The case material herein presented constitutes the third in a set of Tumor Loan collections prepared and distributed by the Department of Pathology and Oncology of the University of Kansas Medical School aided by a Cancer Control Grant (CS-9209) from the National Cancer Institute of the National Institutes of Health, United States Department of Health, Education and Welfare.
History: This 36 year old white woman (grava III, para II, abortions I) was admitted to the hospital for removal of an ovarian tumor on the right which was discovered on routine pelvic examination. No other physical abnormalities were noted.

A complete hysterectomy and right salpingo-oophorectomy were performed. The right ovary was 6 cm. in diameter and somewhat irregular.

Gross Pathologic Findings: The right ovary measured 5 x 3 x 2 cm. It contained a 2.5 x 1.5 cm. cyst and two white bosselated nodules 2 x 1.5 cm. each. These were firm and fibrous in appearance and located on the anti-mesovarian surface of the ovary.

Comment: This tumor is a fibroma. In contrast to the great diversity of opinion which exists about other ovarian tumors, there is singularly little disagreement about this one. This tumor has been perhaps most carefully studied by Lepper (1) who has demonstrated that these lesions, when carefully examined, show dense (and frequently hyaline) connective tissue which makes up the bulk of the tumor, covered by remnants, particularly in gland-like spaces, of the germinal epithelium of the ovary. Careful examination of this section will show cleft-like spaces lined by degenerate epithelium. Lepper feels that this epithelium secretes fluid, accounting for the contents of the cysts that are frequently found. A cyst was present in this specimen. Willis(2) agrees with the above concept and feels that these tumors are analogous to the fibroadenomas of the breast.
The interesting problem concerning these tumors is, of course, their frequent association with Meigs's syndrome. (Meigs's syndrome was not present in this case). Lepper(1) feels that the accumulation of fluid is due to secretion of fluid by the germinal epithelium, which may be found on the external surface of these lesions. This proposition is obviously hard to either prove or disprove, except, as Lepper points out, that cysts filled with fluid are frequently found in these tumors. This hypothesis certainly remains the most attractive explanation that this writer has found for the accumulation of fluid. Meigs's syndrome has recently been briefly reviewed by Crookston(3) in an article written with a sense of humor that is as refreshing as it is rare in modern medical writing.
History: The patient, a 54-year-old white woman, was first admitted to the hospital 2½ months before operation complaining of vaginal bleeding of 2 weeks duration. She had had an uneventful menopause 8 or 9 years before and had had no bleeding since. About two weeks before admission, the patient had first noticed slight spotting. This had persisted and progressed to the point where clots were passed.

The general physical examination on admission was negative. Pelvic examination revealed a small and atrophic vagina and cervix. The fundus and adnexa were not remarkable.

A dilatation and curettage was performed, which yielded a relatively large amount of grossly bloody uterine contents. Pathologic examination of the curettings revealed the presence of an anaplastic papillary adenocarcinoma containing many clear cells. Radium was inserted and the patient subsequently received roentgen radiation therapy.

Two months later, the patient was readmitted and a total hysterectomy and bilateral salpingo-oophorectomy were performed. The postoperative course was uneventful.

Gross Pathologic Findings: The uterus was small and presented 2 small subserous myomas. The endometrial cavity was dilated. Lying free in the endometrial cavity or loosely attached was a mass of mucous membrane and sloughed endometrium. The underlying endometrium was very atrophic, yellow-white, and smooth. There was a polyp on the lower half of the endocervix.
The left ovary measured 2 x 1.5 x 1.3 cm. and was largely occupied by a tumor. This consisted of greyish-white tissue in which there were small yellow foci.

A small parovarian cyst was present. The tubes, the other ovary, and the appendix were not remarkable.

Comment: This is a classical example of a Brenner tumor in an older woman, associated with an anaplastic adenocarcinoma of the endometrium. The origin of Brenner tumors has been the source of considerable debate. The appearance presented in this slide can be used to support any one of the theories that has been suggested. Brenner originally suggested that the lesion arose from the ovarian follicle. There are numerous areas in this slide which suggest the appearance of actual degenerated ova. Meyer\(^4\) made the suggestion that they were derived from Walthard cell rests. This theory was widely accepted and has remained standard until recently. One of the reasons for his theory was the fact that longitudinal groves are present in the nuclei of Brenner tumors and also in those of Walthard rests. These can readily be seen in this example.

Many authorities have commented on the association between pseudomucinous cystadenomas and Brenner tumors. This point of view has recently been upheld by Nidegger\(^5\). He found no resemblance between these tumors and granulosa cell tumors.

This whole problem has been most recently and carefully restudied by Teoh, who has written two articles on the subject\(^6\) and \(^7\). His first article points out that Walthard cell rests are far more common in the tubes, the mesovarium, and the mesosalpinx than in the ovary itself, and when they are found in the ovary they apparently represent metaplasia of the covering mesothelium. In his second article, Teoh points out that Brenner tumors, on the other hand, are found
in the ovary itself, and not in the locations in which Walthard rests are common. There are other differences between the two: namely that ciliated columnar epithelium and pseudomucinous cyst-like epithelium are not infrequent in cystic Brenner clumps, and a single cyst lined with cuboidal epithelium can be seen in this example. Glycogen is abundant in Brenner epithelium and is rare in Walthard rests. On the other hand, Teoh had no difficulty in demonstrating numerous cases where Brenner tumors are similar/or indistinguishable from variants of granulosa cell tumors. His conclusion, therefore, is that Brenner tumors are derived from the ovarian parenchyma itself and that the "stroma" of Brenner tumors is a genuine component of the neoplasm and is identical with theca tissue. This view of course implies that Brenner tumors (contrary to the general impression) might have endocrine effects.

