

CALIFORNIA TUMOR TISSUE REGISTRY  
FIFTY-SEVENTH SEMI-ANNUAL SLIDE SEMINAR  
ON  
TUMORS OF THE FEMALE GENITAL TRACT

MODERATOR:

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ASSOCIATE PROFESSOR OF PATHOLOGY  
&  
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STANFORD UNIVERSITY MEDICAL CENTER  
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PROFESSOR OF PATHOLOGY  
LOMA LINDA UNIVERSITY MEDICAL CENTER  
LOMA LINDA, CALIFORNIA

SUNDAY, APRIL 21, 1974  
9:00 A.M. - 5:30 P.M.

REGISTRATION: 7:30 A.M.

PASADENA HILTON HOTEL  
PASADENA, CALIFORNIA

Please bring your protocol, but do not bring slides or microscopes to the meeting.

CALIFORNIA TUMOR TISSUE REGISTRY

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HAROLD AMSBAUGH, MEDICAL STUDENT, LAC-USC MEDICAL CENTER

NAME: E. G.

APRIL 21, 1974 - CASE NO. 1

AGE: 47 SEX: Female RACE: Caucasian

ACCESSION NO. 13759

CONTRIBUTOR: Shirley Howard, M. D.  
St. John's Hospital  
Santa Monica, California

OUTSIDE NO. S-2658-64

TISSUE FROM: Vagina, left Bartholin's gland

CLINICAL ABSTRACT:

History: This 47 year old female noted pain in the left side of the vagina in the region of Bartholin's gland for several months. When she noted a hard nodule, she consulted her physician immediately. She had a hysterectomy for carcinoma in situ of the cervix three years earlier. She had an abscess involving the right Bartholin's gland at an earlier unknown date.

Physical examination revealed a stony hard 2 cm. nodule possibly fixed to the deeper tissues in the region of the left Bartholin's gland. There was no obvious involvement of vaginal mucosa or of skin. The regional lymph lymph nodes were not palpable.

Radiograph: Chest film was negative.

SURGERY: (June 17, 1964)

Excision biopsy was performed, followed by a radical bilateral vulvectomy on June 19, 1964.

GROSS PATHOLOGY:

The excision biopsy was a circumscribed, tan, very firm nodule, measuring 1.3 cm. in diameter. The nodule bulged from the cut surface of the left Bartholin's gland which was enlarged and measured 3 x 2.5 x 2 cm.

The vulvectomy specimen showed no malignant tumor at the biopsy site, none in the opposite Bartholin's gland, and no tumor in the inguinal, femoral or in iliac lymph nodes.

FOLLOW-UP: (George Hummer, M. D.)

The patient was last seen and examined by her attending surgeon in August 1973 at which time a vaginal Papanicolaou smear was negative. The patient complained of occasional lower extremity edema that was controlled by the use of support type stockings. There was no evidence of malignant disease.

NAME: L. N.

APRIL 21, 1974 - CASE NO. 2

AGE: 64 SEX: Female RACE: Caucasian

ACCESSION NO. 19905

CONTRIBUTOR: Stuart A. Monroe, M. D.  
St. John's Hospital  
Tulsa, Oklahoma

OUTSIDE NO. S72-7932

TISSUE FROM: Uterus

CLINICAL ABSTRACT:

History: This postmenopausal female presented with a three week history of light to heavy intermittent vaginal spotting. There was no contributory pastmedical or surgical history.

Routine laboratory work was normal.

A dilation and curettage revealed chunky, firm tissue fragments in association with a uterus which appeared to be "doubled" in size.

SURGERY: (September 27, 1972)

The uterus was distorted with a profile characteristic of uterine fibroids. A hysterectomy and bilateral salpingo-oophorectomy was accomplished with ease.

GROSS PATHOLOGY:

The specimen was a 340 gram uterus with attached adnexa. The uterine serosa was unremarkable. The myometrium had several nodular leiomyomatous areas with hemorrhage, necrosis, and "mucoid softening". The largest nodule was 8.0 cm. in greatest dimension. A prominent submucosal necrotic nodule (2.5 cm. in diameter) extended into the uterine cavity. The endometrium was otherwise unremarkable. The fallopian tubes and ovaries were normal.

FOLLOW-UP:

Patient was re-admitted on February 19, 1974 with recurrent pelvic mass and was scheduled for exploratory laparotomy (February 22, 1974).

NAME: L. W.

APRIL 21, 1974 - CASE NO. 3

AGE: 60 SEX: Female RACE: Negro

ACCESSION NO. 9559

CONTRIBUTOR: Ethel R. Nelson, M. D.  
White Memorial Hospital  
Los Angeles, California

OUTSIDE NO. 57-3355

TISSUE FROM: Cervix

CLINICAL ABSTRACT:

This 60 year old Negro female presented with two episodes of vaginal bleeding. Thirty years previously she underwent a bilateral salpingo-oophorectomy as treatment for pelvic inflammatory disease. She never received any hormone replacement therapy.

SURGERY: (August 2, 1957)

A total hysterectomy was performed.

GROSS PATHOLOGY:

The uterus measured 7.2 x 5.0 x 3.0 cm. The endometrium measured 0.1 cm. in thickness and was slightly hemorrhagic. A 2.0 cm. tumor, covered by intact mucosa, was present in the posterior lip of the cervix. The mass was light yellow with translucent areas and had the consistency of hard rubber.

FOLLOW-UP:

Thirteen months after surgery, a local recurrence developed in the vaginal cuff and was excised. The patient was then lost to follow up.

NAME: L. Z.

APRIL 21, 1974 - CASE NO. 4

AGE: 12 SEX: Female RACE: Filipino

ACCESSION NO. 20440

CONTRIBUTOR: M. L. Bassis, M. D.  
Kaiser-Permanente Medical Center  
San Francisco, California

OUTSIDE NO. SF 73-2151

TISSUE FROM: Right ovary

CLINICAL ABSTRACT:

History: This 12 year old Filipino girl was in good health until one week prior to admission when she noticed her abdomen was getting larger and harder. She had not started menstruating and had no axillary hair.

On physical examination there was a large hard fixed mass extending from the pelvis to the umbilicus.

Radiograph: An intravenous pyelogram showed a right hydronephrosis and hydroureter secondary to extrinsic pressure by a pelvic mass which also caused lateral displacement of the right ureter. A bone series was negative.

SURGERY: (February 20, 1973)

A large right ovarian mass was found. A total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed.

GROSS PATHOLOGY:

The right ovary measured 18 x 16 x 10 cm. and weighed 1500 grams. The mottled red-gray to yellow surface had bulging cysts containing clear watery yellow fluid with an apparent intact capsule. The cut surface of the tumor disclosed a variegated pattern with multiple yellow lobules interspersed with gray to red-brown necrotic zones admixed with the cysts which measured up to 6 cm. in diameter. The cysts contained watery or viscid yellow fluid and in some instances hemolyzed blood. The fallopian tubes, opposite ovary, and uterus showed no remarkable features.

FOLLOW-UP:

This patient received postoperative cobalt-60 radiation delivering 5,020 rads in 51 days which was well tolerated. She was asymptomatic and free of evident disease until September 1973 when abdominal pain recurred. In early October, left lower quadrant masses and liver enlargement associated with ascites were discovered. Chemotherapy with oral Cytosan, IV vincristine, actinomycin D and mithramycin was started with rapid response. Five weeks after treatment began no masses were palpable abdominally or on pelvic examination. She remained well through mid-February 1974. She was hospitalized with serious deterioration of her condition including gastrointestinal bleeding, suspected cardiac involvement (? pericardial metastasis), ascites, and pelvic tumor recurrence. She died on March 8, 1974.

APRIL 21, 1974 - CASE NO. 4

ACCESSION NO. 20440

At autopsy there was 3.5 liters of ascites and tumor covering the peritoneum. The tumor grew in tan grape-like clusters on the serosa. The cut surface was soft whitish tan and homogenous. A single adhesion was seen kinking the sigmoid colon. Lymph nodes showed two microscopic tumor emboli. No abdominal organs had intraparenchymal tumor except for mild degree of direct extension into the right lobe of the liver. There were no distant metastases. Superficial stress ulcer of the gastric fundus were seen.

NAME: I. C.

APRIL 21, 1974 - CASE NO. 5

AGE: 57 SEX: Female RACE: Caucasian

ACCESSION NO. 13317

CONTRIBUTOR: Daniel Krag, M. D.  
Los Gatos Community Hospital  
Los Gatos, California

OUTSIDE NO. R63-32

TISSUE FROM: Cervix

CLINICAL ABSTRACT:

History: This 57 year old white housewife, whose last normal menstrual period was age 45, complained of watery vaginal discharge and intermittent spotting of blood for an unknown length of time.

On physical examination, she was a robust-appearing woman. The pelvic organs could not be easily palpated because of vaginal stricture, but a polypoid lesion presented at the cervix.

On December 15, 1962, cervical conization and uterine curettement were done at another hospital.

SURGERY:

On January 8, 1963 an abdominal hysterectomy and bilateral salpingo-oophorectomy was performed.

GROSS PATHOLOGY:

The uterus was 10 x 5 x 6 cm. The corpus was nodular and irregularly enlarged by several intramural fibroids. The entire cervical region was enlarged and thickened by an infiltrating pinkish yellow sticky tumor that surrounded the endocervical canal. The cervical tumor measured 4.5 x 3.2 x 3.0 cm. and extended to the margins of excision in the cervical region. There was evidence of cervical conization and curettement of the endometrial cavity. Both ovaries, oviducts and appendix were normal.

FOLLOW-UP:

Follow-up information not available.

NAME: H. S.

APRIL 21, 1974 - CASE NO. 6

AGE: 60 SEX: Female RACE: Caucasian

ACCESSION NO. 13900

CONTRIBUTOR: D. R. Dickson, M. D.  
Santa Barbara Cottage Hospital  
Santa Barbara, California

OUTSIDE NO, S64-4386

TISSUE FROM: Vulva

CLINICAL ABSTRACT:

History: This patient had vulvar pruritus at irregular intervals. The pruritus persisted despite medical treatment and became more intense, increased in frequency, and finally the patient noticed a white discoloration of the vulvar skin. The last menstrual period was 10 years earlier. There was no vaginal discharge. She had never been married. One year , previously she had radiologic evidence of a peptic ulcer that responded to routine medication and diet.

On physical examination she was normal except for several confluent white plaques that encircled the vulva, forming a horseshoe-shaped area with the clitoris in the central portion.

Laboratory studies showed hemoglobin of 12.4 gm., WBC 7700, and a normal urinalysis.

SURGERY:

A vulvectomy was performed on September 17, 1964.

GROSS PATHOLOGY:

The oval specimen was the clitoris and anterior portions of the labia majora and minora, measuring 85 x 50 x 10 mm. Irregular white plaques extended from the prepuce of the clitoris superiorly and laterally, and also to the medial aspects of each labia majora, a zone 35 x 25 mm. in greatest dimension. No ulceration or erosion of the skin or mucosa was evident..

COURSE:

Because of apparent incomplete excision as determined by microscopic study, further excision was performed on October 1, 1964, removing an 80 x 30 x 17 mm. oval portion of skin and subcutaneous fat, with the linear recent healing surgical excision in the central portion.

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APRIL 21, 1974 - CASE NO. 6

ACCESSION NO. 13900

FOLLOW-UP:

The patient was free of disease for eight years. In November 1972, she returned to her surgeon with a few suspicious plaques. A biopsy showed the same disease with no underlying carcinoma. She was treated by ointments for a year and the lesion spread. There is now erythema and skin thickening from the pubis to the anus and extending 1" on the medial aspects of both thighs. A radical vulvectomy including the clitoris is being considered.

NAME: M. C.

APRIL 21, 1974 - CASE NO. 7

AGE: 36 SEX: Female RACE: Caucasian

ACCESSION NO. 12799

CONTRIBUTOR: George Kypridakis, M. D.  
White Memorial Hospital  
Los Angeles, California

OUTSIDE NO. WMH 63-380

TISSUE FROM: Uterine fundus

CLINICAL ABSTRACT:

The patient was a single Caucasian female, gravida 0, who has been under medical care most of her life for grand mal epilepsy and mental retardation. An abdominal mass thought to be fibroids was first diagnosed in 1957. The familial history and remaining examination were negative. Her menses began at 18 years of age, occurred at 24-26 day interval and lasted 4 days.

SURGERY:

An abdominal hysterectomy was performed on January 29, 1963.

GROSS PATHOLOGY:

The total uterus measured 15 x 15.5 x 9 cm., weighed 1200 grams, and included a pedunculated mass, 13 x 12 x 10 cm. The serosa was covered by adhesions and there were small subserosal blebs filled with hemorrhagic fluid. In addition to the pedunculated tumor which had the typical gross appearance of a leiomyoma, there were multiple intramural leiomyomata, the largest measuring 6.5 cm. in diameter. The latter presented a different gross appearance with a bulging cut surface composed of closely oriented multifaceted kernels of homogeneous yellow tissue, resembling kernels of corn. These were separated by slit-like spaces. The endometrial cavity was hemorrhagic and somewhat roughened due to previous curettage (done at surgery). The cervix was smooth with a nulliparous os.

FOLLOW-UP:

Patient is lost to follow-up.

NAME: A. P.

APRIL 21, 1974 - CASE NO. 8

AGE: 83 SEX: Female RACE: Caucasian

ACCESSION NO. 12903

CONTRIBUTOR: John Blanchard, M. D.  
Santa Barbara General Hospital  
Santa Barbara, California

OUTSIDE NO. A63-25

TISSUE FROM: Uterus

CLINICAL ABSTRACT:

History: The patient was first admitted on February 23, 1955 for epidermoid carcinoma of the uterine cervix. The diagnosis was made by cytology studies and biopsy. The patient was given radium implants and followed in clinic. In July 1955 she had a maxillary sinusotomy for chronic sinusitis, and in August 1960 she had sigmoidoscopy and intravenous pyelogram. She was treated for diverticulosis and diverticulitis.

Rectal examination showed hemorrhoids and a pelvic examination was "deferred".

Final admission was February 23, 1963 for bowel obstruction secondary to metastatic carcinoma of the uterus. At surgery, a huge mass filled the pelvis, and many lymph nodes were involved with metastatic tumor. A colostomy was performed. She died suddenly on March 16, 1963.

