarcation between the two types of tumor is reminiscent of a similar relationship between the seminoma and the embryonal carcinoma of the testis, and their coexistence in this case emphasizes the necessity of examining all germ cell tumors with care, searching for areas of hemorrhage and necrosis, which may be the clue to the presence of the most malignant elements of the tumor. The embryonal carcinoma is one of the forms of tumor that Schiller originally called "mesonephroma". However, Teilum has reinterpreted it as being of germ cell origin. He compared its structure to that of the labyrinthine placenta of the rat, identifying the glomerulus-like papillary projections with the so-called endodermal sinuses, i. e., diverticula of yolk sac endoderm dissecting around the branches of the allantoic vessels. Confirmatory evidence for the germ cell origin of this tumor are its occasional association with other forms of germ cell tumor (teratoma, dysgerminoma and choriocarcinoma) and its occurrence in the testis, especially of infants and young children. Other authors prefer the term "embryonal carcinoma". One puzzling feature of this type of tumor is the fact that it can be seen in the cervix and vagina of infants, a location in which other germ cell tumors have not been reported, to our knowledge. This tumor has an extremely poor prognosis when it arises in the ovary, but cures are not uncommon when it is found in the testis of the infant or young child.

It is of considerable interest that this tumor arose in an individual with abnormal gonads and secondary sex organs. The uterus was infantile and the opposite gonad appeared to be a streak, suggesting that the patient had either gonadal dysgenesis or atypical gonadal dysgenesis in which there is a streak on one side and a testis on the opposide side. The buccal smear was negative, but attempts at karyotyping were unsuccessful. The patient died of recurrent tumor less than 1 year after the operation.

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FEBRUARY 26, 1966 ACCESSION NO. 12843 (8B)

MODERATOR'S DIAGNOSES: Solid teratoma, malignant.

This tumor contains many types of tissue of varying degrees of differentiation, representing all three germ layers. Among the ectodermal tissues are squamous epithelium, neuroepithelium and glia. As is often the case, the neural elements make up a large part of the tumor. Representing mesoderm are embryonal mesenchyme, cartilage, bone and smooth muscle. Epithelium resembling respiratory epithelium are among the endodermal elements. There are many mitoses in the various types of tissue and there is extensive necrosis. The term "solid teratoma" is not entirely accurate because many cysts of various sizes may be present, and rarely the neoplasm is predominantly cystic. A commonly held misconception is that the solid teratoma is invariably malignant and the term "malignant teratoma" has been used as a synonym by many authors. However, in our experience between 1/3 and 1/2 of the tumors in the category of solid teratoma are composed entirely or almost entirely of adult tissues with little or no mitotic activity, and such tumors generally have a benign clinical course. Even when the tumor is embryonal in appearance occasional cures are obtained by its surgical removal. The tumor is rarely bilateral and in our opinion, if biopsy of the opposite ovary reveals no tumor, there is little evidence that opposite salpingo-oophorectomy and hysterectomy add favorably to the prognosis. An interesting historical feacture of the present case is the prior removal of the opposite ovary for a dermoid cyst and a more recent resection of the same ovary for a dermoid cyst. Although resection of dermoid cysts is effective therapy in the vast majority of the cases, on rare occasions a more primitive germ cell tumor may be found incidentally in the wall of the cyst or may be discovered in the residual ovary at a subsequent operation, as in this case.

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FEBRUARY 26, 1966 ACCESSION NO. 5584 (12A)

MODERATOR'S DIAGNOSES: Squamous cell carcinoma arising in a dermoid cyst.

Between 1 and 2% of dermoid cysts are the site of malignant transformation and squamous cell carcinomas account for approximately 80% of the cases. Adenocarcinomas and sarcomas comprise most of the remainder. The 5-year survival rate of malignant dermoid cysts is only about 15%, although if one considers only squamous cell carcinomas confined to the ovary and removed without spillage the salvage rate is 63%. No 5-year survivors have been reported among the patients with adenocarcinoma or sarcoma. Malignant transformation is easily overlooked at operation and should be suspected if one encounters thickening or nodulation of the wall of the cyst, adherence to surrounding structures or necrosis. In this case one of the sections shows squamous cell carcinoma-in-situ lining the cyst wall; this does not have the appearance of squamous cell carcinoma of the skin, but resembles more closely mucous membrane carcinoma-in-situ. The in-situ growth is quite similar to that encountered in a case of a bronchogenic type of squamous cell carcinoma that arose in a dermoid cyst.