It is apparent from reviewing the literature that in some cases Brenner tumors may be associated with menstrual abnormalities of the type suggested. They may, in fact, be secreting estrogen. Bland and Goldstein(8), in a review of the literature, collected no fewer than 19 out of 52 cases of Brenner tumor which showed irregular uterine bleeding. If this be the case, the association of this tumor with a carcinoma of the endometrium, as in this instance, may not be entirely fortuitous. Two similar cases have been described, one of them by Teoh(7) and another by Bettinger(9).
Case 3
Pseudomucinous Cystadenoa

University of Kansas Medical Center
Kansas City, Kansas
Surgical No. 1301-55

History: The patient, a 72 year old white woman, first noticed distention of the abdomen 4 years prior to admission to this hospital. She had been treated with repeated paracenteses and was ultimately referred to this hospital.

A repeat paracentesis in this hospital obtained 1100 ml. of thick white viscid fluid which obviously had not been completely removed. Following the procedure, a mass could be felt in the left side of the pelvis. Cytologic examination of the fluid revealed numerous clumps of malignant cells.

At the operation a large cyst of the left ovary was found. This grossly appeared to be a benign tumor, and so only the cyst was resected.

Gross Pathologic Findings: The collapsed specimen measured 17 X 20 cm. The peritoneal surface was smooth but the internal surface revealed multiple sessile and polypoid masses. Multiple smaller loculations contained a mucoid, viscid fluid.

Comment: This tumor is a pseudomucinous cystadenoma. The histologic and cytologic features are too well known to require further comment. There are certain features of interest, however. One is the misleading cytologic examination of the fluid withdrawn for cytologic study, which was thought to show the presence of malignant cells. In retrospect, the fluid withdrawn was the contents of the cyst itself. Re-examination of the smear revealed numerous clumps that were obviously epithelial cells. These epithelial cells, however, showed less variation in the size, shape, and staining of the nuclei than are ordinarily associated with malignancy. It is possible that this error might have been avoided if the cytologist had realized that this represented cyst contents rather
than abdominal fluid. Unfortunately, it is more probable the same mistake will be made again.

Tumors of this type present two interesting problems. One of course is the histogenesis. Numerous theories have been advanced. The frequent co-existence with Brenner tumors has been commented on previously. Novak(10) believes strongly that these are made up of intestinal epithelium and represent one-sided overgrowth of a teratoma. The most complete and carefully studied group of these tumors that has been described recently is that collected by Cariker and Dockerty(11) who report 355 cases personally studied from the Mayo Clinic. They found that obvious teratomas were incorporated in the wall of 4.5% of these cases, and nodules that proved to be Brenner tumors were found in the walls of only .5%. It certainly lends considerable weight to the theory that most of these represent one-sided development of a teratoma. Another surprising finding in this series was that 38.9% were malignant, which is a higher proportion by far, than that of many other series. Seventy per cent of the grade I malignancies survived 5 years, suggesting that possibly their criteria of malignancy were too generous.

The chemical contents of these tumors has been the subject of extensive study. One of the best papers to appear on this subject recently is that by Fisher(12) which demonstrates that the content of these cysts is a mucopolysaccharide, and therefore the term pseudomucinous is a misnomer. They should be referred to as mucinous cystadenomas. Jensen(13) found hyaluronic acid in 2 out of 3 cysts that he studied chemically.
History: The patient, a 48 year old white woman, was first admitted to the hospital 33 months before operation complaining of obesity and diabetes. The onset of the present illness was said to date back 19 years when the patient weighed 120 pounds. At that time she developed an illness characterized by fever and delirium which was diagnosed as encephalitis. The patient gained 70 pounds in the next three months, and gained steadily ever since, finally arriving at 310 pounds. About 4 years before admission the presence of both hypertension and obesity were discovered. Eleven years prior to admission the patient had received radiation therapy for uterine myomas. She had not menstruated since, but had had episodes of bleeding at yearly intervals until admission except for the last interval which had been six months.

Physical examination on admission revealed a white woman 5' 2" in height who weighed 314 pounds. Her blood pressure was 210/120. Grade II sclerosis was seen in her eyegrounds. There was 2+ pretibial pitting edema. Pelvic examination revealed a tiny nulliparous cervix. The upper pelvis could not be palpated.

It was thought that the irregular bleeding was due to hormonal imbalance, but the diagnosis of malignancy was entertained and a dilatation and curettage was recommended. It was thought that a program of weight reduction should be carried out first to minimize the operative risk. The patient was placed on an 800 calorie diet. She responded well, losing 19 pounds in weight (to 295 pounds). Her blood pressure fell to 140/70 and her diabetes could be managed with no insulin.
The patient returned to the hospital 7 months later weighing 299 pounds. Her blood pressure was elevated and her diabetes was out of control. She had some vaginal bleeding which ceased spontaneously. In order to rule out the (apparently) remote possibility of a malignancy, the patient had a pelvic examination under anesthesia and a dilatation and curettage was performed. This procedure revealed the presence of a large suprapubic mass thought to be a uterine myoma and proliferative endometrium with a continuous endocrine effect. The uterine bleeding, therefore, was apparently explained by the presence of two benign conditions and further pelvic surgery was deferred until the patient could lose more weight. She was reduced to 254 pounds at the time of discharge.