AUTOPSY:

The pelvic mass was primarily an intrauterine tumor. The upper portion of the vagina was narrowed and thick walled. The canal of the uterine cervix was obliterated and the mucosa was thickened; on the anterolateral right quadrant there was a flat irregular plaque of dense neoplasm that measured up to 10 mm. in diameter. The uterine fundus contained a polypoid gray-white, granular, soft, polypoid tumor, measuring 6 cm. in length by 3.4 cm. in diameter. There was a 2 cm. diameter focal zone of brown-red necrosis in the polypoid tumor. The wall of the uterus was thin (5 mm.). The tumor had grown through the uterine wall and obliterated both adnexal structures. The adnexal tumors communicated directly with the lymph nodes in the pelvic area and to nodes adjacent to the lower aorta. Other autopsy findings were right hydroureter, generalized arteriosclerosis, and peritoneal fibrous adhesions.

NAME: I. C.

APRIL 21, 1974 - CASE NO. 9

AGE: 24 SEX: Female RACE: Caucasian

ACCESSION NO. 12998

CONTRIBUTOR: William P. Snider, M. D.  
Queen of the Valley Hospital  
West Covina, California

OUTSIDE NO. 596-63

TISSUE FROM: Endometrium

CLINICAL ABSTRACT:

History: Patient was admitted on April 25, 1963 for the removal of a left ovarian cyst which had increased in size since discovered one year previously. The patient was gravida I, para I, who delivered an infant in 1960. In 1961, a right ovarian cyst was removed elsewhere and the details are not known. She has had amenorrhea despite of cyclic hormone therapy.

Physical examination: There was a movable, nontender, 6 cm. mass in the left adnexal region.

Laboratory data was normal and a pregnancy test was negative.

SURGERY:

A hysterectomy and left salpingo-oophorectomy was performed on April 26, 1963.

GROSS PATHOLOGY:

The uterus measured 10 x 6.5 x 4.5 cm. in greatest dimension. The external cervical os was slightly roughened and irregular. The myometrium was tan and trabeculated and averaged 2.5 cm. in thickness. Near the origin of the left tube, a 0.4 cm. poorly delineated nodule bulged from the serosal surface. No other myometrial lesions were seen. The endometrial cavity was enlarged by a lobulated, yellowish tan tumor that measured 4 x 2.5 x 1.5 cm. and was attached along the posterosuperior wall. The tumor was partially cystic, friable, and blended into the underlying myometrium. The remaining endometrium was a thin tan layer that measured about 1 mm. in thickness. The attached right tube was normal. The left ovary measured 6.5 x 5.5 x 5 cm. and was multiloculated and cystic. The ovarian cyst linings were smooth and only a small amount of ovarian tissue was found along one portion of the wall.

FOLLOW-UP:

The patient was asymptomatic with normal pelvic examination and negative chorionic gonadotropin test up to 1968 when she was lost to follow-up.

NAME: R. M.

APRIL 21, 1974 - CASE NO. 10

AGE: 15 SEX: Female RACE: Caucasian

ACCESSION NO. 12802

CONTRIBUTOR: J. J. Bocian, M. D.  
Fresno Community Hospital  
Fresno, California

OUTSIDE NO. S63-578

TISSUE FROM: Ovary

CLINICAL ABSTRACT:

History: This young woman was in good health until one week prior to admission when she had generalized lower abdominal pain, slight abdominal enlargement and abdominal tenderness on coughing. Menarche was at age 12; her last menstrual period was 10 days prior to admission and was normal, although the flow was less than usual.

On physical examination, she was well developed and alert, but ill. The lower abdomen was moderately protuberant. There was a very hard, tender mass extending from the symphysis to the umbilicus. A second firm slightly tender mass was balloted in the epigastric area. On rectal examination, there was a hard smooth tender mass filling the pelvis.

Laboratory report: Hemoglobin 11.5 gm%, WBC 12,300 with 63 segs, 25 lymphocytes, 4 monocytes, 2 eosinophils, and 2 basophils.

Roentgenography: No calcifications were found in the abdominal tumors.

SURGERY: (February 1963)

An appendectomy and a bilateral salpingo-oophorectomy were performed.

GROSS PATHOLOGY:

The left ovary weighed 630 gms., measured 15 x 12 x 8 cm., and was a solid fairly soft tumor that on cut section was smooth and light tan. There was some mucinous change, and a few cystic areas that measured up to 2 cm. The attached fallopian tube was normal. The right ovary was 800 grams and similar to the left one. A small gray nodule was attached to the serosa of the Fallopian tube and there was another nodule 0.8 cm. in diameter attached to the mesosalpinx.

FOLLOW-UP:

The patient developed jaundice on March 2, 1963 (Bilirubin was 5.3 total). She died in May 1963 and there was no autopsy.

NAME: O. A.

APRIL 21, 1974 - CASE NO. 11

AGE: 51 SEX: Female RACE: Caucasian

ACCESSION NO. 11497

CONTRIBUTOR: H. R. Fisher, M. D.  
Memorial Hospital of Glendale  
Glendale, California

OUTSIDE NO. 4748

TISSUE FROM: Uterus

CLINICAL ABSTRACT:

History: Patient had been feeling weak and "sick" for 4 years. She had a long history of dysmenorrhea, but for the past year menorrhagia was more severe and flow was extremely heavy. There had been almost continuous flow for three months prior to admission to the hospital in March 1961.

Physical examination was not remarkable other than pallor and obvious weakness. Pelvic examination revealed that vaginal bleeding was present and a polyp protruded from the cervical os. The fundus appeared enlarged to 3½ times normal size. The adnexae were normal.

SURGERY:

On March 15, 1961, a dilatation and curettage was done and a large amount of yellow polypoid smooth material was obtained. A hysterectomy was performed.

GROSS PATHOLOGY:

The uterus measured 11.5 x 9 x 7 cm. and weighed 261 grams. The cervical segment measured 4 cm. in length. The corpus and fundus were globular in configuration. On the serosal surface of the posterior aspect of the fundus there was a reddish tan nodularity covering an area of 1.5 cm. in diameter area x 3 mm. in thickness. A similar serosal nodularity of endometriosis was noted at the insertion of the left tube to the fundus. The entire fundus of the uterus was expanded diffusely to form an ill-defined tumor, measuring 7 x 6 x 5 cm. The cut surface of the myometrium showed innumerable, soft, yellowish, nodular, well demarcated masses extending to the serosa

FOLLOW-UP:

She was seen in 1963 and advised she would need additional therapy. She was never heard from again and attempts to contact her in 1967 failed.

NAME: M. G.

APRIL 21, 1974 - CASE NO. 12

AGE: 62 SEX: Female RACE: Caucasian

ACCESSION NO. 19913

CONTRIBUTOR: Walter Coulson, M.D.  
William H. Johnston, M.D.  
UCLA School of Medicine  
Los Angeles, California

OUTSIDE NO. 72S-5538

TISSUE FROM: Ovary

CLINICAL ABSTRACT:

This 62 year old Caucasian female presented with a three week history of dull pain and pressure in the left lower quadrant of her abdomen.

Past history: The patient had a right oophorectomy at age 44 for a mucinous cystadenoma.

SURGERY: (July 18, 1972)

At laparotomy, a cystic left ovarian tumor was found which measured 7.0 cm. in diameter. A total hysterectomy and left salpingo-oophorectomy was performed. The cystic tumor ruptured during the procedure.

GROSS PATHOLOGY:

The cystic mass weighed 140 grams. The inside of the cyst was lined with purple, friable papillary material. In one portion of the wall was a lobulated, multicystic, white and yellow mass the size of a walnut.

Gross and microscopic examination of the fallopian tube revealed no abnormality. The uterus showed multiple leiomyomas, mild proliferation of the endometrium and focal squamous metaplasia of the cervix.

FOLLOW-UP:

As of February 1974 the patient is alive and there is no evidence of either recurrent or metastatic tumor.

NAME: F. B.

APRIL 21, 1974 - CASE NO. 13

AGE: 44 SEX: Female RACE: Caucasian ACCESSION NO. 19739

CONTRIBUTOR: Aaron A. Dubrow, M.D. OUTSIDE NO. P-72-127  
Pacoima Memorial Lutheran Hospital  
Pacoima, California

TISSUE FROM: Uterine Cervix

CLINICAL ABSTRACT:

This 44 year old gravida VIII, para VI, Caucasian female was admitted for diagnostic procedures after a Papanicolaou smear revealed cells that were suspicious for malignancy.

PHYSICAL EXAMINATION:

There was moderate uterine procidentia. The cervix was parous and the upper lip was extremely large. There were focal cervical erosions. The adnexae were normal.

SURGERY: (January 26, 1972)

A dilatation and curettage and a conization of the cervix were performed.

GROSS PATHOLOGY:

The resected portion of the cervix measured 3.4 x 2.4 x 1.0 cm. The epithelial surface was granular. On cut section there were multiple small cysts, measuring up to 0.3 cm., which were filled with mucinous material. The tissue had a firm consistency.

Microscopic examination of the uterine curettings revealed proliferative phase endometrium and mild cystic changes.

FOLLOW-UP:

The patient received postoperative internal and external radiotherapy. As of February 1974 there is no evidence of recurrent or metastatic tumor.

NAME: H. J. G.

APRIL 21, 1974 - CASE NO. 14

AGE: 58 SEX: Female RACE: Unknown

ACCESSION NO. 20287

CONTRIBUTOR: Paul Thompson, M. D.  
St. Luke Hospital  
Pasadena, California

OUTSIDE NO. 463-73

TISSUE FROM: Uterine cervix

CLINICAL ABSTRACT:

This 58 year old gravida IV, para IV, female was noted to have contact bleeding from the external cervical os during her annual physical examination. A biopsy of the cervix was obtained.

In 1968 she had some irregular bleeding and an endometrial biopsy demonstrated proliferative hyperplasia. In 1970 because of some bleeding after stopping hormones, an endometrial biopsy was done and reported as negative.

SURGERY: (March 7, 1973)

A total hysterectomy with a vaginal cuff and a bilateral salpingo-oophorectomy was performed.

GROSS PATHOLOGY:

The entire specimen weighed 180 grams. The cervix was extremely hard up to the endometrial junction, having the appearance and consistency of a raw potato. The endometrial mucosa and the myometrium appeared normal.

Gross and microscopic examination of the fallopian tubes and ovaries revealed no significant abnormalities.

FOLLOW UP:

She was last seen on December 19, 1973 after a full course of cobalt. There was moderate lymph edema which was decreasing. There was no evidence of disease.

NAME: V. E. G.

APRIL 21, 1974 - CASE NO. 15

AGE: 50 SEX: Female RACE: Caucasian

ACCESSION NO. 20304

CONTRIBUTOR: John D. Silverthorne, M. D.  
Doctors Hospital of Lakewood  
Lakewood, California

OUTSIDE NO. DL-1621-73

TISSUE FROM: Uterus

CLINICAL ABSTRACT:

History: This gravida I, para I, 50 year old female presented with menometrorrhagia of one year duration.

Physical examination was essentially negative except that the uterus was 2 to 2½ times normal size and consistent with a large fibroid uterus.

Radiographs: Numerous radiolucent lesions suggestive of metastatic tumor involving many bones were seen on the chest radiograph and on intravenous pyelogram. Mammography was negative.

Laboratory report: Serum levels of calcium, phosphorus, and alkaline phosphatase were within normal limits. No myeloma proteins were detectable in the serum. A 24-hour urine for 5 hydroxyindole acetic acid (5HIAA) was well within normal limits.

SURGERY: (August 20, 1973)

A total hysterectomy and bilateral salpingo-oophorectomy was performed.

GROSS PATHOLOGY:

The uterus weighed 410 grams and measured 17 x 11 x 7 cm. The cervix had a few erosions. There were numerous submucosal and intramural leiomyomas which measured up to 5 cm. in diameter. One large intramural leiomyoma, located in the fundus, had a different appearance than the others. Although it was well delineated, on cut section it had a tan color, coarsely granular surface, serpiginous foci of hemorrhage and central cystic degeneration. The lesion was surrounded by a thin rim of overlying myometrium and serosa, and had no connection with the endometrium.

Both fallopian tubes appeared grossly normal. The ovaries were also regular in gross appearance, both averaging 3 cm. in maximum dimension. Sectioning of both revealed small cysts and corpora albicantia.

FOLLOW-UP:

Currently the patient is receiving intermittent treatment with alkeran and is able to do her own housework.

NAME: K. P.

APRIL 21, 1974 - CASE NO. 16

AGE: 71 SEX: Female RACE: Caucasian

ACCESSION NO. 11830

CONTRIBUTOR: T. C. Nelson, M.D.  
Fresno Community Hospital  
Fresno, California

OUTSIDE NO. S-61-3472

TISSUE FROM: Endometrial cavity

CLINICAL ABSTRACT:

History: This 71 year old Caucasian female presented with a history of intermittent vaginal bleeding of 8 months' duration. Menopause occurred at age 53. The patient had been taking digitalis for the past 8 years for a heart condition.

Laboratory: A Papanicolaou smear was interpreted as showing atrophic changes.

SURGERY: (July 1961)

A hysterectomy and bilateral salpingo-oophorectomy was performed.

GROSS PATHOLOGY:

The uterus weighed 135 grams and measured 8.5 x 6.5 x 5 cm. Within the endometrial cavity was a 4.0 x 2.5 cm. mass of cystic, papillary and nodular tissue attached to the posterior and lateral walls. The margins were distinct and there was no apparent invasion of the myometrium. The fallopian tubes and ovaries were atrophic.

FOLLOW-UP:

As of 9 years post-surgery the patient had no symptoms referable to the gynecologic system. In 1970 the patient moved and has been lost to follow up.

NAME: S. T.

APRIL 21, 1974 - CASE NO. 17

AGE: 25 SEX: Female RACE: Unknown

ACCESSION NO. 20565

CONTRIBUTOR: Paul Herrmann, M. D.  
Alameda Hospital  
Alameda, California

OUTSIDE NO. P 71-55

TISSUE FROM: Ovary

CLINICAL ABSTRACT:

History: This 25 year old female presented with a four year history of irregular menses and periods of amenorrhea. A dilatation and curettage four years prior to admission revealed mild hyperplasia of the endometrium. Three years later (1970) a 3 cm. left adnexal mass was noted, which slowly increased in size. Although she had been married for 7 years, she had not conceived.

Physical examination: The breasts were normally developed. Pelvic examination revealed a 6 cm. mass in the region of the left ovary.

SURGERY: (1971)

A left oophorectomy was performed. The surgeon reported that the uterus was slightly enlarged and boggy to palpation. The right ovary was small but normal in appearance. The left ovary was enlarged and bound down to the posterior leaf of the broad ligament. The fallopian tubes were slightly nodular.

GROSS PATHOLOGY:

A solid bosselated, tan-yellow tumor, measuring 6 cm. in diameter, replaced the left ovary.

FOLLOW-UP:

As of 3 years after surgery, the patient is alive and well.

NAME: E. A.