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FEBRUARY 26, 1966

ACCESSION NO. 7928 (8A)
ACCESSION NO. 14254 (24B)

MODERATOR'S DIAGNOSES: Teratomas containing thyroid tissue (struma ovarii) with and without other elements.

Tumor 8A is a typical example of struma ovarii, having a pattern simulating that of a macro- and microfollicular adenoma of the thyroid gland. Although 5 to 20% of dermoid cysts and other teratomas contain thyroid tissue on careful sectioning, the term "struma" is not appropriate unless thyroid is the predominant or sole teratoid element, or is grossly recognizable. Occasional examples of struma causing or contributing to the production of thyrotoxicosis have been reported, but well documented and convincing cases are rare because of the difficulty in disentangling the relative roles of cervical and ovarian thyroid tissue in the causation of the abnormal endocrine state. Malignancy is said to occur in approximately 5% of cases of struma. The cancers may be follicular or papillary and spread may consist of local implants, or regional or distant metastases. As is true of metastases of cervical thyroid neoplasms, those of malignant strumas may be exceedingly well differentiated and resemble normal thyroid tissue.

Tumor 24B contains a large area of well differentiated thyroid tissue, which may not be present in all the slides that were distributed. The major portion of the tumor is composed of islands of epithelial cells, some of which are solid and others of which are made up of anastomosing ribbons of epithelial cells with round to oval moderately hyperchromatic nuclei. In some areas the tumor cells are forming small acini, some of which contain eosinophilic material. A few rare acini are lined by epithelium that resembles intestinal epithelium, containing well developed goblet cells; these acini merge imperceptibly with the solid epithelial cords. The stroma varies from moderately cellular to hyaline and contains numerous foci of large rounded cells with spongy cytoplasm; these cells are rich in lipid. Our interpretation of this tumor is that it is of teratomatous origin with a predominant endodermal differentiation. The islands, cords and ribbons of epithelial cells constitute a pattern that is common to a number of epithelial tumors. The resemblance of the neoplasm to a carcinoid tumor is striking, but efforts to demonstrate argentaffin granules in the cytoplasm were unsuccessful. Other possibilities of an endodermal nature include an islet cell tumor, a pituitary tumor and a thyroid tumor. Evidence in favor of this being a tumor of thyroid type is the prominence of thyroid tissue elsewhere in the neoplasm and the fact that epithelial neoplastic patterns of this type have been described on a number of occasions in association with struma ovarii. Against a thyroid nature of this portion of the tumor are the areas of transition between the cord-like pattern and the intestinal type of epithelium containing goblet cells. The patient

appears to have had a recent acceleration of virilization although apparently hirsutism had been recognized since early life. Was the masculinization related to the tumor? Apparently, there was no evidence of postoperative regression; generally there is some improvement, even though it may be minimal. If the neoplasm was responsible for the virilism, the androgenic elements could have been the lipid-laden luteinized cells in the stroma; in other words, this may have been a tumor with functioning stroma. Another interpretation of this neoplasm is that it is at least in part a Sertoli-Leydig cell tumor. The cells with the spongy cytoplasm are consistent with Leydig cells and a carcinoid pattern has been observed in a few Sertoli-Leydig cell tumors; but the presence of thyroid tissue has never been reported. Hughesdon has coined the term "trabecular adenoma" or "adenofibroma" for this type of neoplastic growth in association with struma ovarii; we prefer to place it in a low-grade-malignant category and use the term trabecular adenocarcinoma, not only on morphological grounds, but because one neoplasm having this pattern metastasized. (Woodruff, 1966). In summary, we believe that this tumor is of endodermal origin, contains thyroid tissue and is of a low grade of malignancy. The exact nature of the cells that are growing in ribbons, cords and nests cannot be determined. They may be related to the thyroid tissue or may represent a non-specific type of endodermal differentiation. The possibility that this tumor is a Sertoli-Leydig cell tumor cannot be entirely excluded. With regard to the possiblity of a carcinoid tumor there is a recent report of a carcinoma of presumed thyroid origin associated with the carcinoid syndrome, so a combination of thyroid and carcinoid differentiation should not be excluded, especially when one is dealing with a teratomatous type of tumor.

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