The patient was admitted twice more during the next two years, each time primarily for weight reduction. She weighed 308 pounds and 299 pounds on admission respectively. It was apparent on the fourth admission that little was accomplished by this program, even when the patient was put on a 400 calorie diet, and it was felt that no further delay of operation was justifiable even though it was obvious that the patient was an extremely poor operative risk. Operation revealed a large carcinoma of the ovary with multiple peritoneal implants. The patient withstood the operation surprisingly well and has received postoperative radiation. Follow-up (4 months) is essentially negative except that the patient is again gaining weight.

**Gross Pathologic Findings:** The right ovary was replaced by a multicystic mass weighing 1320 gm. and measuring 20 X 13 X 8 cm. On section many cysts of varying sizes were seen. They contained a clear yellow fluid. Scattered over the inner surface of the cysts were numerous polypoid granular masses which were pale pearly white in color. These same granular masses were seen on the external
surface of the tumor. The left ovary was similar to the right, but smaller in size. The uterus showed endometrial polyps, two small leiomyomas and a serosal implant of carcinoma.

Comment: This is a typical serous cystadenocarcinoma. The features of this tumor are too well-known to require further discussion. The tragic situation presented by this case, however, is the fact that this woman's obesity was so extreme that it interfered with making an accurate diagnosis, even when the unusual precaution was taken of examining the patient under anesthesia. Even under these circumstances, the tumor of the ovary was confused with a leiomyoma of the uterus, which provided an apparent explanation of the patient's symptoms on the basis of a benign lesion. The patient's obesity was so extreme as to make an exploratory operation ill-advised. Unfortunately, she did at long last prove to have a malignancy anyway.

The cause of the obesity in this patient remains obscure. During her several hospitalizations, she was repeatedly studied to see if an endocrine basis could be found for it, and none was ever found. The possibility suggested by the history, however, that it was due to a hypothalamic lesion produced by an attack of encephalitis was neither ruled in nor ruled out. Obviously, this is a hard lesion to study.

The histogenesis of serous cystadenocarcinomas is a controversial matter. Barzilai(14) feels that these tumors are derived from Mullerian epithelium and therefore are lined by tubal epithelium. She is so convinced of this origin as to call these tumors "endosalpingiomas". There is no question that the epithelium that lines these tumors frequently simulates that of the fallopian tube. It has always been a little hard to understand, however, why tumors with
this derivation should be common in the ovary and rare in the tube. Woodruff and Novak(15) have recently published a review article on this subject based on the material in the ovarian tumor registry.

One further possibility suggested by this case history is that the radiation the patient received many years before to the pelvis might have been the etiologic factor in producing such tumors. This has occurred in experimental animals(16). Not enough is known about this problem as far as human tumors are concerned to warrant a dogmatic statement one way or the other.
History: The patient, a 48 year old white woman (grava II, para II) entered the hospital because a routine survey roentgenogram had disclosed the presence of a pleural effusion. Several paracenteses were performed, and varying quantities of fluid were removed. The fluid continued to re-accumulate and the patient was referred to this hospital.

On admission to this hospital, the general physical examination was not remarkable. A further history of vague abdominal complaints was elicited which suggested the possibility of a primary intestinal malignancy. Another paracentesis was performed. Cytologic examination of the fluid removed revealed the presence of large numbers of malignant cells more suggestive of a primary ovarian carcinoma than of a primary intestinal carcinoma. Pelvic examination revealed a 6 cm. mass attached to the left ovary.

An exploratory laparotomy was performed. The left ovary was found to be 8 cm. in diameter and firm. No peritoneal implants were seen, but 250 ml. of ascitic fluid were found. A complete hysterectomy and bilateral salpingo-oophorectomy were done.

Postoperatively the patient did well. Radioactive gold was instilled in the pleural cavity, and the patient was discharged in fair condition. The patient has since died.

Gross Pathologic Findings: The left ovary measured 8 cm. in diameter. There were several large, round, white nodules apparent on the surface.
Comment: The interesting clinical problem presented by this tragic situation is that the patient's first symptom was due to a metastatic lesion. This produced a persistent pleural effusion in which malignant cells were ultimately found. The large signet ring cells which were seen suggested the possibility of this being a primary ovarian tumor. This was subsequently confirmed by laparotomy.

It is impossible to characterize the nature of this tumor beyond saying it is an adenocarcinoma. Obviously it might be derived from any one of the other tumors presented in this group of cases, but it is so anaplastic that its derivation cannot be accurately determined at present. The whole problem involved in classifying ovarian tumors is brilliantly discussed in a thoughtful article by Emge (17) emphasizing the difficulties in attempting to classify ovarian tumors on a histologic, histogenetic, or functional basis. As Emge states, any attempt at classification is fundamentally arbitrary, and "man's habit of classifying is an acquired discipline which stems from his inherent addiction to collecting everything from things to thoughts".
Case 6
Krukenberg tumor

History: This 69 year old white woman had been known to have had pernicious anemia for 25 years. She had, in fact, set a record for continuous treatment with liver extract (and subsequently other forms of specific therapy) since her treatment dated almost from the time that Kinot and Murphy had first demonstrated its effectiveness.

Approximately 6 1/2 months before death the patient developed upper gastrointestinal complaints, ascites and a pleural effusion. Examination of the pleural fluid revealed numerous malignant cells of the typical signet ring variety. Further work-up confirmed the clinical impression of a carcinoma of the stomach. The patient was treated with instillation of radioactive gold into both pleural and peritoneal cavities. This procedure slowed the re-accumulation of fluid, but the patient ultimately developed signs of a chronic intestinal obstruction and died.