APRIL 21, 1974 - CASE NO. 18

AGE: 43 SEX: Female RACE: Caucasian

ACCESSION NO. 20562

CONTRIBUTOR: Roger Terry, M. D.  
LAC-USC Medical Center  
Los Angeles, California

OUTSIDE NO. 74-2464

TISSUE FROM: Uterus

CLINICAL ABSTRACT:

History: This 43 year old Caucasian female had regular menses until six weeks prior to admission when she developed continuous vaginal bleeding.

Physical examination: There was a fungating, friable, soft mass present which filled the upper vagina. No other abnormalities were found.

SURGERY:

A bilateral salpingo-oophorectomy and total hysterectomy was performed.

GROSS PATHOLOGY:

The shape of the uterus was normal. The cervix was replaced by a 6.0 x 6.0 x 5.0 cm. fungating, necrotic, papillary tumor. On opening the endocervical canal, the tumor tissue was seen to extend up to the uterine cavity. The uterine cavity also contained three polyps, the largest measuring up to 3.0 cm. Both ovaries and tubes were normal.

NAME: N. D.

APRIL 21, 1974 - CASE NO. 19

AGE: 44 SEX: Female RACE: Caucasian

ACCESSION NO. 12141

CONTRIBUTOR: R. F. Hufner, M.D.  
Los Angeles, California

OUTSIDE NO. E-445-62

TISSUE FROM: Uterus

CLINICAL ABSTRACT:

History: This 44 year old gravida 0, para 0 Caucasian female complained of irregular menstrual periods and prolonged heavy flow ever since menarche. She stated that she never had a regular cycle.

Physical Examination: The uterus was enlarged and to the left of the midline.

SURGERY: (January 29, 1962)

A total hysterectomy and bilateral salpingo-oophorectomy was performed.

GROSS PATHOLOGY:

The uterus weighed 131 grams and measured 11.8 x 5.2 x 4.4 cm. Occasional serosal nodules, measuring up to 0.6 cm., were present. The cervix was normal. The endometrium generally measured 0.1 cm. in thickness. There was a bulging, pink-tan 2 cm. mass present in the fundus. The entire myometrium was speckled with innumerable slightly raised, grey-white areas, 0.2 - 0.6 cm. in diameter.

Both ovaries contained lesions which were interpreted microscopically as endometriosis.

FOLLOW-UP:

No information is available.

NAME: L. S.

APRIL 21, 1974 - CASE NO. 20

AGE: 27 SEX: Female RACE: Caucasian

ACCESSION NO. 20056

CONTRIBUTOR: Robert Sifton, M. D.  
LAC-USC Medical Center  
Los Angeles, California

OUTSIDE NO. 73-8829

TISSUE FROM: Uterus

CLINICAL ABSTRACT:

History: This 27 year old Caucasian female presented with a pelvic mass of 5 months' duration. A pregnancy test was negative.

Past history: Two years prior to admission a left mastectomy was performed after a biopsy revealed malignant tumor. One year prior to admission a right mastectomy was performed when a similar tumor developed there.

Laboratory report: A blood count showed a hemoglobin of 9.6 and a white cell count of 10,400 with 32 segmented neutrophils, 1 band, 39 lymphocytes, 2 monocytes, 1 promyelocyte and 25 blast forms.

SURGERY: (May 29, 1973)

At laparotomy a firm large pelvic mass was seen arising from the uterus and involving loops of small bowel, the sigmoid colon, and the side walls of the pelvis. The liver and spleen appeared normal, although they both were slightly enlarged. Numerous tumor implants were seen involving the omentum. A supracervical hysterectomy and bilateral salpingo-oophorectomy was performed.

GROSS PATHOLOGY:

The tumor involved and markedly distorted the uterus and both adnexae (the ovaries were not recognizable as such). The mass was irregular, focally friable, focally necrotic and some areas contained thick gelatinous material.

FOLLOW-UP:

Following surgery the patient received chemotherapy. As of February 1974 she is alive and doing well.

NAME: A. R.

APRIL 21, 1974 - CASE NO. 21

AGE: 32 SEX: Female RACE: Caucasian

ACCESSION NO. 20542

CONTRIBUTOR: Vivian Gildenhorn, M. D.  
Inter-Community Hospital  
Covina, California

OUTSIDE NO. 60-74

TISSUE FROM: Endometrial cavity

CLINICAL ABSTRACT:

This 32 year old gravida IV, para V, Caucasian female presented with almost constant uterine bleeding of 3 months' duration. She had a long history of irregular menstrual bleeding. At the age of 17 she had undergone surgery for the removal of a "grapefruit" sized right ovarian cyst.

SURGERY: (January 7, 1974)

A total hysterectomy was performed.

GROSS PATHOLOGY:

The uterus measured 9 x 5 x 3 cm. and had a normal contour. The ectocervix was covered by wrinkled pink-tan mucosa. The endocervical lining and endometrial mucosa appeared diffusely hemorrhagic and focally roughened. The myometrium measured up to 2 cm. in thickness.

FOLLOW-UP:

Current follow-up is not available.

NAME: D. C.

APRIL 21, 1974 - CASE NO. 22

AGE: 18 SEX: Female RACE: Caucasian

ACCESSION NO. 20525

CONTRIBUTOR: David G. Porter, M. D.  
El Camino Hospital  
Mountain View, California

OUTSIDE NO. S72-2433

TISSUE FROM: Vagina

CLINICAL ABSTRACT:

History: This 18 year old Caucasian female presented with an 8 month history of mild premenstrual spotting and a recent episode of profuse vaginal bleeding. The remainder of the gynecologic history was non-contributory.

Familial history: Patient's mother had been placed on large doses of diethylstilbestrol for the treatment of a threatened miscarriage at 13 weeks gestation.

Physical examination: A papillary mass with superficial necrosis was evident in the upper third of the vagina on the right lateral wall. The remainder of the pelvic examination was normal.

SURGERY: (March 16, 1972)

A total hysterectomy, partial vaginectomy, left salpingo-oophorectomy and lymph node dissection were performed.

GROSS PATHOLOGY:

The vaginal tumor was dome-shaped, measured 1.5 x 1.5 cm., and contained multiple cystic spaces, measuring up to 0.3 cm. which were filled with mucin. The lesion appeared limited to the superficial portion of the vagina. The uterus, left ovary, and left fallopian tube were normal. The thirteen iliac lymph nodes resected did not contain tumor.

FOLLOW-UP:

As of 2 years post surgery, the patient remains well and totally asymptomatic.

NAME: B. Z.

APRIL 21, 1974 - CASE NO. 23

AGE: 18 SEX: Female RACE: Unknown

ACCESSION NO. 20528

CONTRIBUTOR: Paul Miller, M. D.,  
Kaiser Hospital  
Santa Clara, California

OUTSIDE NO. S73-5252

TISSUE FROM: Ovary

CLINICAL ABSTRACT:

History: This 18 year old female presented with abdominal discomfort and enlargement of one year's duration. She also complained of occasional amenorrhea.

Physical examination: A huge pelvic mass was found which displaced the uterus.

SURGERY: (1973)

A right ovarian tumor was discovered at laparotomy. A solitary small peritoneal "implant" was noted in the pelvic cavity.

GROSS PATHOLOGY:

The tumor was solid but demonstrated extensive hemorrhagic necrosis in all areas, except the periphery. The viable peripheral portions were pale gray to slightly yellow and semi-translucent.

FOLLOW-UP:

As of approximately 6 months following surgery, the patient has no evidence of recurrent tumor.

NAME: S. J.

APRIL 21, 1974 - CASE NO. 24

AGE: 20 SEX: Female RACE: Caucasian

ACCESSION NO. 20526

CONTRIBUTOR: David Porter, M. D.  
El Camino Hospital  
Mountain View, California

OUTSIDE NO. S72-1844

TISSUE FROM: Uterine Cervix

CLINICAL ABSTRACT:

This 20 year old gravida II, para I, Caucasian female had a 5-6 month history of post-coital bleeding. Cervical cytology done in her early pregnancy was "atypical" and on pelvic examination there were two discoid lesions over the cervix.

SURGERY: (February 29, 1972)

A cold knife cervical conization was performed at 14 weeks' gestation.

GROSS PATHOLOGY:

A circular mass of cervix was present, the most peripheral portion of which was smooth epithelium, the entire remaining surface of which had a very velvety, somewhat papillary appearance. There were focal lesions at 12, 6, 7, and 8 o'clock positions which were more plaque-like in appearance. This velvety appearance was rather granular and pale-yellow throughout and elevated 0.15 cm. above the background of smooth portion epithelium.

FOLLOW-UP:

Labor was induced at 38 weeks' gestation for toxemia of pregnancy. a 7½ lb. normal female infant was delivered. Both mother and child remained well as of January 28, 1974.

NAME: G. P.

APRIL 21, 1974 - CASE NO. 25

AGE: 47 SEX: Female RACE: Unknown

ACCESSION NO. 20527

CONTRIBUTOR: Richard Kempson, M. D.  
Stanford University Medical Center  
Stanford, California

OUTSIDE NO. S73-14798

TISSUE FROM: Ovary

CLINICAL ABSTRACT:

History: This 47 year old female was first noted to have an abdominal mass during an admission for replacement of aortic, mitral and tricuspid valves. Following her cardiac surgery she was referred to a gynecologist in her home town but did not see him until one year later. At that time the mass had grown considerably larger.

Physical examination: There was a soft, nontender, movable, smooth mass, 8 x 8 cm. present in the left lower quadrant. By pelvic examination the mass seemed to involve the left adnexa and was movable and cystic.

SURGERY: (1973)

At surgery, a smooth cystic mass was seen occupying the left adnexa. There was no evidence of tumor on the outside of the cyst and no evidence of tumor elsewhere in the pelvis or abdomen. A total hysterectomy and bilateral salpingo-oophorectomy was performed.

GROSS PATHOLOGY:

The mass measured 15 x 10 cm. and had a smooth exterior. The interior contained sticky thick fluid and was lined by innumerable yellow pink papillae varying from 0.5 to 2.0 cm. in height. The left fallopian tube was stretched over the mass. No residual left ovarian tissue was identified. The opposite ovary was normal.

FOLLOW-UP:

The patient is well as of three months postsurgery.

NOTE: Slide 25 has two tumors. The papillary tumor belongs to Case 25 and due to an error in preparation there is a piece of Case 17 also on the slide.

A D D E N D A

CALIFORNIA TUMOR TISSUE REGISTRY  
FIFTY-SEVENTH SEMI-ANNUAL SLIDE SEMINAR  
ON  
TUMORS OF THE FEMALE GENITAL TRACT

MODERATOR:

RICHARD L. KEMPSON, M. D.  
ASSOCIATE PROFESSOR OF PATHOLOGY  
&  
CO-DIRECTOR OF SURGICAL PATHOLOGY  
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LOMA LINDA, CALIFORNIA

APRIL 21, 1974  
PASADENA HILTON HOTEL  
PASADENA, CALIFORNIA

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General Discussion of Cases 3,5,13, and 14:

These 4 cases represent different histologic types of adenocarcinoma of the cervix. Adenocarcinoma of the cervix may be subdivided into 2 major groups depending on the cell of origin: gland-cell carcinoma and reserve cell carcinoma (1). Gland-cell carcinomas represent approximately 5% of all carcinomas of the cervix and arise from the columnar cells which cover the endocervical surface and line the gland cleft spaces. There has been an apparent increase in the incidence of gland-cell carcinoma and they may represent as many as 10% of all carcinomas of the cervix. The second major category of adenocarcinoma of the cervix is the tumor arising from the subcolumnar reserve cells. These tumors often remain undifferentiated or show mixed patterns of differentiation.

Abell has classified the gland cell carcinomas as follows (1):

1. Cervical cell type -- this type of tumor has a true adenomatous appearance and consists of well-defined glandular spaces formed by columnar or cuboidal cells. Many of these tumors are well differentiated and have complex branching patterns reminiscent of that of the normal endocervix. Typically, the nuclei are enlarged, hyperchromatic, and variable in size, but often basilar in location. Mitoses are invariably present. The tumor glands are irregular and often have jutting sharp angles sometimes in a lobster claw configuration. Because adenocarcinoma of the endocervix can closely mimic the normal endocervix, careful examination of the shape of glands and determining the presence of mitoses and abnormal nuclei is always indicated when examining the endocervix. The cervical cell carcinomas are divided into well, moderately, and poorly differentiated.
2. Medullary carcinoma - is the next most common type of cervical carcinoma and is composed of compact masses of neoplastic cells with little stroma. The gland formation is abortive and the cells are palisaded at the periphery of the cell nests. Clear cells can be present. This type of adenocarcinoma is often confused with squamous carcinoma.

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3. Papillary carcinoma - arises from the surface epithelium and the cells are arranged over papillary stalks resulting in a histologic pattern reminiscent of papillary serous carcinoma of the ovary. Mitoses are easily found and invasion is often superficial. The prognosis is better than for the other types of adenocarcinoma.
4. Mucinous carcinoma - resembles mucinous carcinoma of the rectum and colon. The histologic pattern varies from tumor gland spaces filled with mucin and lined by cells having intracytoplasmic mucin to lakes of mucin containing floating neoplastic cells. Signet ring cells may be present. Unless adenocarcinoma in situ is found, mucinous carcinoma may be difficult to separate from metastatic adenocarcinoma.
5. Endometrioid carcinoma has a histologic pattern identical with, or very similar to, primary corpus adenocarcinomas. They are very difficult to separate from primary adenocarcinoma of the endometrium unless the entire uterus is available for examination. Usually, these tumors are well differentiated and may have areas of squamous metaplasia.
6. Scirrhous carcinoma - (poorly differentiated or anaplastic carcinoma of the cervix) encompasses most of the anaplastic and poorly differentiated adenocarcinomas. Characteristically, the tumor cells grow as individual cells or in small cords and strands and infiltrating fibrous stroma. There is often intense stromal proliferation in response to the tumor cells.
7. Clear cell adenocarcinoma is the same neoplasm as found in the ovary, vagina, and endometrium. Formerly, these were thought to be of mesonephric origin, but it is now apparent that the majority of them arise from Mullerian sources. There is a correlation between Stilbestrol therapy in the mother and an increased incidence in clear cell adenocarcinoma of the vagina and cervix in their daughters which will be discussed in

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Case 22. In addition, clear cell adenocarcinoma may occur in older women and has a better prognosis than many of the other forms of carcinoma of the cervix. Histologically, clear cell adenocarcinoma has a characteristic pattern with tubules lined by clear to eosinophilic cells with hobnail or protruding nuclei. Clear cell areas and papillary structures may also be present, as well as a solid type of carcinomatous growth.

Reserve cell carcinomas are classified by Abell as follows:

1. Undifferentiated reserve cell carcinomas are composed of, small basaloid undifferentiated cells with scant cytoplasm. Mitoses are frequent. These tumors are often diagnosed as poorly differentiated squamous carcinoma or undifferentiated carcinoma.
2. Adenosquamous carcinomas shows both squamous and glandular differentiation and both the squamous and glandular components are malignant. These tumors are often called mixed carcinomas and the two types of carcinoma may be mixed together intimately or may be infiltrating in separate areas. Mixed carcinomas spread rapidly to the regional lymph nodes.
3. Mucoepidermoid carcinomas are squamous carcinomas in which varying numbers of cells contain intracytoplasmic mucin. There are no glandular formations. They appear to be more common in pregnancy.
4. Adenoid cystic carcinomas have the histologic appearances of adenoid cystic carcinoma elsewhere except that they frequently contain areas of squamous metaplasia and squamous carcinoma, as well as undifferentiated carcinoma. They are often large and bulky and occur in an older age group with an average age in the sixties.

Adenocarcinoma of the cervix (1,2,3,4,5) occurs at any average age of 52, approximately five years higher than the average age for squamous carcinoma. However, the patients are generally younger than those with adenocarcinoma of the endometrium. About three fourths of the patients are over the age of fifty. Sociosexual factors such as early age of intercourse, multiple sexual partners, and low socio-economic status are not of importance in adenocarcinoma of the cervix as they are in squamous carcinoma. The usual patient with adenocarcinoma of the cervix, in fact, is more closely akin to the patient with endometrial adenocarcinoma. Patients with adenocarcinoma of the cervix most often present with abnormal vaginal bleeding and one half of them will have an exophytic or polypoid mass. In 15%, no gross

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lesion can be discerned; the remainder present as ulcero-infiltrating lesions.

In general, gland cell carcinomas of the cervix are more aggressive than squamous cell carcinoma of the cervix, or adenocarcinoma of the endometrium, and have a metastatic spread similar to that of squamous carcinoma. Extension beyond the cervix occurs early and lymph node metastases are frequent, particularly in Stages II and III. In general, the five year survival stage for stage is 10-15% lower than for squamous cell carcinoma. The prognosis depends upon the stage of the tumor, the histologic type of adenocarcinoma, and, to a lesser extent, the grade of the carcinoma. As with squamous carcinoma, the lower the stage the better the survival. The histologic type of tumor seems to be important in determining the survival (6). Patients with papillary carcinoma, and the older female with clear cell carcinoma, definitely have a better prognosis than patients with more poorly differentiated tumors (7). The poorest prognosis is with the medullary, endometrioid, and scirrhous types. The grade of the tumor within each of the histologic types is of some importance, however it must be remembered that very well differentiated adenocarcinomas of the cervix can be aggressive and some of the more poorly differentiated varieties can be treated successfully. In Abell's series, the cervical cell carcinomas represented 35% of the tumors and had a 30% five year survival; medullary carcinomas represented 21% of the tumors and had a 14% five year survival; and papillary carcinomas represented 15% of the tumors and had a 57% five year survival. Squamous cell carcinoma can also be subclassified as to cell type.

The best method of treatment of adenocarcinoma of the cervix has not been determined and both radiation and radical surgery are utilized. Overall, the survival is approximately 55% at five years and the survival will be altered by the prognostic factors discussed above. When adenocarcinoma is found in the cervix, the possibility of metastasis must be considered. One-third of the metastatic adenocarcinomas to the cervix will be from the endometrium. The next most frequent primary site will be ovary, followed in order by colon, rectum, breast, and the genitourinary tract.

#### REFERENCES:

1. Abell, M. R.: Invasive carcinomas of the uterine cervix. In: Norris, H. J., Hertig, A. T. & Abell, M. R. Eds: The Uterus, IAP monograph #14, Baltimore, 1973. The Williams and Wilkins Co. p. 437.
2. Rombaut, R. P. et. al: Adenocarcinoma of the cervix. A clinico-pathologic study of 47 cases. Cancer 19:391, 1966.
3. Abell, M. R. and Goshing, J. R. G: Gland cell (adenocarcinoma) carcinoma of the uterine cervix. Am. J. Obstet. & Gynecol. 83:729, 1962.

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4. Kagan, A. R. et. al: Adenocarcinoma of the uterine cervix. Am. J. Obstet. & Gynecol. 117:464, 1973.
5. Tasker, J. T. & Collins, J. A: Adenocarcinoma of the uterine cervix. Am. J. Obstet. & Gynecol. 118:344, 1974.
6. Swan, D. S. and Roddick, J. W: A clinical pathologic correlation of cell type classification for cervical cancer. Am. J. Obstet. & Gynecol. 116:666, 1973.
7. Hameed, K: Clear cell carcinoma of the uterine cervix. Am. J. Obstet. & Gynecol. 101:954, 1968.

APRIL 21, 1974 - CASE NO. 1

ACCESSION NO. 13759

MODERATOR'S DIAGNOSIS: Adenoid cystic carcinoma of the Bartholin's glandCLINICAL ABSTRACT:

This 47 year old female noted a hard nodule in the region of the left Bartholin's gland. She had previously had an abscess involving the right Bartholin's gland at an earlier unknown date. Examination revealed a stony hard 2 cm. nodule in the region of the left Bartholin's gland. When excised the nodule was circumscribed, tan, very firm, and measured 1.3 cm. A radical vulvectomy and bilateral node dissection was done. No tumor was found in any of the lymph nodes.

MICROSCOPIC DESCRIPTION:

The sections show an infiltrating tumor in which the tumor cells are arranged in nests and cords with a microcystic pattern. The tumor cells are small, with hyperchromatic nuclei, and scant eosinophilic cytoplasm and are arranged in a pseudoacinar formation around spaces containing eosinophilic hyaline-like material, fibrillar, eosinophilic material, or rarely basophilic mucoid material. The hyaline is noted to be in continuity with similar material outside the cell nests. The tumor cells are surrounding cylinders of this material giving rise to the microcystic pattern noted at low power. Tumor cells are noted around nerves and remnants of the Bartholin's gland. A PAS stain with a diastase digestion shows the hyaline material to stain intensely and emphasizes its continuity with similar material in the stroma of the tumor.

DISCUSSION:

Recent ultrastructural studies have shown that the hyaline material in the cystic spaces of adenoid cystic carcinoma is basement membrane matrix and not mucin (1). This basement membrane matrix is arranged in parallel arrays both in the pseudoacinar spaces and around the tumor nests. Tiny true acini can be found and are lined by tumor cell containing microvilli on their surface. The more empty appearing pseudoacini contain microfilaments of basement membrane material with stellate granules. Thus, electron microscopy confirms that the pseudoacini in adenoid cystic carcinoma are not glandular lamina but rather are in continuity with the extra cellular space and contain basement membrane matrix arranged in a laminar fashion.

The differential diagnosis in this case would include basal cell carcinoma which may have an adenoid cystic pattern simulating adenoid cystic carcinoma and also may involve the vulva (2). However, the tumor in this case

shows none of the features of basal cell carcinoma such as peripheral nuclear palisading, atypical nuclei, and pleomorphism. In addition, basal cell carcinoma does not form pseudoacini containing basement membrane material. Secondly, one would want to consider adenocarcinoma, since poorly differentiated adenocarcinoma may have a glandular pattern simulating adenoid cystic carcinoma. This would include adenocarcinoma of the Bartholin's gland, sweat gland carcinoma, adenocarcinoma of the urethra and metastatic adenocarcinoma. None of these tumors have the uniform tumor cells as seen in this case and none show the proliferation of tumor cells around hyaline cylinders.

Metastatic carcinoma is an important entity in the vulva since it represents the third most frequent type of malignancy of that organ (3). The most common primary metastatic tumor to the vulva is from the cervix, while adenocarcinoma of the endometrium and ovarian carcinoma are the next most frequent. The last consideration in the differential diagnosis would be hidradenoma papilliferum (4). This is a benign tumor, almost invariably less than 2 cm., and circumscribed. It has a papillary glandular pattern and contains both columnar and apocrine cells which are not seen in the tumor in this case. It is a benign tumor of the apocrine glands limited to the genital area of the adult female.

Carcinoma of the vulva represents 3-5% of all genital malignancies and carcinoma of the Bartholin's gland represents about 3-4% of all carcinomas involving the vulva. Carcinomas involving the Bartholin's glands are fairly evenly divided between squamous and adenocarcinoma with squamous carcinoma predominating in those tumors arising near the orifice of the gland and adenocarcinoma more common in those tumors from the deep acinar area (5). Carcinomas of the Bartholin's gland should occur in the typical vulvar site, with the overlying skin intact, and contain residual Bartholin's gland tissue. All of these criteria may be impossible to establish in each case. The treatment of Bartholin's gland carcinoma is the same as other malignancies of the vulva, i.e., radical vulvectomy and bilateral nodal dissection. Adenoid cystic carcinoma occurs in a somewhat younger age group than other carcinomas of the vulva and arises exclusively from the Bartholin's and minor vestibular glands (6,7). It presents as a lump which is often painful. It may be confused clinically with an abscess or cyst. The histology is identical to that of adenoid cystic carcinoma occurring in other sites such as salivary gland, tracheal bronchial tree and the breast. The course is one of local recrudescence and progressive infiltration, often for long periods of time, and eventual metastases. The treatment is complete vulvectomy. Whether the nodes should be removed is uncertain but most authorities advocate prophylactic dissection. In Abell's series 25% of patients were alive tumor free at 5 years, 25% were alive with tumor and 50% were dead with tumor (6).

REFERENCES :

1. Tandler, B: Ultrastructure of adenoid cystic carcinoma of salivary gland origin. *Lab. Invest.* 24:504, 1971.
2. Palladino, V. S., Duffy, J. L. and Burls, G. J: Basal cell carcinoma of the vulva. *Cancer* 24:460, 1969.
3. Dehner, L: Metastatic and secondary tumors of the vulva. *Obstet. & Gynecol.* 42:47, 1973.
4. Woodworth, H. et. al: Papillary hidradenoma of the vulva: A study of 69 cases. *Am. J. Obstet. Gynecol.* 110:501, 1971.
5. Barclay, D. L., Collins, C. G., and Macey, H. B.: Cancer of the Bartholin's gland. *Obstet. and Gynecol.* 24:329, 1964.
6. Abell, M. R.: Adenocystic basal cell carcinoma of vestibular glands of vulva. *Am. J. Obstet. Gynecol.* 86:470, 1963.
7. Tchang, F. et. al: Adenocarcinoma of Bartholin's gland associated with Paget's disease of the vulvar area. *Cancer* 31:221, 1973.

APRIL 21, 1974 - CASE NO. 2

ACCESSION NO. 19905

MODERATOR'S DIAGNOSIS: Leiomyosarcoma of the uterus.

CLINICAL ABSTRACT:

This 64 year-old female had a three week history of vaginal bleeding. A D&C revealed chunky firm tissue fragments and an enlarged uterus. The hysterectomy specimen contained several nodular masses with hemorrhage, necrosis, and mucoid softening. The largest mass measured 8 cm. in diameter.

MICROSCOPIC DESCRIPTION:

This tumor is composed of cells with vesicular, irregular nuclei and eosinophilic to clear cytoplasm. In some areas the tumor cells appear cuboidal, while in others they are spindle. Giant cells are present as are large cells with bizarre pleomorphic nuclei. Areas of necrosis are frequent, and surrounding areas of necrosis, the tumor cells are closely packed and spindle. Some of the tumor cells with clear cytoplasm have an epithelioid arrangement; however, the overall impression is that of a mesenchymal tumor. Hyalinization is prominent. Mitoses are frequent and some are abnormal. Mitotic counts revealed some areas of the tumor to contain over 20 mitoses per 10 high power fields. A trichrome stain shows irregular collagen present in the tumor but most of the tumor cells have red cytoplasm. A PTAH stain failed to reveal myofibrils.

DISCUSSION:

This neoplasm is somewhat difficult to definitely classify as originating from smooth muscle; however, the elongated and relatively clear tumor cells as well as the arrangement of the tumor cells indicates to me that this is a leiomyosarcoma. The pattern is not that of endometrial stromal sarcoma and there is no evidence of cross striations or bone formation. When a sarcoma is found in the uterus, malignant mixed Mullerian tumor should be considered, but there is no evidence of a carcinoma in any of the sections. Undifferentiated and clear cell carcinomas also have to be considered; however, the pattern, to me, is definitely that of a mesenchymal tumor which does not have the epithelial arrangement of carcinoma. A reticulum stain is of value in differentiating between carcinoma and sarcoma since sarcomas generally have reticulum fibers around individual or small groups of tumor cells. In this case reticulin is related to individual cells.

Sarcomas of the uterus are relatively rare but pose problems in diagnosis and classification. We use a modification of the classification suggested by Ober which is reproduced in Table 1 (1). Pure sarcomas are those

which contain only one type of sarcoma, and the sarcoma is considered homologous if the tumor is differentiating towards structures normally found in the uterus, such as smooth muscle or endometrial stroma. The sarcoma is considered heterologous if it is differentiating into tissues not normally found in the uterus such as bone or skeletal muscle. Mixed sarcomas contain more than one type of sarcoma and may be either homologous or heterologous. The third major group of sarcomas are the malignant mixed Mullerian tumors which contain sarcoma and carcinoma. The sarcoma may be any of several types and it is common to have several sarcomas mixed together in the same tumor. The carcinoma may be either adeno, squamous, undifferentiated or combinations of these three. The malignant mixed Mullerian tumors are subclassified as to whether the sarcomatous element is homologous or heterologous. In much of the recent literature the homologous tumors are called carcinosarcomas and the heterologous tumors are designated as mixed mesodermal tumors. A simpler classification of the uterine sarcomas which includes only the commonly encountered types is presented in Table 2.

The major problem in diagnosing smooth muscle tumors of the uterus is separating leiomyoma from leiomyosarcoma (1,2,3,4). Many different criteria have been advanced and there is still controversy about the relative value of each of these (1,4). In our experience, the number of mitoses per 10 high power fields is the single most important criteria for separating benign from malignant uterine smooth muscle tumor (1). Obviously, any tumor which has infiltrated contiguous organs, or which has invaded blood vessels and is not intravenous leiomyomatosis, must be considered malignant. We also think that any smooth muscle tumor of the uterus which contains over 10 mitoses in 10 high power fields is malignant regardless of other histologic features. Any smooth muscle tumor which contains less than one mitoses in 10 high power fields is benign regardless of the degree of pleomorphism or the presence of giant cells. Tumors which contain between 1 and 10 mitoses per 10 high power fields are more difficult and are considered to be neoplasms of uncertain malignant potential. It has been our experience that tumors with 5-10 mitoses and pleomorphism can be aggressive and we designate them as leiomyosarcomas. Tumors with 5-10 mitoses and no pleomorphism or atypia we designate as borderline malignant as we do tumors which contain 1-5 mitoses in 10 high power fields and are pleomorphic. We must accept the fact that there are borderline smooth muscle tumors for which we cannot be certain of future behavior. The number of such smooth muscle tumors is small and most smooth muscle tumors can be accurately diagnosed using mitotic counts as outlined above. It must be emphasized that at least 3 or 10 sections of every questionable smooth muscle tumor should be taken and if the tumor is very large one section per cm. of tumor diameter is our rule. One should count at least four 10 power fields in each section from a borderline lesion. The presence of giant cells and pleomorphic cells is not sufficient criteria for malignancy. Fechner has shown atypism in smooth muscle tumors in patients receiving contraceptive medication (5).