Autopsy revealed, as anticipated, infiltrating, limitis plastica type of carcinoma of the stomach in which signet cells were conspicuous. This had arisen in a field of atrophic gastritis showing extensive intestinal metaplasia. There were metastases to the lungs, regional lymph nodes, uterus, and ovaries.

Gross Pathologic Findings: Grossly the ovaries were normal in size and shape.
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Comment: This is a classical Krukenberg tumor. The only thing that is unusual about is is that it is so very typical. The other feature of interest in this case, of course, is the occurrence of carcinoma of the stomach in a woman with a long history of treated pernicious anemia.

In recent years, there has been considerable disagreement, in/literature, as to just exactly what Krukenberg described. This is easily resolved by referring to his original article(18). He describes six cases with the following characteristics: The tumor is a bilateral one. Ascites is present. The tumor produces enlargement of the entire ovary which in general maintains its original shape although the surface may be somewhat nodular. The cut surface usually is composed of compact, homogeneously dense material, especially just beneath the surface, although the inner portion sometimes shows a combination of some dense areas and some myxomatous ones. In some areas, large smooth walled cysts are present, apparently due to degeneration.

Microscopically, the histologic picture shows extreme variation. The dense portion shows a great proliferation/spindle cells of the ovarian stroma, while the myxomatous portion shows a fibrillar network with spindle or star shaped cells. In the cell rich areas, there are small or large masses of rounded cells with swollen cytoplasm and fine vacuoles, frequently containing genuine mucus, which are situated between the spindle shaped cells of the stroma. In the myxomatous areas, they are frequently present in larger masses where they may form acini.

As everybody knows, Krukenberg assumed this was a bilateral tumor of the ovary. In only two of his six cases, however, were autopsies described. In one of these, his first and best studied case, a tumor was found in the wall of the stomach, which microscopically showed similar cells located beneath the serosa
and between the muscle bundles. Unfortunately, according to Krukenberg, there was so much autolysis of the mucosa that it could not be seen on the section.

It is also well known that Krukenberg thought that this was a sarcoma. In reading his article, however, it is apparent that he is not too sure about this and states repeatedly that the cells, in many instances, resemble epithelium. He particularly makes a point that in all areas excepting in the ovary, itself, in his first case, the appearance is strikingly epithelial with lymphatic permeation of large spindle cells which seem to form acini. He stated, however, that in his cases he could see no evidence of derivation of the tumor from the surface epithelium or the follicles of the ovary and, therefore, concluded that the tumor arose directly from the stromal connective tissue. Since Krukenberg defined a sarcoma as a malignant tumor of connective tissue origin, regardless of the histologic appearance of the tumor, he was forced by his own reasoning to classify this tumor as a sarcoma.

It is perhaps somewhat ironical that Krukenberg's name is associated with these tumors because, by his own account, he is far from the first person to describe them. His article refers to no less than 5 publications describing these tumors as sarcomas of the ovary and 6 publications referring to these tumors as carcinomas of the ovary. In addition, there were two publications (one of which apparently was a review of the literature) describing endotheliomomas of the ovary, again apparently the same tumor. It seems that Krukenberg's chief contribution is that he clarified the confusion existing at his time concerning the nature of these tumors.
Case 7
Teratoma

History: This 26-year-old white woman was admitted to the hospital because of right lower quadrant pain of 2 years duration. The pain was intermittent in nature and had become more severe shortly before admission.

On physical examination, a 12-15 cm. solid mass was felt in the right adnexe. At operation, a 14 cm. cystic mass was found which was twisted on its pedicle.

Gross Pathologic Findings: The specimen weighed 394 grams and measured 14 cm. in diameter. Externally, it was smooth and felt cystic and fluctuant. Upon sectioning the mass, 310 cc. of yellow, greasy, thick fluid exuded. The inner surface revealed a nodular projection with the appearance of scalp, and from which a mass of hair flowed. This also contained a piece of bone and a tooth.

Comment: This is a classical teratoma of the ovary. As is usual in these structures, the most conspicuous element present is skin, a rather bizarre skin in which tooth buds appear to be growing out of sebaceous glands. There are other ectodermal elements that are equally conspicuous, such as nervous tissue that appears to be both central in some areas and peripheral in others. With a little closer examination it is possible to find a tube lined by bronchial epithelium in the neighborhood of a large mass of cartilage and what could be tracheal glands, and therefore an entodermal derivative also is present.

There is, of course, a large amount of connective tissue of mesenchymal origin.

The origin of these tumors is one of the most fascinating problems in oncology. It has been the subject of a great deal of speculation and relatively little in the way of investigative work. Nicholson(19, 20 and 21), to mention just a few of many of his works on the subject, has been a thoughtful student of
this subject over a period of many years. These papers of his are far more than studies on teratomas. They are wise, witty and delightfully written essays on the philosophy of science in general and the philosophy of pathology in particular. They cannot be recommended too highly. His conclusions are in essence that the development of a teratoma is not necessarily an attempt to reproduce the development of a fetus, but is an unorganized collection of tissues. The lack of organization, of course, is fully apparent in this specimen. Nicholson, then, tends to believe that teratomas are derived from the adult host rather than being derived from abnormal development of germ cells.