We consider leiomyomas with borderline mitotic counts as described above to be of uncertain malignant potential and use the designation atypical leiomyoma of borderline malignancy. We use the term atypical for leiomyomas which contain bizarre cells, atypical cells or giant cells but do not demonstrate sufficient mitotic activity to be considered malignant or of borderline malignancy. We use the term cellular leiomyoma for those tumors without pleomorphism or increased mitotic activity which contain large numbers of cells closely packed together (6). The term bizarre leiomyoma is reserved for those smooth muscle tumors with unusual histologic appearances such as leiomyoblastoma, clear cell leiomyoma and epithelioid cell leiomyoma. These are discussed in Case 7. Finally there is a lesion known as benign metastasizing leiomyoma (7). This is a histologically benign smooth muscle tumor which metastasizes. There is no known way to separate these from leiomyomas and they cannot be accurately diagnosed by present criteria. Fortunately they are extremely rare.

Patients with leiomyosarcoma may be in their twenties to old age. The most common symptom is abnormal vaginal bleeding. The tumors usually are soft gray-white-tan with bulging surfaces but may be hemorrhagic and necrotic. When examining hysterectomy specimens, all grossly unusual myomas should be sectioned. Leiomyosarcoma in the uterus is often solitary but may be associated with other myomas elsewhere in the uterus. In our experience leiomyosarcomas do not arise within benign leiomyomas. Microscopically leiomyosarcomas demonstrate a wide range of patterns, the most common of which is spindled cells closely packed together with large numbers of mitoses. Bizarre and anaplastic cells may also be present. Giant cells may be found in either benign or malignant smooth muscle tumors. Cytoplasmic nuclear inclusions are commonly found in leiomyosarcomas and may be helpful diagnostically. The prognosis of leiomyosarcoma depends upon the extent of the tumor, the mitotic activity, the extent of infiltration of contiguous organs and the length of time the patient has had the tumor. Age is also a significant factor since premenopausal women have a better prognosis than post menopausal. The treatment is surgical and the overall survival is approximately 20% at 5 years.

In summary, most smooth muscle tumors of the uterus can be accurately diagnosed by carefully performed mitotic counts. There are a few tumors with equivocal mitotic activity and uncertain malignant potential but these represent a very small percentage of the smooth muscle tumors occurring in the uterus. It must be emphasized that the use of mitotic counts for diagnosis as outlined above applies only to smooth muscle tumors of the uterus, not smooth muscle tumors originating in other organs.

REFERENCES :

1. Kempson, R. L.: Sarcomas and related lesions. In: The Uterus. IAP monograph #14 Ed.: Norris & Hertig p. 298. Williams & Wilkins Co., Baltimore, 1973.
2. Christopherson, W. M., et al: Leiomyosarcoma of the uterus. Cancer 29: 1512, 1972.
3. Taylor, H. D. and Norris, H. S.: Diagnosis and prognosis of leiomyosarcoma. Arch. Path. 82:40, 1966.
4. Silverberg, S. G.: Leiomyosarcoma of the uterus. Obstet. & Gynecol. 38: 613, 1971.
5. Fechner, R. E.: Atypical leiomyomas and synthetic progestogen therapy. Am. J. Clin. Pathol. 49:697, 1968.
6. Ferenczy, A., et al: A comparative ultrastructural study of leiomyosarcoma, cellular leiomyoma, and leiomyoma of the uterus. Cancer 28: 1004, 1971.
7. Spiro, R. H. and McPeak, C. J.: On the so-called metastasizing leiomyoma. Cancer 19:544, 1966.

Table 1

## Classification of Uterine Sarcomas

- 
- I. Pure sarcomas
    - A. Pure homologous
      - 1. Leiomyosarcoma
      - 2. Stromal sarcoma
      - 3. Endolymphatic stromal myosis
      - 4. Angiosarcoma
      - 5. Fibrosarcoma
    - B. Pure heterologous
      - 1. Rhabdomyosarcoma (including sarcoma botryoides)
      - 2. Chondrosarcoma
      - 3. Osteosarcoma
      - 4. Liposarcoma
  
  - II. Mixed sarcomas
    - A. Mixed homologous
    - B. Mixed heterologous
      - Mixed heterologous sarcomas with or without homologous elements
  
  - III. Malignant mixed Mullerian tumors (mixed mesodermal tumors)
    - A. Malignant mixed Mullerian tumor, homologous type
      - Carcinoma plus leiomyosarcoma, stromal sarcoma or fibrosarcoma, or mixtures of these sarcomas
    - B. Malignant mixed Mullerian tumor, heterologous type
      - Carcinoma plus heterologous sarcoma with or without homologous sarcoma
  
  - IV. Mullerian adenosarcoma (See Case 18)
  
  - V. Sarcoma, unclassified
  
  - VI. Malignant lymphoma

Table 2

## Simplified Classification of Uterine Sarcomas

- 
- I. Leiomyosarcoma
  - II. Malignant mixed Mullerian tumor with or without heterologous elements
  - III. Endometrial stromal sarcoma
    - A. Low grade stromal sarcoma (endolymphatic stromal myosis)
    - B. Stromal sarcoma
  - IV. Malignant lymphoma
  - V. Rare specific types
  - VI. Sarcoma unclassified

Table 3

## Histologic Features of Benign and Malignant Smooth Muscle Tumors of the Uterus

- 
- I. Histologic features indicative of leiomyosarcoma
    - A. Greater than 10 mitoses in 10 HPF with or without cellular pleomorphism
    - B. Mitotic activity of 5 to 10 mitoses in 10 HPF with cellular pleomorphism
    - C. Extrauterine infiltration into contiguous structures
  - II. Histologic features indicative of leiomyoma
    - A. Less than 1 mitosis per 10 HPF regardless of the presence or absence of cellular pleomorphism.
    - B. Less than 5 mitoses in 10 HPF if tumor cells are not pleomorphic
  - III. Histologic features in smooth muscle tumors of uncertain malignant potential
    - A. 5 to 9 mitoses in 10 HPF without cellular pleomorphism
    - B. 1 to 4 mitoses in 10 HPF with significant cellular pleomorphism

APRIL 21, 1974 - CASE NO. 3

ACCESSION NO. 9559

MODERATOR'S DIAGNOSIS: Adenoid cystic carcinoma of the cervix.

CLINICAL ABSTRACT:

This 60 year old patient presented with 2 episodes of vaginal bleeding. A hysterectomy was performed and a 2 cm. tumor covered by intact mucosa was present in the posterior lip of the cervix. The mass was light yellow and hard. Thirteen months after surgery a local recurrence occurred in the vaginal cuff and was excised. The patient was lost to follow-up.

MICROSCOPIC DESCRIPTION:

The cervix is infiltrated by a carcinoma with a histologic pattern, identical to that seen in the vulvar lesion in case 1. Cords and nests of uniform cells are forming pseudoacinar structures by encompassing cylinders of hyaline basement membrane matrix. In addition to the adenoid cystic areas, there are areas of squamous differentiation with nests of bland looking squamous cells as well as nests of undifferentiated basaloid carcinoma and histologically malignant squamous cells. Large portions of the tumor are composed of hyaline matrix containing cords of solid cells.

DISCUSSION:

The differential diagnosis of adenoid cystic carcinoma of the cervix should include microglandular hyperplasia which occurs in patients taking contraceptive medications and in pregnant patients (1). Microglandular hyperplasia is characterized by crowded small glandular spaces containing mucus with polys and lined by flattened bland appearing cells. The lesion may protrude above the cervix. The pseudoacinar and cylindromatous pattern of adenoid cystic carcinoma is not present. Microglandular hyperplasia is invariably found in the superficial portion of the cervix. Mucification of the cervical glands, in which there is inspissation of secretion such that the endocervical glands appear to contain colloid, can also superficially resemble adenoid cystic carcinoma but the cells are flattened endocervical type cells, not the basaloid cells seen in adenoid cystic carcinoma (1). Mesonephric remnants are found in the lateral portions of the cervical stroma and are composed of tubule-like structures lined by cuboidal epithelium which often contain central eosinophilic material. The cells do not resemble the basaloid cells of adenoid cystic carcinoma and cylinders of hyaline material are not found in the lumens.

Adenoid cystic carcinoma of the cervix (2,3,4) occurs in older women than most other types of adenocarcinoma of the cervix, the average patient being in her 60's. There are no characteristic symptoms and most patients present

with vaginal bleeding. It is an uncommon tumor with only about 36 cases previously reported. On physical examination there is always extensive erosion and ulceration, and the tumors are often large and bulky. There has usually been extensive growth within the cervix before symptoms and the tumor is often visible. Microscopically, these tumors are frequently associated with either overlying squamous carcinoma-in-situ or dysplasia of the cervical epithelium or with invasive squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma. About 1/3 of cervical adenoid cystic carcinomas will contain areas of squamous cell carcinoma. Adenoid cystic carcinoma infiltrates the stroma of the cervix and other nearby tissues extensively and lymphatic permeation is common. The tumor is thought to arise in the reserve cells beneath the columnar mucinous epithelium. Since these cells can differentiate toward both squamous and columnar types of epithelium either type of differentiation may be seen in reserve cell carcinomas. Unlike adenoid cystic carcinoma in other locations, the cervical tumor is probably not a distinct pathologic entity but part of the spectrum of reserve cell carcinoma. Adenoid carcinoma of the endometrium has also been reported, but is very rare.

In summary, this is a case of adenoid cystic carcinoma of the cervix. There have been approximately 36 reported cases and these tumors are thought to arise from the reserve cells of the cervix. They are almost always mixed with other types of carcinomas and are probably not a distinct pathologic entity.

#### REFERENCES:

1. Kyriokos, M., Kempson, R.L. and Konikov, N.F.: A clinical and pathologic study of endocervical lesions associated with oral contraceptives. Cancer 22:99, 1968.
2. Miles, P.A. and Norris, H.J.: Adenoid cystic carcinoma of the cervix. Obstet. & Gynec. 38:103, 1971.
3. Gallager, H.E. et al.: Adenoid cystic carcinoma of the uterine cervix. Cancer 27:1398, 1971.
4. Gordon, H.W. et al: Adenoid cystic carcinoma of the uterine cervix. Am. J. Clin. Path. 58:51, 1972.

APRIL 21, 1974 - CASE NO. 4

ACCESSION NO. 20440

MODERATOR'S DIAGNOSIS: Endodermal sinus tumor (yolk sac carcinoma) of the ovary)

CLINICAL ABSTRACT:

This 12 year old prepubertal Filipino girl noted that her abdomen was getting larger and harder. Examination revealed a large fixed mass extending from the pelvis to the umbilicus. At surgery, the right ovary was replaced by a tumor measuring 18 x 16 x 10 cm. and weighing 1500 gms. The tumor had a mottled red-gray-yellow surface with bulging cysts containing clear yellow fluid. The solid portion of the tumor was variegated with multiple yellow lobules interspersed with gray to red-brown necrotic zones. Postoperatively, the patient received radiation. However, within a few months she had extensive metastatic tumor and died approximately one year following her original surgery. At autopsy, there was ascites and tumor covering the peritoneum. The tumor grew in grape-like clusters from the serosa. There were no distant metastases.

MICROSCOPIC EXAMINATION:

This tumor is composed of small cells with basophilic nuclei which forms a loose vacuolated network of spaces of varying sizes and shapes. More solid areas are present and contain cystic areas which are lined by cuboidal tumor cells. The overall appearance is that of a labyrinth of interconnecting sinuses. At one edge of the tumor there are honeycombed areas lined by flattened mesothelial-like cells interspersed within a myxoid stroma. Throughout the tumor there are eosinophilic globules which are PAS positive after diastase digestion. These globules are both intra and extracellular and are of varying sizes. In the section available in the set, yolk sac structures are not found; however, in other sections characteristic palisading of tumor cells about mesenchymal tissue containing a central capillary are present. Mitoses are very numerous.

DISCUSSION:

The differential diagnosis of endodermal sinus tumor must always include clear cell adenocarcinoma. Schiller in 1939 described both clear cell carcinoma and the endodermal sinus tumor under the category of mesonephroma, and these two tumors have been frequently confused with one another for the past thirty-five years. Clear cell adenocarcinoma, which occurs in the ovary as well as other sites, can be differentiated from endodermal sinus tumor because it has a tubular pattern and the tumor cell nuclei, which are hyperchromatic, often appear to be extruding from the tumor cells. The network pattern noted in endodermal sinus tumor is not present in the clear cell adenocarcinoma. Both

tumors may have clear cells, however, and structures resembling glomeruli can be found in both tumors. The PAS positive eosinophilic globules found in endodermal sinus tumor are not present in clear cell carcinoma. Most importantly, the yolk sac pattern of palisaded endodermal cells about vessels is not seen in clear cell carcinoma.

Endodermal sinus tumor must also be separated from the embryonal carcinoma of the adult testicular type which has only rarely even been encountered in the ovary. Embryonal carcinoma of the adult testicular type is composed of pleomorphic cells arranged in sheets or a syncytium with a gland-like pattern rather than the network pattern noted in endodermal sinus tumors. The tumor cells in the endodermal sinus tumor are small cuboidal, columnar, unlike the large anaplastic cells characteristically found in embryonal carcinoma.

Teilum first recognized the germinal origin of the endodermal sinus tumor and its reproduction of extra-embryonic yolk sac structures (1,2). Figure 1 from Pierce and Teilum shows current concepts of the differentiation of germ cell neoplasms for both the ovary and the testicle (1,3). The primitive germ cells may differentiate as germ cells giving rise to seminomas and dysgerminomas. They may remain primitive and undifferentiated, giving rise to the adult testicular type of embryonal carcinoma. Embryonal carcinoma cells may differentiate to either, embryonic structures, giving rise to a teratoma, or, extra-embryonic structures, giving rise to tumors of the placenta and yolk sac, namely choriocarcinoma and endodermal sinus tumor. This scheme is supported by experimental work of Pierce (3) who has shown that experimental teratocarcinomas will differentiate into yolk sac (extra-embryonic) type of structures when grown either in vitro or ascitic fluid. Endodermal sinus tumor may be associated with, or mixed with, teratoma indicating its close relationship to embryonic structures. Thus, experimental models support the germ cell origin of this group of tumors and the morphologic evidence that they may differentiate to extra-embryonic structures.

Endodermal sinus tumors also occur in other sites than the ovary. They have been reported to arise in the retroperitoneum, the sacrococcygeal area, the anterior mediastinum, the pineal, the vagina, and the testicle. They occur both in the infant testicle and the adult testicle and have a different prognosis depending on the age of the patient. In the infant testicle, endodermal sinus tumors have also been designated as orchiblastoma or adenocarcinoma of the infant testicle and have a relatively good prognosis of approximately 65% at five years. In the adult testicle, the tumor is very rare and is highly metastatic with a poor prognosis. Drs. Huntington and Bullock have pointed out the similarities of the endodermal sinus tumor in the testicle and the ovary and have concluded that both tumors are of similar origin (4). Endodermal sinus tumor is the most common expression of embryonal

carcinoma in the ovary whereas it is unusual and rare in the adult testicle. The adult embryonal carcinoma on the other hand is extremely rare in the ovary and common in the adult testicle. In the infant testicle, endodermal sinus tumor is the most common expression of the embryonal carcinoma.

Endodermal sinus tumor in the ovary occurs in a sharply limited range from two to forty years (5,6). The average age is twenty and the symptoms are the result of an expanding mass, namely pain and a protuberant abdomen. Occasionally, the tumors will rupture and result in acute abdominal pain. They are usually unilateral with only about 5% bilateral incidence. Grossly, they are usually large tumors measuring from 5 to 30 cms, thinly capsulated, nodular, and multicystic. On the cut surface, there is extensive hemorrhage and necrosis alternating with yellowish areas. The fluid in the cyst is yellow-brown to clear. Some patients have elevated alpha-fetoprotein levels (7).

Histologically, one or more of the following patterns will be found (1):

1. A loose vacuolated network with cystic spaces lined by flattened cells. PAS diastase resistant globules are present both intra and extracellularly. This pattern is present in all endodermal sinus tumors and is usually predominant.
2. Endodermal sinus structures consisting of a vessel surrounded by mesenchyme which, in turn, is surrounded by palisaded endodermal cells. This entire structure is usually within a cystic space which is surrounded by endodermal cells. This structure is similar to the yolk sac of the rat embryo and gives the tumor its name.
3. On some occasions cystic structures festooning in a complex fashion and lined by cuboidal cells can be found. These are endodermal sinuses and some of the cells may show mucinous differentiation.
4. Compact aggregates of undifferentiated embryonal cells.

In all tumors mitoses are frequent and one may find giant cells. As noted above, the endodermal sinus tumor may be associated with embryonal carcinoma, teratoma, dysgerminoma, and teratocarcinoma.

The therapy for endodermal sinus tumor is usually surgery followed by radiotherapy. The prognosis is practically hopeless with only a few known survivors. The value of chemotherapy has not been fully explored.

Recently the World Health Organization has adopted a classification of ovarian tumors which should become the standard for ovarian tumor nomenclature (8). The germ cell tumors represent one of the the major subtypes of ovarian tumors and our working classification of the germ cell tumors based on the WHO classification is reproduced below. Of interest and importance is that the teratoma group has been divided into mature and immature types. The mature tumors consist exclusively of adult structures, while the immature teratomas contain embryonal tissue, almost always with mitoses. Mature cystic teratomas are benign except for the rare instances of carcinomatous and sarcomatous transformation. The mature solid teratomas of the ovary are also almost invariably benign unlike the solid mature teratomas of the testis which are frequently malignant (9). Immature teratomas, whether solid or cystic, must be considered malignant and care must be taken to search all teratomas carefully for areas of immature tissues which almost always contain mitoses as well as primitive embryonal structures. The presence of implants of mature glia on the peritoneum has not been associated with a malignant course (10).

Classification of Germ Cell Tumors of the Ovary  
(World Health Organization) (8)

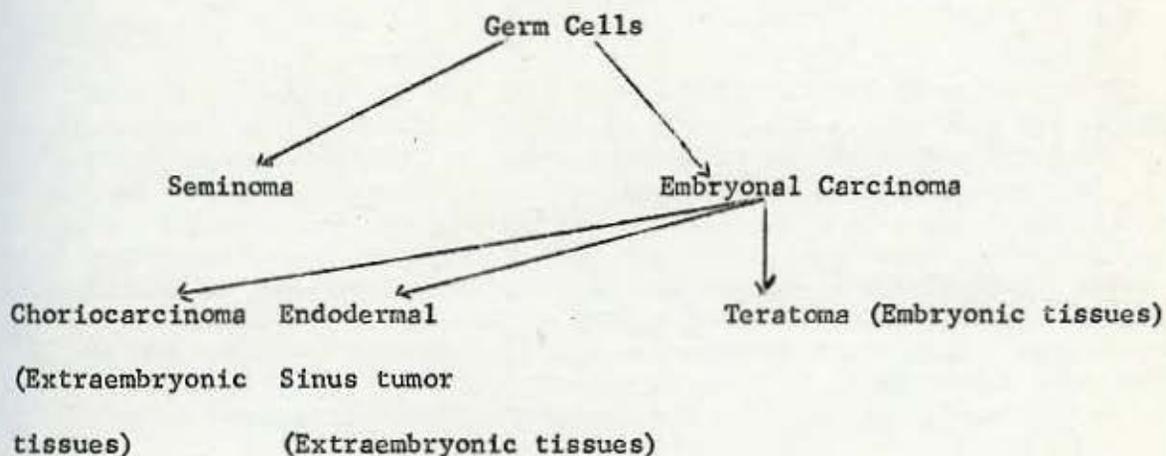
- A. Dysgerminoma
- B. Endodermal Sinus Tumor (yolk sac carcinoma)
- C. Embryonal Carcinoma
- D. Choriocarcinoma
- E. Teratomas
  - 1. Immature
  - 2. Mature
    - a). Solid
    - b). Cystic (with and without malignant transformation)
  - 3. Highly Specialized
    - a). Struma ovarii
    - b). Carcinoid
    - c). Stromal carcinoid
    - d). Others
- F. Mixed Forms.

REFERENCES:

1. Teilmum, G.: Special Tumors of Ovary and Testis, Phila. 1971. J.B. Lippincott Co.
2. Teilmum, G.: Classification of endodermal sinus tumors and so-called "embryonal" carcinoma of the ovary. *Acta Pathol. Microbiol. Scand.* 64: 407, 1965.

3. Pierce, G.B. and Abell, M.R.: Embryonal carcinoma of the testis. *Pathol. Ann.* 5:27, 1970.
4. Huntington, R.W. and Bullock, W.K.: Endodermal sinus and other yolk sac tumors, a reappraisal. *Acta Pathol. Microbiol. Scand.* 233:(Suppl) 26, 1972.
5. Huntington, R.W. and Bullock, W.K.: Yolk sac tumors of the ovary. *Cancer* 25:1357, 1970.
6. Neubecker, R.D. and Breen, J.L.: Embryonal carcinoma of the ovary. *Cancer* 15:546, 1962.
7. Wilkinson, E.J. et al.: Alpha-fetoprotein and endodermal sinus tumor of the ovary. *Am. J. Obstet. Gynecol.* 116:711, 1972.
8. Serov, S.F. and Scully, R.E.: Histologic typing of ovarian tumors. Geneva, 1973. World Health Organization.
9. Scully, R.E.: Recent progress in ovarian cancer. *Hum. Pathol.* 1:73, 1970.
10. Robboy, S. J. and Scully, R. E.: Ovarian teratoma with glial implants in the peritoneum. *Hum. Pathol.* 1:643, 1970

Figure 1



APRIL 21, 1974 - CASE NO. 5

ACCESSION NO. 13317

MODERATOR'S DIAGNOSIS: Well differentiated adenocarcinoma of the cervix, cervical cell type.

CLINICAL ABSTRACT:

This is a 57 year old patient with vaginal discharge and intermittent spotting of blood. Examination revealed a polypoid lesion of the cervix and a cervical conization and D&C were done. The conization specimen showed the cervical stroma to be thickened by an infiltrating pinkish-yellow sticky tumor that surrounded the endocervical canal. The tumor extended to the margin of the cone. Following the conization a hysterectomy was performed.

MICROSCOPIC DESCRIPTION:

Sections of the tumor show large numbers of endocervical glandular structures present in the cervical stroma. These glandular structures have irregular shape, are crowded together in focal areas, appear to be infiltrating the cervical stroma, and are forming bizarre glandular configurations. In addition many of the glands have pointed, jagged angles and a lobster claw configuration can be noted in many of the tumor glands. High power examination indicates nuclear crowding, mild pleomorphism, and hyperchromaticity. There is stratification of the nuclei and mitoses are numerous in all of the tumor glands. Budding and branching of tumor glands are prominent.

DISCUSSION:

This is an example of the well differentiated type of cervical cell adenocarcinoma of the cervix. Such adenocarcinomas can be very well differentiated and can be difficult to separate from endocervical hyperplasia (1). At low power the most significant findings are the glandular crowding, the irregular formation of the glands, and the pointed angles and lobster claw-like configurations. At higher power, the nuclei are almost always stratified, hyperchromatic, and, most significantly, mitoses are found in large numbers (2,3). Mitoses are very unusual in benign cervical epithelium, and when they are present, well differentiated carcinoma must be considered. Because this type of adenocarcinoma is well differentiated it is often missed when care is not taken to examine the endocervical glands at high magnification.

Endocervical glandular hyperplasia may be found in a number of abnormal states including progestogen medication, pregnancy and inflammation. Hyperplasia is characterized by crowding and increased numbers of glands as well as unusual configurations. However mitoses are very rare and the nuclei show only minor degrees of atypia and stratification. Also the bizarre shapes

and angles of glands seen in carcinoma are not present in hyperplasia. Microglandular hyperplasia, as described in Case 3, may be confused with well differentiated carcinoma but the nuclei are flat, the glands are rounded, and there is mucus with polys in the center. The Aria-Stella reaction can also occur in the endocervical epithelium, but the history of pregnancy, lack of mitoses and absence of invasion should allow separation from well differentiated adenocarcinoma (2). Mesonephric remnants can also appear similar to well differentiated adenocarcinoma but they are not jagged and irregular and do not contain mitoses.

Adenocarcinoma-in-situ occurs in the endocervix and the cellular atypia and the numbers of mitoses will be similar to that seen in carcinoma except there is no invasion. Proposed criteria for the diagnosis of adenocarcinoma-in-situ of the cervix are as follows (4):

1. Anaplastic and neoplastic cells lining glands which are clearly endocervical in type.
2. Transitions between benign and malignant epithelium within the glands which retain a normal or organoid pattern
3. Cells have the cytologic features of carcinoma including mitoses.
4. The supporting stroma-gland relationship is normal.
5. Invasion or infiltration by carcinoma cells or clusters of glands is not found.

In summary, this is a case well differentiated adenocarcinoma of the cervix of the cervical cell type. The importance of this type of lesion is that it can be so well differentiated as to be confused with endocervical gland hyperplasia and normal endocervical glands. It is very easy to miss this type of carcinoma if inspection of endocervical sections is casual and careful examination of the endocervix is required to make the diagnosis. The presence of mitoses, altered nuclear-cytoplasmic ratio, nuclear hyperchromatism and stratification are all features of carcinoma as is irregular shape of the glands. This type of carcinoma has also been designated as adenoma malignum, a term which should not be used (1).

REFERENCES:

1. McKelvey, J.L. and Goodlin, R.R.: Adenoma malignum of the cervix. Cancer 16:549, 1963.
2. Abell, M.R.: Invasive carcinomas of the uterine cervix. In: Norris, H.J., Hertig, A.T. & Abell, M.R. Eds.: The Uterus, IAP Monograph #14. Baltimore 1973. The Williams & Wilkins Company. p. 437.
3. Abell, M.R. and Gosling, J.R.G.: Gland cell (adenocarcinoma) carcinoma of the uterine cervix. Am.J.Obstet.Gynecol. 83:729, 1962.
4. Weisbrot, I.M. et al.: Adenocarcinoma-in-situ of the uterine cervix, Cancer 29:1179, 1972.

APRIL 21, 1974 - CASE NO. 6

ACCESSION NO. 13900

MODERATOR'S DIAGNOSIS: Extramammary Paget's disease of the vulva.

CLINICAL ABSTRACT:

The patient is a 60 year old who had a long history of vulvar pruritis which persisted despite treatment and became more intense. Finally white plaques developed on the vulvar skin and these became confluent forming a horseshoe-shaped area with the clitoris in the central portion. A vulvectomy was performed and the specimen showed irregular white plaques extending from the prepuce of the clitoris on to the labia majora in a zone measuring 35 x 25 mm. in greatest dimensions. The lesion was re-excised following the initial excision and the patient was free of disease for eight years. In 1972, plaques again developed and a biopsy showed Paget's disease. She was treated conservatively for a year and the lesion spread from the pubis to the anus.

MICROSCOPIC DESCRIPTION:

The epithelium is focally hyperplastic with mild hyperkeratosis in many areas. Within the epidermis are large cells with clear to grainy eosinophilic cytoplasm arranged singly or in clusters. Most of these cells are in the basal portion of the epithelium but they extend to the upper parts of the epidermis. In some areas the nests of cells are arranged around a glandular lumen in which secretion products can be found. This glandular formation is a constant feature of Paget's disease and is most helpful in its diagnosis. The Paget's cells are also present in the outer portions of the hair shafts and in the ducts of the sweat glands. There is no evidence of dermal invasion. At high power the cells are noted to have a prominent nucleolus and foamy to clear cytoplasm. PAS staining with diastase digestion demonstrates that most, but not all, of the tumor cells contain intracytoplasmic mucin. An aldehyde fuchsin stain shows approximately 30% of the cells to contain aldehyde fuchsin positive material in their cytoplasm. There is extensive glycogen within the tumor cells which is removed with diastase. Mast cells are present in the dermis.