Within the last year, this problem has been solved, however. The most important contribution has been made by Hunter and Lennox(22). This consisted in determining the sex of teratomas by looking for sex chromatin bodies. This showed that in women the sex of the teratomas (12 out of 12 cases) was always female while of those born by men and boys, 4 were male and 5 were female. In other words, in this series of cases, the sex of the teratoma was always that of the host where the host happened to be a female but was not necessarily that of the host where the host happened to be male. This is only explainable on the assumption that teratomas are derived from germ cells or as the authors put it, the fusion of two haploid cells "which would always produce an XX zygote in the female but in the male, would, in theory, produce XX, XY or even YY." (Just for the record, in a rough application of this method on this case, this teratoma appears to be female.) It seems that the derivation of teratomas from adult diploid cells must be excluded. This observation also excluded the possibility of these tumors being the outcome of accidental fertilization of a polar body. This process would produce as many male teratomas in women as female teratomas and would not account for the development of
teratomas in men at all. Teratomas, then, must represent "sons" and "daughters" of the hosts in which they are found rather than "brothers" and "sisters" or adult tissues themselves.
History: The patient, a 27-year-old white woman, was admitted with a chief complaint of increasing growth of hair on the face. This had progressed to the point where she had become quite self-conscious about it. The onset of the present illness was rather indefinite. The patient had begun menstruating at the age of 14, and her periods had been regular at approximately 33-day intervals and had lasted 5 days. Seven years before admission, the patient had had a normal pregnancy during which growth of hair on the face was first noticed. This progressed and was accompanied by increased growth of pubic hair. The patient had 3 abortions at about the fifth month of pregnancy 5, 4, and 2 years before admission respectively, but stated she was Rh negative. The menstrual cycle had continued normally until the last abortion after which she had only two menstrual periods at 11 months and 3 weeks before admission.

General physical examination revealed a blood pressure of 105/65. There were a few dark hairs on both submandibular areas and some coarse light hair over both cheeks. A masculine escutcheon was present. Pelvic examination revealed that the clitoris was of normal size. The cervix was somewhat patulous. The uterus was rather large. The right ovary was normal in size. The left ovary measured 4-6 cm. and was firm, cystic, and slightly tender.

Laboratory examination showed a fasting blood sugar of 72 mg. per cent with the following values on the glucose tolerance test at hourly intervals: 109, 108, 86, 73, 60, 62 mg. per cent. The 24 hour excretion of 17-ketosteroids was 7.5 mg. (normal, 5-0.4 mg.) and of 11-oxysteroids was 1.3 mg. (normal, 1-2 mg.). There was less than 96 mouse units of follicle stimulating hormone excreted in 24 hours.
A Thorne test showed a base line of 50 eosinophils per mm.\(^3\) which dropped to 16 per mm.\(^3\) in 4 hours.

Laparotomy revealed that both ovaries were about 6 cm. in diameter, yellow in color, and contained numerous small cysts. A ruptured hemorrhagic follicle was seen on one. Bilateral partial oophorectomies were performed.

**Gross Pathologic Findings:** The specimens consisted of several portions of ovarian tissue, that from the left ovary weighing 18 grams, and from the right weighing 11 grams. Both showed a thickened yellow surface, beneath which numerous cysts measuring up to about 3 mm. in diameter were seen. A hemorrhagic corpus luteum was present in the left ovary.

**Comment:** It is rare indeed for a syndrome to be so well described in its original publication that nothing can be added to this description later on. In the syndrome under discussion, this is indeed the case. The original description by Stein and Leventhal of cases of amenorrhea associated with polycystic ovaries\(^{23}\) is so complete that there is little to be added to this subject. In brief, these women have bilateral polycystic ovaries accompanied by menstrual disorders usually consisting of amenorrhea. Sterility is a prominent symptom. Hirsutism is quite common and the hair distribution is usually masculine. Other, more definite, evidences of masculinization such as enlargement of the clitoris and voice changes are also rather common. Stein and Leventhal's original publication also described the definitive therapy, namely bilateral wedge resection of the ovaries. This is usually followed by normal menstrual cycles and frequently by pregnancies. The hirsutism, however, is usually unaffected. These authors have continued to work on this subject and, writing together or with other collaborators, have produced a series of important papers. There are two of them which specifically describe the pathologic changes present\(^{24}\) and \(^{25}\).
The lesion is bilateral. The ovaries showed symmetrical enlargement. On section, there is a dense fibrous capsule present, beneath which there are numerous cysts frequently lined with granulosa cells and surrounded by an extensive amount of theca lutein cells. Normally developed follicles are rare, though they may be observed.

The original observations have been confirmed repeatedly. This interesting syndrome has given rise to a great deal of speculation as to the mechanisms involved. No theories, so far advanced, are entirely satisfactory. A somewhat similar condition can be produced in animals with injections of crude extracts of the anterior pituitary. Whether or not this is the etiology in human beings remains not clear. Other suggestions are that the thick fibrous capsule offers a mechanical obstruction to the rupture of the follicles and therefore perhaps produces both sterility and interruption of the normal menstrual cycle. It has also been suggested that some of the anomalies are due to abnormalities of the adrenal cortical mechanism. Evidence for this hypothesis is fairly unconvincing as, in most cases, biochemical studies have failed to support this contention. The first two explanations altogether fail to explain why, in addition to amenorrhea and sterility, masculinization is also a prominent part of the picture. Apparently, the only diseased organ is the ovary itself. This raises the possibility that in these women, the ovary itself is producing an excessive amount of masculinizing hormone.

It is equally mysterious as to why simple, bilateral, wedge resection of the ovary so frequently, though admittedly not invariably, results in even a partial cure. Normal menstrual cycles and sometimes fertility have been restored by this procedure, although the hirsutism may remain unaffected. (26)
Case 9  
Granulosa cell tumor with hyperplasia of the endometrium

History: This 56 year old white woman (gravidaVI, para V, abortions I) was admitted to the hospital complaining of irregular intermittent vaginal bleeding of 4 years duration. The menopause had occurred 7 years previously. The patient had taken hormone shots for 12 years before admission. This was said to be intended to treat her hypertension.

Physical examination on admission revealed a blood pressure of 190/110. On pelvic examination a 5-6 cm. tumor of the left ovary was felt. The uterus was slightly enlarged and displaced to the right by the mass. The cervix was clean.

A dilatation and curettage was performed. Surgical pathological examination of the endometrium revealed adenomatous hyperplasia.

Gross Pathologic Findings: The left ovary weighed 105 gms. and measured 11 X 5 X 5 cm. It was dumb-bell shaped with a solid mass at one pole and a cystic mass at the other pole. On section the solid mass was composed of soft, bright yellow, hemorrhagic material. It was roughly encapsulated. The cystic mass was filled with mucoid material and had a thin wall.

Comment: Granulosa cell tumors are common, and their histologic features are well known. Barzilai(14) has a beautiful series of illustrations of different types. More recently, Burslem, Langley and Woodcock(27) have reviewed a large series of these tumors and give illustrations of different patterns. The fact that these tumors produce estrogens and may be associated with post-menopausal bleeding and endometrial hyperplasia is also well known.

Recent literature, however, is interesting in that some experimental work
has been done on the production of tumors of this type and related ones. The original work was done by Furth and Butterworth (16) who produced tumors in mice with irradiation. More recently, it has been discovered that transplantation of ovaries into the spleens of castrated mice will produce granulosa cell tumors in the transplants. This work has been done by many investigators. The original explanation was that the liver detoxified the estrogenic hormone produced by the transplanted ovary, thereby preventing the inhibition of the pituitary by estrogen. This permitted the prolonged and excessive production of pituitary gonadotropic hormone and ultimately resulted in the production of granulosa cell tumors in the transplant. This is in contrast to the situation which would exist in the normal animal where estrogen is not detoxified by the liver since the blood from the ovary does not pass directly through the liver. Normally, excessive estrogen production does inhibit the release of pituitary gonadotropin. The whole subject of ovarian transplantation into the spleen has been recently reviewed by Iglesias, Mardones and Lipschutz (28). They have been working in this field for many years and point out that the situation is even more complicated than the original theory. It is impossible to review this brilliant article in a few words, but, as these writers point out, enough estrogen is produced by these transplants to produce obvious estrogenic changes in the vagina and elsewhere so it is apparent that not all estrogen has been detoxified by the liver. Tumors are produced in the transplants, none the less. Most recently, Zondek and co-workers have succeeded in again transplanting some of the tumors formed in these transplants to other rats (29).
Case 10
Thecoma

University of Kansas Medical Center
Kansas City, Kansas
Surgical No. 3828-53

History: This 62 year old white woman (grava 0, para 0) was admitted to the hospital for treatment of an upper respiratory infection. Physical examination revealed a pelvic mass.

Examination under anesthesia revealed a tumor of the right ovary. A dilatation and curettage was performed. Examination of the curettings demonstrated hyperplastic endometrium with polyps. A right salpingo-oophorectomy was then carried out.

Gross Pathologic Findings: A large mass measuring 9 X 5 X 7 cm. was attached to the right ovary. This was orange in color and on section appeared mottled. It was firm and fibrous in consistency.

Comment: The comments just made in the preceding case would apply equally well to thecomas: The same tumor usually contains areas consisting largely of theca cells in one part of the tumor and areas consisting largely of granulosa cells in another part. As Traut and Marchetti(30) have pointed out, however, rarely the tumors may appear in pure form. Despite the fibrillar appearance, microscopically, these tumors usually contain a large amount of fat, as demonstrated by fat stains and by an orange-yellow color, grossly. They also produce estrogenic hormone and produce hyperplasia of the endometrium, as in this case, with post-menopausal bleeding or other anomalies of menstruation.
Case 11
Virilizing lipoid cell tumor
with atrophic endometrium

University of Kansas Medical Center
Kansas City 12, Kansas
Surgical No. 2385-53

History: The patient, a 46-year-old colored woman, was first seen in this hospital 17 years before operation (at age 29) when she came to the outpatient department complaining of abdominal pain. The patient had married 13 months previously, and dated the onset of her symptoms to 11 months previously. At that time, she had developed abdominal cramps, amenorrhea, hirsutism of the face, arms, and abdomen, and a 40 pound weight gain. Her menstrual history had apparently been normal prior to that time. Physical examination at this time revealed a weight of 225 pounds, a blood pressure of 130/90, excessive hair on the face and abdomen, abdominal striae and questionable exophthalmos. The Wasserman and Kahn reactions were both 4+. The basal metabolic rate was -3 and the hemoglobin was 11.5gm%. The patient was treated with a course of eight injections of neoarsphenamine, and was then given large doses of thyroid extract. She was followed in the outpatient department for 18 months, and had occasional irregular periods. An endometrial biopsy revealed atrophic cystic endometrium.

The patient returned to the clinic 13 years and 15 years later for treatment of a recurrent conjunctivitis (thought to be herpetic in origin) and presbyopia. There was no further investigation of her endocrine status until seventeen years after her initial hospital visit when she was again seen in the Medical Clinic complaining of abdominal pain, a yellowish vaginal discharge, nervousness, and hirsutism. At this time, she was hospitalized for study.

The interval history is not entirely clear. Apparently, the patient continued to take thyroid extract for at least a year after her last previous clinic visit. Her periods had been fairly regular for a total of 12 years, but she had not menstruated at all for the last 4-5 years. Hirsutism had increased
in extent so that she was forced to shave every two days. She had experienced a gradual loss of sexual desire over a period of about ten years. On two occasions during the interval (the second time 18 months prior to this hospitalization) the patient had been told that she had an abdominal tumor. This was associated with intermittent pain in the left lower quadrant.