DISCUSSION:

Extramammary Paget's disease of the vulva (1,2,3) occurs in older individuals at an average age of sixty. It is rare under the age of fifty and practically unknown under the age of thirty. Paget's disease of the vulva represents one part of the spectrum of ano-genital Paget's, which may also involve the perineum, perianal region, the thighs, and the male genitalia. There are no known causative factors. Clinically, the lesions are characteristically reddened, eczematoid, elevated, edematous, and indurated but may

be plaque-like and white as in this case. Thus, Paget's disease must be considered in the differential diagnosis of so-called leukoplakia. The lesions are frequently ulcerated with oozing, crusting, and scaling. Pruritis is universal and severe. The duration of the disease is usually long and the lesions are often initially interpreted clinically as dermatitis, vulvar dystrophy, hyperkeratosis, or other inflammatory diseases. Paget's disease is just one of the many entities which emphasize the necessity of early biopsy as a part of the diagnostic procedures for patients with vulvar skin lesions.

The histogenesis of Paget's disease is controversial but recent studies indicate origin in the epidermis (1). Observations which support intra-epidermal origin are the following:

- A. The lesion invariably occurs first in the epidermis and dermal involvement is secondary. Adnexal involvement alone is not seen.
- B. When invasive carcinoma is present, the invasion occurs from the epidermis into the dermis, not from the dermis into the epidermis.
- C. Ultrastructural studies support, but do not prove, an epithelial origin. Ultrastructurally, there are desmosomes between Paget's cells and squamous cells, and between Paget's cells and Paget's cells (4).

Ultrastructural studies suggest an in-situ transformation of squamous epithelial cells to Paget's cells. The evidence also supports a multifocal origin along wide areas of the epidermis and within eccrine ducts. Other theories of origin have also been suggested. These include intra-epithelial spread of an adenocarcinoma from underlying sweat glands. There is little support for this theory. It has also been suggested that Paget's disease is a form of melanoma; however, melanin is not present in the tumor cells and desmosomes are not seen between melanocytes as are present between Paget's cells. Paget's cells may contain melanosomes, but so may squamous cells (4).

I interpret Paget's disease as adenocarcinoma-in-situ involving the epidermis, whether it occurs in the breast or in the ano-genital region. In vulvar Paget's disease, about one-sixth of the patients will have underlying invasive adenocarcinoma. The incidence of invasive carcinoma associated with Paget's disease varies with the site, with 100% incidence in the breast, and about 80% incidence in perianal Paget's disease (1,3).

The course of Paget's disease is prolonged and the lesion usually spreads slowly. However, until invasion of the dermis occurs, the lesion is localized

to the epidermis and does not metastasize. If invasive carcinoma is present, it often can be detected clinically because of ulceration or the presence of a mass. Patients with Paget's disease should have multiple biopsies to rule out invasion and to determine margins. At the time of excision, frozen sections of the surgical margins is often advised because Paget's cells can be found outside what appears to be the clinical margins of the lesion. Recommended therapy is complete local excision as long as invasion has not occurred. When invasion is present radical vulvectomy with node dissection is the treatment of choice. Thirty percent of the patients with Paget's disease have malignancies in other organs including rectal, anal, and sweat gland carcinomas (3).

The differential diagnosis in Paget's disease must always include malignant melanoma (5). The nodular form of malignant melanoma is usually little trouble clinically or histologically. However, superficial spreading malignant melanoma clinically may be erythematous and weeping and thus somewhat resemble Paget's disease. Histologically, the so-called "Pagetoid" cells in superficial spreading malignant melanoma can very closely resemble true Paget's cell (6). However, the tumor cells in malignant melanoma do not involve the sweat glands as Paget's disease frequently does, melanoma cells are not mucin positive as are Paget's cells, and most importantly, melanoma cells do not form glandular acini containing mucin. In our experience the PAS with diastase is the most reliable stain to determine the presence of mucin within tumor cells although Helwig has advocated use of the aldehyde fuchsin reaction because melanoma cells may occasionally contain small amounts of PAS diastase resistant material (3). The combination of gland formation by tumor cells, eccrine sweat gland involvement, and a positive mucin stain, allow separation of Paget's disease from superficial spreading malignant melanoma (1). Another entity which may be confused with Paget's disease is Bowen's disease (7). Although this entity usually causes no trouble Bowenoid cells may have clear cytoplasm but such cells are mucin negative. The presence of mucin as well as the involvement of the sweat glands and glandular formation by tumor cells, serves to separate Paget's disease from Bowen's disease.

#### REFERENCES:

1. Koss, L.G. et al.: Paget's disease of the vulva. Report of 10 cases. *Obstet. & Gynecol.* 31:513, 1968.
2. Fenn, M.E., Morley, G.W. and Abell, M.R.: Paget's disease of the vulva, *Obstet. & Gynecol.* 38:660, 1971.
3. Helwig, E.G. and Graham, J.H.: Anogenital (extra-mammary) Paget's disease, *Cancer* 16:387, 1963.

4. Sagebiel, R.W.: Ultrastructural observation on epidermal cell in Paget's disease of the breast. *Am. J. Path.* 57:49, 1969.
5. Fenn, M.E. and Abell, M.R.: Melanomas of vulva and vagina. *Obstet. & Gynecol.* 41:902, 1973.
6. Clark, W.H. et al.: The histogenesis and histologic behavior of primary malignant melanomas of the skin, *Cancer Res.* 29:705, 1969.
7. Abell, M.R. and Gosling, J.R.G.: Intraepithelial and infiltrating carcinomas of the vulva, Bowen's type. *Cancer* 14:318, 1961.

APRIL 21, 1974 - CASE NO. 7

ACCESSION NO. 12799

MODERATOR'S DIAGNOSIS: Epithelioid leiomyoma present in spaces consistent with intravenous leiomyomatosis

CLINICAL ABSTRACT:

This patient is a 36 year old female who developed a pelvic mass thought to be a leiomyoma six years prior to hysterectomy. At hysterectomy, the uterus weighed 1200 grams and included a pedunculated mass, 13 cms. in diameter. In addition to the pedunculated tumor, which had the gross appearance of a leiomyoma, there were multiple intramural leiomyomas, the largest measuring 6.5 cms. in diameter. The latter had a bulging cut surface composed of closely oriented multifaceted nodules of homogeneous tissue resembling kernels of corn. These were separated by slit-like spaces.

MICROSCOPIC DESCRIPTION:

This tumor is composed of cords, clusters and sheets of cells with vesicular somewhat irregular nuclei. There is extensive hyalinization present throughout the tumor and many of the tumor cells are completely surrounded by hyaline. Vessels are present in the mass but are not strikingly thick walled. The tumor is somewhat more cellular at the periphery, and in these areas, the tumor cells have an epithelioid appearance with striking clearing of the cytoplasm. At the edge of the section there is a small fragment of normal myometrium which appears to be lined by elongate endothelial-like cells suggesting that the mass is present in a vascular space. The tumor cells do not contain mitoses. There is only minimal pleomorphism and giant cells are not found.

DISCUSSION:

I consider this tumor to be of smooth muscle origin and to belong to the group of smooth muscle tumors known as "bizarre" leiomyomas. These were first described by Stout under the title "leiomyoblastomas of the stomach" and several varieties have since been described in the stomach, and other sites, including the uterus (1,2,3). The classic leiomyoblastoma is a cellular tumor in which the tumor cells have cytoplasmic clearing around a central nucleus resulting in a unique "fried egg" appearance. In addition to the leiomyoblastoma type of bizarre leiomyoma, we have encountered clear cell leiomyomas in the uterus and lesions such as this one, which have been designated as "epithelioid cell" leiomyomas because of the epithelial-like appearance of the tumor cells (2,3). The epithelioid type of leiomyoma is characterized by cells having varying degrees of cytoplasmic clearing which are arranged in a linear and often epithelial-like arrangement. The epithelioid leiomyomas always contain extensive amounts of hyaline. The importance of recognizing these bizarre leiomyomas is to avoid mistaking them for either leiomyosarcoma or other malignancies. In this case, the absence

of mitosis eliminates the possibility of leiomyosarcoma. Because of the apparent presence of tumor tissue in vascular spaces, the possibility of endolymphatic stromal myosis must be considered. However, the tumor cells do not resemble endometrial stromal cells.

Intravenous leiomyomatosis is distinctly a consideration. Certainly, the gross description would fit that entity and the sections show the lesion to be present in what I think is a vascular space although this is not definitive in the material available to us for examination. Intravenous leiomyomatosis is a rare condition in which benign smooth muscle is present in vascular spaces (4,5). It occurs in older patients, usually in their fifties or sixties. There are no specific symptoms and the patients are almost always operated on because of an enlarged uterus thought to be due to leiomyomas. The lesion is seen grossly as intravascular tumor masses which can usually be easily pulled out of the vessels. In about half of the cases the tumor has extended into the veins of the broad ligament or beyond at the time of surgery. The lesion is benign in spite of the vascular invasion and, in most instances, even if tumor is left behind in vessels, nothing further happens. In two instances, however, intravenous masses of smooth muscle extended up the vena cava and caused the death of the patient (5). This is an extremely rare event and in all other instances, the lesion has been perfectly harmless. Histologically, the material inside the vessels is benign smooth muscle without evidence of mitoses or significant atypism. Characteristically there is extensive hyalinization of the smooth muscle and thick walled blood vessels are frequently prominent. At low power, the most distinctive feature histologically is the proliferation of smooth muscle tumor tissue in vascular spaces. The pathogenesis is unknown but the most current theories suggest that the lesion is the result of proliferation of the smooth muscle of the media of vessels.

#### REFERENCES:

1. Stout, A. P.: Bizarre smooth muscle tumors of the stomach. *Cancer* 15: 400, 1962.
2. Rywlin, A. M., et al: Clear cell leiomyoma of the uterus, *Cancer* 17: 100, 1964.
3. Kempson, R. L.: Sarcomas and related lesions. In: Norris, H. J., Hertig, A. T. and Abell, M. R. Eds. The Uterus, IAP monograph #14. Baltimore, 1973. The Williams and Wilkins Co. Page 298.
4. Harper, R. S. and Scully, R. E.: Intravenous leiomyomatosis of the uterus. *Obstet. and Gynecol.* 18:519, 1961.
5. Edwards, D. L. and Peacock, J. F.: Intravenous leiomyomatosis of the uterus. *Obstet. Gynecol.* 27:176, 1966.

APRIL 21, 1974 - CASE NO. 3

ACCESSION NO. 12903

MODERATOR'S DIAGNOSIS: Malignant mixed Mullerian tumor, heterologous type.

CLINICAL ABSTRACT:

The patient is an 83 year old female who had radium therapy in 1955 for carcinoma of the cervix. In 1963, she developed intestinal obstruction secondary to metastatic carcinoma. At surgery a huge mass filled the pelvis and many of the lymph nodes contained metastatic tumor. She died following a colostomy. At autopsy the pelvic mass was noted to be primarily an intrauterine tumor which was polypoid and gray white with areas of brown and red necrosis. The tumor was 6 cm. in length and 3.4 cms. in diameter and had grown through the uterine wall and obliterated both adnexal structures.

MICROSCOPIC DESCRIPTION:

This tumor presents several different histologic patterns. In some areas there is adenocarcinoma present with well formed gland spaces lined by neoplastic cells containing numerous mitoses. In other areas, the tumor appears to be formed by undifferentiated mesenchyme while in other areas there is malignant stroma suggesting smooth muscle differentiation. Yet other areas resemble neoplastic endometrial stroma and in these latter areas, islands of squamous epithelium can also be found. The stroma is definitely sarcomatous and the pleomorphic tumor cells contain numerous mitoses. As mentioned above, the epithelial elements also demonstrate the changes of carcinoma. In areas, there is cartilaginous differentiation and the cartilage has the histologic appearance of chondrosarcoma.

DISCUSSION:

The differential diagnosis of malignant mixed Mullerian tumors must always include undifferentiated and poorly differentiated carcinomas since some carcinomas may be so poorly differentiated as to resemble sarcoma. This is particularly true in those carcinomas which have a basophilic hyalinized stroma somewhat resembling cartilage. Before making a diagnosis of malignant mixed Mullerian tumors, one should be sure that there is a sarcomatous element present in the tumor. In this tumor, I think there is little doubt that leiomyosarcoma, stromal sarcoma and chondrosarcoma are present. Mixed sarcomas must also be included in the differential diagnosis. However, there is definitely carcinoma present in this tumor, thus indicating a malignant mixed Mullerian tumor. Malignant mixed Mullerian tumors must always be differentiated from teratomas. This is particularly true in the ovary where mixed Mullerian tumors may also occur. As pointed out by Dehner

and Norris, teratomas are seen in a younger age group. There is a broader range of tissue differentiation in teratoma, neural tissue and germ cell elements are found in teratomas, and the stroma in mixed Mullerian tumors is sarcomatous rather than immature or adult as seen in teratomas (1).

Malignant mixed Mullerian tumors represent one of the more common types of uterine sarcomas and, as mentioned in the discussion of case 2, are designated as heterologous or homologous depending upon the differentiation of the sarcomatous tissue present (2,3). Other terms used are carcinoma sarcoma and mixed mesodermal tumor to designate the homologous and heterologous tumors respectively (4,5). Malignant mixed Mullerian tumors represent approximately 1% of all uterine malignancies and are equal in frequency to leiomyosarcoma in most of the larger series. The tumor mainly affects older patients and it is rare under the age of 30. Most patients are in their 50's and 60's. Abnormal vaginal bleeding is a universal symptom and the uterus is often enlarged at the time of diagnosis. The tumor may protrude from the cervical os and at times can be botryoid. Malignant mixed Mullerian tumors should not be designated as sarcoma botryoides however, since that term implies embryonal rhabdomyosarcoma. Grossly, malignant mixed Mullerian tumors are usually polypoid fungating hemorrhagic necrotic masses often involving large portions of the uterus. They frequently have invaded the myometrium deeply at the time of diagnosis.

The treatment is hysterectomy. Survival depends on the extent of the tumor, the depth of myometrial invasion and, to a lesser extent, on the type of tumor tissue differentiation (6). Patients who have survived are almost invariably those whose tumors were small with only superficial or no invasion of the myometrium. When the heterologous elements are skeletal muscle and bone, survival is very poor; it is somewhat better when heterologous element is cartilage. Patients with homologous tumors have been reported to have a better survival than those with heterologous tumors (4,5).

The histogenesis of malignant mixed Mullerian tumors is unknown but they are thought to arise from the endometrium. Whether they represent simultaneous malignancy of the mesenchyme around the Mullerian tube and the Mullerian epithelium, or, whether a malignancy of the mesenchyme induces epithelial malignancy, or, whether a carcinoma occasionally induces mesenchymal neoplastic change is not known. Ultrastructural studies have suggested that the mesenchymal elements of the tumors differentiate into sarcoma but not into the epithelium which apparently arises de novo (7). The survival is approximately 25 to 35% at 5 years. Whenever a patient presents with tumor mass protruding from the cervical os or when the curettage contains anaplastic malignant tumor the possibility of malignant

mixed Mullerian tumor must be considered. Curettage and biopsy material will not be representative if only the carcinomatous element or only the sarcomatous tissue is present in the biopsy. Malignant mixed Mullerian tumors also occur in the fallopian tubes and ovaries where they are considered to arise from the coelomic (surface) epithelium (8,9). They have a similar prognosis in these locations. Twelve to fifteen percent of patients with malignant mixed Mullerian tumors have had prior radiation therapy to the pelvis. A history of prior radiation is rarely elicited in patients with other types of sarcoma (10).