Physical examination on admission revealed an obese woman weighing 188 pounds who did not have a Cushingoid type of fat distribution. A beard was present on the face. The escutcheon was of the masculine type and there was excessive hair on the arms, legs, back and breasts. Xanthomas were present around/eyelids. The voice was not hoarse. The blood pressure was 130/100.

The pelvic examination revealed that the uterus was enlarged about twice normal size, smooth, symmetrical, and fairly easily movable. The right ovary was normal. There was a 4 cm. firm, slightly irregular mass in the region of the left ovary. The clitoris measured 5 x 1 1/2 cm. and was possibly erectile. The vagina showed loss of rugation and thinning of the mucosa.

Laboratory studies revealed a hemoglobin of 11.1 gm.%. The VDRL was negative. The non-protein nitrogen was 32 mg.%, cholesterol 296 mg.% with 65% esterification, sodium 136 mEq./l and potassium 5.0 mEq./l. The glucose tolerance test showed a fasting level of 225 mg.% with hourly levels of 366, 398, 404, and 242 mg.%. An insulin tolerance test showed a fasting level of 250 mg.%, with half-hourly levels of 177, 163, 159, and 188 mg.%.

17-Ketosteroid excretion was 13.5 mg./24 hours (normal 5-0.4) and 11-Oxysteroid excretion was 2.9 mg./24 hours (normal 1-2). The I131 uptake was 25% in 24 hours. The protein bound iodine was 4.22%. The Thorne test with 20 mg. of ACTH showed a base line of 83 eosinophils/mm3. The 4 hour specimen contained 83 eosinophils per mm3.

A laparotomy was performed. Exploration revealed that the left kidney was
enlarged and there was thought to be a small nodule in the left adrenal. The uterus was enlarged about $1\frac{1}{2}$ times normal size. The right ovary was creamy and small in size. The left ovary was enlarged and showed irregular mottled orange and deep red papilliferous areas on the surface. A total hysterectomy and bilateral salpingo-oophorectomy were performed.

The patient's postoperative course was uneventful. She was readmitted to the hospital two months later for postoperative endocrine studies. Workup at this time revealed a blood pressure of 120/80, and a diffuse non-toxic goiter. The clitoris was still enlarged, but not erectile. The cholesterol was 316 mg.

Hirsutism continues to be a great problem to this patient. This has apparently responded somewhat to topical alcoholic diethylstilbestrol. She has gained weight and not followed her diabetic diet well.

**Gross Pathologic Findings:** The left ovary measured 3.5 x 3.5 x 1.3 cm. Its surface was slightly irregular with yellow discoloration. Cut section revealed a mottled, grayish-yellow appearance with firm and soft areas.

**Comment:** These tumors are quite rare. They have been known by a multiplicity of names including, masculinovoblastoma, luteoma, hypernephroma of the ovary and cortico-adrenal carcinoma of the ovary. This multiplicity of names has served further to complicate the situation. Thoughtful reviews of this subject have been published by Rottino and McGrath(31), Kepler, Dockerty and Priestly(32) and by Burket and Abell(33).

The origin and classification of these tumors is still highly debatable. The consensus is that masculinization can be produced by tumors arising from at least two if not three kinds of cells found in the ovary. One group are the ovarian hilus or Leydig cells which usually contain crystaloids of Reinke. Others are the adrenal rests. A third, more doubtful group are lutein cells, themselves, an
idea which is supported by the finding of masculinization in the Stein-Leventhal syndrome in which lutein cells are the chief cells found. Ovarian hilus (Leydig) cells and adrenal cortical cells are virtually indistinguishable except as previously stated by the presents of crystaloids of Reinke in the former, and their absence, in the latter. In addition, as Kepler, et.al. (32) have pointed out, cells derived from the adrenal cortex produce evidence of Cushing's syndrome in addition to evidence of masculinization pure and simple. In other words, they produce hypertension, diabetes and polycythemia in addition to hirsutism, enlargement of the clitoris, deepening of the voice and loss of hair on the scalp.

The tumor in this case, then, is similarly functionally as well as morphologically to the tumor derived from adrenal cortical cells. Careful search in this case has failed to reveal any crystaloids of Reinke. The origin of these tumors is from adrenal rests in the ovary. These adrenal rests are not uncommon. As previously stated, however, tumors clearly derived therefrom are rare.
History: This 17-year-old white woman had noticed a gradually enlarging mass in the abdomen for several months. The menstrual periods had been regular in time, but for 3 months menorrhagia had been present. Pelvic examination revealed a large, firm, well-circumscribed mass in the left adnexa. At operation, this mass was found completely to replace the ovary. The right ovary and uterus were not remarkable.

Three years later, the patient is entirely well. She has recently married.

Gross Pathologic Findings: The mass was firm, yellowish-white in color, and lobulated in appearance. On cut section it was firm and fibrous.

Comment: Dysgerminomas are relatively rare ovarian tumors. Their clinical course and pathological picture have been well reviewed by Meyer(34) (who originally introduced the name), Seegar(35) and Sailer(36). Originally, these tumors were thought both to be benign and to be unrelated to sexual disturbances. As experience accumulates, however, it is apparent that a considerable portion of these are associated with evidence of a hormonal imbalance though many of them may present no such features and show only the presence of an abdominal mass. In addition, a significant number of them, somewhere between a quarter and a half, show a tendency to metastasize and are obviously malignant. Despite this, Seegar(35) feels that conservatism in operation is desirable as these tumors usually occur in young people and frequently the removal of the affected ovary alone has been followed not only by continued well-being of the patient but also by one or more successful pregnancies. Seegar feels that the best criterion of malignancy at the time of original operation is whether or not there is extension through the capsule of the tumor and into surrounding tissues at the time. The microscopic appearance
is often quite bizarre and cannot be relied on as an indication of the future behavior of the tumor.
History: This 14-year-old girl was admitted complaining of amenorrhea. The menses had been regular, beginning at the age of 11, until 6 months previously. Since then, the patient had had only occasional spotting. Three months before admission, the patient had had an acute sore throat and hoarseness had been present ever since.

Physical examination revealed a large abdominal tumor and increased growth of hair on the upper lip. Laryngoscopic examination showed bridging of the vocal cords.

Laparotomy revealed a large partially cystic tumor replacing the right ovary. A right salpingo-oophorectomy was performed.

Menstruation returned 4 months later. The hirsutism gradually disappeared, but the hoarseness has persisted. The patient is apparently well 2 years later.

Gross Pathologic Findings: The specimen consisted of a cystic mass of ovarian tissue measuring approximately 16 cm. in diameter. Cut section revealed many multilocular cysts alternating with yellow gelatinous solid areas.

Comment: This case was originally observed and reported by Kassebaum(37). The pathological material was studied at the Lattimore-Fink Laboratories. We are indebted to both Dr. Kassebaum and Dr. Fink for the material and for permission to use it in this loan collection.

The term "arrhenoblastoma," is supposed to apply to tumors of the ovary which look like male spermatice tubules and which produce masculinization, but that
something is wrong with this concept has been pointed out repeatedly, for other tumors can produce masculinization and, furthermore, androgen is secreted in the testicle by the Leydig cells and not by the tubules themselves. The masculinizing effect, then, of these tumors in the female is presumably due to the Leydig cells which are apparently analogous to the ovarian hilus cells. These cells are characterized by the presence of crystaloids of Reinke. Careful inspection of the tumor that is present here will show a few, larger, pale staining cells at the edge of the slide. Careful inspection fails to reveal any crystaloids in these cells, however. It is probable that these cells are, in fact, the source of the masculinizing hormone. It is to be noted that much of the tumor that makes up this specimen consists of small dark cells somewhat suggestive of granulosa cells. That this problem has been troublesome before is suggested by the review of the literature by Mechler and Black in which they discuss the concept of gyandroblastoma which would have both masculinizing and feminizing hormones. The review of the literature is given in this article.

A further inspection of the tumor presented reveals that much of this consists of rounded masses filled with deep pink staining material. While this may suggest tubules of the testicle, closer inspection indicates that this is more suggestive of thyroid follicles containing colloid. A particular reason for saying so is the presence of numerous vacuoles around the outer portion of these colloid masses, a feature quite characteristic of thyroid colloid. It does not have the hyalinized stroma which Nicholson feels is essential to make the diagnosis of struma ovarii (ovarian goiter). Emge has, however, described two clear cut cases which lack this change in the stroma and which are perhaps even less suggestive of thyroid tissue than the example presented here. These cases were accompanied by definite evidence of hyperthyroidism which receded when the tissue was removed.
at operation. In a case of this type, however, there is not enough evidence to warrant a definite diagnosis of struma ovarii although the rather tantalizing possibility remains.
Conclusions

In reviewing this series of ovarian tumors as a whole, is there anything that can be said in general conclusions? It is possible that the following statements are justified:

First of all, the classification of ovarian tumors is a difficult one as Emge\(^{(17)}\) has already emphasized. The reasons for this difficulty are of course due to the presence of intermediate forms between one classical example and another, the fact that one tumor can show one appearance in one area and another appearance in another area and the fact that histologic appearance and endocrinological effect do not always go hand in hand. To consider the last problem first, endocrinological effects ordinarily attract attention by their effect on the host. The host, herself, sometimes has another ovary and always has, in addition, a functioning hypophysis at the time when the ovarian tumor is discovered. Furthermore, the responsiveness of primary sex characteristics, to say nothing of the secondary sex characteristics, depends on the age of the individual. Therefore, in doing a titration on the host, we are using a rather variable test object, shall we say, in addition to the fact that other hormones are present which may be influencing the results. A more accurate idea of hormone function, or otherwise, can only be gathered from studies on castrated animals. Unfortunately, because of the inherent difficulties of the problem, this has been done only rarely. As far as the other difficulties are concerned, this is a more fundamental problem perhaps and depends on one's philosophical approach to the whole problem. The writer is tempted to go a little further than Emge and say that classification of ovarian tumors is not only difficult but is impossible, and is impossible precisely for the reasons mentioned. These tumors do show variation from one to
another. Various kinds of cells are present. Or one kind of cell in different physiological states, if one prefers, can be seen in different areas. Both masculinizing and feminizing hormones are quite similar to each other chemically and it is quite possible for the same cell or the same kinds of cells to secrete more than one hormone or secrete hormones with different effects on different organs.

Finally, the writer is tempted to agree with Willis(2) in feeling that tumors of the ovary are derived from the ovarian stroma itself and that all tumors of the ovary, including teratomas, are derived from this fascinating and versatile tissue. The unlimited variety, in structure and function, shown by different ovarian tumors and sometimes by different parts of the same tumor, can then be explained on the basis of the great variety of potentialities of this interesting stroma. This hypothesis also leads to the conclusion that the classification of ovarian tumors is fundamentally arbitrary and therefore impossible.
References


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