#### REFERENCES:

1. Dehner, L. P., Norris, H. J. and Taylor, H. B.: Carcinosarcomas and mixed mesodermal tumors of the ovary. *Cancer* 27:207, 1971.
2. Kempson, R. L.: Sarcomas and related lesions. In: Norris, H. J., Hertig, A. and Abell, M. R. Eds. The Uterus, IAP monograph #14. Baltimore 1973. The Williams and Wilkins Co. p. 298.
3. Kempson, R. L. and Bari, W: Uterine sarcomas. *Hum. Path.* 1:331, 1970.
4. Norris, H. J. et al: Mesenchymal tumors of the uterus. II - A clinical and pathologic study of 31 mixed mesodermal tumors. *Obstet. & Gynecol.* 28:57, 1966.
5. Norris, H. J. and Taylor, H. B: Mesenchymal tumors of the uterus. III - A clinical and pathologic study of 31 carcinosarcomas. *Cancer* 19: 1459, 1966.
6. Schaeppman-Van Geuns, E. J: Mixed tumors and carcinosarcomas of the uterus evaluated 5 years after treatment. *Cancer* 25:72, 1970.
7. Silverberg, S. G.: Malignant mixed mesodermal tumor of the uterus: an ultrastructural study. *Am. J. Obstet. Gynecol.* 110:702, 1971.
8. Wu, J. P. et al: Malignant mixed Mullerian tumor of the uterine tube. *Obstet. & Gynecol.* 41:707, 1972.
9. Fenn, M. E. and Abell, M. R.: Carcinosarcoma of the ovary. *Am. J. Obstet. & Gynecol.* 110:1066, 1971.
10. Norris, H. J. and Taylor, H. B.: Post irradiation sarcomas of the uterus. *Obstet. and Gynecol.* 26:689, 1965.

APRIL 21, 1974 - CASE NO. 9

ACCESSION NO. 12998

MODERATOR'S DIAGNOSIS: Syncytial endometritis (implantation site).

CLINICAL ABSTRACT:

This 24 year old female was admitted in 1963 for removal of a left ovarian cyst which had increased in size since it had been discovered one year previously. She was gravida 1, para 1 and had delivered an infant in 1960. In 1961, a right ovarian cyst had been removed but the type of cyst is unknown. She had been receiving cyclic hormone therapy. Pelvic examination revealed a movable non-tender 6 cm. mass in the left adnexal region and a hysterectomy and left salpingo-oophorectomy were performed. Grossly, near the left tube, there was a 0.4 cm. poorly delineated nodule which bulged from the serosal surface of the uterus. There were not other myometrial lesions. The endometrial cavity was enlarged by a lobulated, yellowish tan tumor that measured 4 x 2.5 x 1.5 cm. This tumor was attached along the posterosuperior wall. The mass was partially cystic, friable, and blended into the underlying myometrium. The left ovary was multiloculated and cystic. The sections in this case are apparently taken from the endometrial mass.

MICROSCOPIC DESCRIPTION:

The endometrium in the areas from which the sections were taken shows a florid decidual reaction. Overlying the decidua are round cystic spaces, which at low power, resemble chorionic villi, but are noted to be surrounded by decidua at high power, and represent dilated endometrial glands demonstrating so-called secretory exhaustion. Within the decidua and in the myometrium are large numbers of cells with abundant eosinophilic cytoplasm and atypical nuclei. Many of these cells are multinucleated and they infiltrate the walls of blood vessels and interdigitate among muscle fibers in the upper portion of the myometrium. Abnormal mitoses are occasionally noted. There is focal, and rather minimal, chronic inflammation without evidence of hemorrhage or necrosis. The muscle fibers surrounded by the cells appear to be viable and occasional muscle giant cell forms are also present. The remainder of the myometrium is not remarkable.

DISCUSSION:

Although it is unusual to find syncytial metritis presenting as a gross mass in a patient who has not been known to be pregnant, I think this is syncytial metritis and represents a missed abortion. Closer questioning of the patient might have revealed a history of abnormal uterine bleeding in the recent past. The main consideration in the differential diagnosis is, of course, choriocarcinoma. Choriocarcinoma is inevitably composed of both cyto and syncytial trophoblasts with the syncytial trophoblasts usually

arranged over and around the clusters of cytotrophoblast as a cap (1). In addition, choriocarcinoma is always associated with hemorrhage and necrosis which is not found in these sections (2). The degree of cellular atypia and the presence of mitoses and abnormal mitoses are not particularly helpful since they can be found in both syncytial metritis and choriocarcinoma. In fact, cellular pleomorphism and atypia are usually more marked in syncytial metritis, than in choriocarcinoma. Features which are helpful in separating syncytial metritis from choriocarcinoma are: 1. In syncytial metritis, the cells infiltrate along tissue spaces singly and not in groups and clusters as is characteristic of choriocarcinoma. 2. In syncytial metritis the cells produce none of the destructive and lytic effect on the muscle cells which is characteristic of invasive choriocarcinoma. In other words, the muscle is not destroyed in syncytial metritis and it is in choriocarcinoma. 3. Syncytial metritis may be associated with focal lymphocytic and plasma cell collections, but it is not associated with extensive hemorrhage and necrosis (2).

The second entity to be considered in the differential diagnosis is hydatidiform mole. I think mole can be ruled out in this case because chorionic villi, which are invariably present in a mole, are not identified in the multiple sections that I have examined from this uterus. Differentiation of hydatidiform mole from atypical villi and degenerated villi from an abortion can be difficult. Features that we find more characteristic of mole are marked villar enlargement with loss of villar vessels and trophoblastic proliferation on the surface of the villi. In degenerated pregnancies, the trophoblasts are frequently degenerated and do not show the proliferative changes found in moles. Frequently the villi are also smaller and more degenerated. Whenever there is doubt in the curettings whether the villar structures represent a mole or an abortion with atypical hydropic degeneration, follow-up of the patients with gonadotrophin titers for a period of 3 to 6 months is indicated (4). The presence of stable or rising titers would indicate a repeat curettage is in order.

Choriocarcinoma can be very difficult to diagnose from curettings and atypical trophoblastic proliferation in pregnancies can be troublesome (3,5). It is probable that choriocarcinoma cannot be diagnosed histologically from curettings in more than one third of the cases. However, the combination of clinical pattern, chorionic gonadotropin titers and the histology often allow a proper diagnosis. In some instances accurate classification of the trophoblastic process is not possible and a diagnosis of trophoblastic disease must be made.

Invasion of the myometrium by the trophoblast is a characteristic of all pregnancies (6). The degree of invasion is variable but can be extensive and trophoblasts can invade rather deeply into the myometrium and into vessel

walls. The invasive cells are both syncytial and cytotrophoblasts and differentiation of these cell types is sometimes difficult when they are in the uterine wall (6). It is often difficult to separate trophoblasts from atypical decidual cells and muscle giant cells. In some instances, the trophoblasts may persist at the implantation site for a long period of time after a pregnancy as in this case, and careful separation from mole and choriocarcinoma is imperative.

REFERENCES:

1. Park, W.W.: Choriocarcinoma; a study of its pathology. Phila. 1971, F.A. Davis, Co.
2. Elston, C.W.: Cellular reaction to choriocarcinomas, J. Pathol. 97:261, 1969.
3. Elston, C.W. and Bagshawe, K.D. The diagnosis of trophoblastic tumors from uterine curettings. J. Clin. Pathol. 25:111, 1972.
4. Ishizuka, N. et al.: Gonadotropin and steroid hormone excretion in trophoblastic neoplasia. Obstet. & Gynecol. 42:1, 1973.
5. Jequier, A.M. and Winterton, W.R.: Diagnostic problems of trophoblastic disease in women aged 50 or more. Obstet. & Gynecol. 42:378, 1973.
6. Driscoll, S.G.: Placental-uterine inter-relationships. In: Norris, H.J., Hertig, A., Abell, M.R. Eds. The Uterus IAP monograph #14. Baltimore 1973. The Williams and Wilkins Co. p.213

APRIL 21, 1974 - CASE NO. 10

ACCESSION NO. 12802

MODERATOR'S DIAGNOSIS: Malignant lymphoma, unclassified (? Burkitt's lymphoma, ? poorly differentiated lymphocytic lymphoma diffuse)

CLINICAL ABSTRACT:

This 15 year old female noted lower abdominal pain and abdominal enlargement one week prior to admission. She had had a normal menstrual period 10 days prior to admission. Physical examination revealed a very hard tender mass extending from the symphysis to the umbilicus with a second mass near the epigastric area. Her white count was 12,300 with 63 segs and 25 lymphocytes. No mention of a bone marrow examination is made. An appendectomy and bilateral salping-oophorectomy were performed. The left ovary was replaced by 630 gms. mass measuring 15 x 12 x 8 cm. This was solid, soft, smooth and light tan with a few cystic mucoid areas. The right ovary weighed 800 gms. and was similar to the left one. There was a small nodule on the serosa of the fallopian tube and one in the mesosalpinx.

MICROSCOPIC DESCRIPTION:

Unfortunately, the tissue in this case is not ideally preserved making interpretation difficult. The tumor is composed of monotonous masses of lymphoid like cells which have irregularly shaped nuclei and are of variable size. Mitoses are present and the cells appear to have a small amount of amphophilic cytoplasm. Necrosis is prominent. At low power in some areas of the tumor, histiocytes are present surrounded by a space resulting in the so-called starry sky appearance. A MGP stain was negative as were the ASD chloracetate esterase stain and PAS. Cytoplasmic vacuoles are not noted.

DISCUSSION:

The differential diagnosis in this case would include lymphoma, leukemia and the group of small round cell malignant tumors which occur in childhood, namely neuroblastoma, Ewing's tumor, embryonal rhabdomyosarcoma and Wilm's tumor. I have interpreted this case as a malignant lymphoma and a primary consideration is, of course, Burkitt's lymphoma. Burkitt's lymphoma is a form of undifferentiated malignant lymphoma for which clinicopathologic criteria were established in 1969 (1). According to the Rappaport classification, Burkitt's tumor would fall into the category of undifferentiated diffuse malignant lymphoma and under the new classification of Dorfman, Burkitt's lymphoma would be included under the lymphomas and diagnosed as such (2). Criteria for the diagnosis of Burkitt's lymphoma include cells with little variation in size and shape, increased numbers of mitoses, and starry sky pattern with nuclear debris in the cytoplasm of the histiocytes.

The tumor cells usually have a narrow rim of amphophilic cytoplasm and cytoplasmic vacuoles are common. These latter can be best seen under oil immersion. The nuclei contain coarse chromatin, are uniform in size, and have prominent, and often multiple nucleoli. Rapid and thorough fixation are necessary to bring out the uniformity of the cells and the cytoplasmic characteristics. In addition, imprints are very helpful in making the diagnosis of Burkitt's lymphoma accurately since the Romanofsky stain brings out cytologic details, fat stains will demonstrate the lipid in the vacuoles, and cytoplasmic pyrinophilia can be demonstrated. The tumor cells are MGP positive, PAS and esterase negative (1,3).

In this case, I think the cells are too irregular in size and shape for this tumor to be diagnosed unequivocally as Burkitt's tumor although sub-optimal fixation may be responsible for the cellular irregularity. Additionally, the MGP is negative and it should be positive in Burkitt's tumor. Poorly fixed cells will lose pyrinophilia and this may have been the case here. This emphasizes the necessity for imprints and rapid fixation. I would consider this tumor to be malignant lymphoma which I cannot further classify. It could be a Burkitt's tumor in which the tissue has been poorly fixed resulting in loss of cellular uniformity and cytoplasmic pyrinophilia. It could also be a poorly differentiated lymphocytic lymphoma of the diffuse type. The "starry sky" pattern is not specific for Burkitt's and can be found in a number of other lymphomas and leukemias. I do not think this is histiocytic lymphoma since the cells in that tumor should have abundant cytoplasm and large cytoplasmic vacuoles. The cytoplasmic vacuoles in histiocytes are fat negative and there is variable MGP staining. Nodular poorly differentiated lymphocytic lymphoma cells are irregular and have so-called nuclear clefts or indentations which are not seen in this case. The MGP and PAS stains are also negative.

Leukemia should be considered in the differential diagnosis. In lymphoblastic leukemia, the nuclei are somewhat smaller than histiocytes, have delicate chromatin and somewhat resemble the cells seen in this tumor. Therefore, a bone marrow examination would be indicated for this patient. Lymphoblastic leukemia cells have weak to no MGP staining but do contain PAS positive diastase resistance sensitive granules. These were not found in this case and therefore, I doubt that this is lymphoblastic leukemia. I also doubt that this is myeloblastic leukemia since eosinophilic myelocytes are not present. The ASD chloracetate esterase was negative whereas it should be positive in myelocytes, and PAS positive granules were not found.

There is a group of neoplasms occurring primarily in childhood which should also be considered in the differential diagnosis. These include neuroblastoma, Ewing's tumor, embryonal rhabdomyosarcoma and Wilm's tumor.

Rosettes are not found in this tumor and I do not think this is neuroblastoma. However, catecholamine determinations should be done since urinary catecholamines will be elevated in neuroblastoma. A diagnosis of neuroblastoma can often be made quickly by electron microscopy or tissue culture. In Ewing's sarcoma the tumor cells usually contain glycogen and the PAS stains should be positive. Embryonal rhabdomyosarcoma has a myxoid stroma which is not present in this tumor. Wilm's tumor may have evidence of tubular differentiation.

It is rare for lymphomas to present primarily in the ovary. However, one of the features of Burkitt's tumor is involvement of the gonads in females (4,5). It characteristically occurs in children and young adults and ordinarily there are no tumor cells in the blood and a frankly leukemic blood picture is almost never present. Extranodal involvement is prominent in Burkitt's tumor, particularly in the retroperitoneal soft tissue, abdominal viscera, gonads and other endocrine organs. The spleen is either minimally or not involved. Frequently there is sparing of the peripheral lymph nodes and the retroperitoneal lymph node may be spared even in the presence of massive involvement of the retroperitoneal soft tissue. Mediastinal lymph node involvement is very rare (6,7). The clinical presentation in this case is compatible with Burkitt's tumor, but definitive histopathologic criteria are not present as noted above. Other types of lymphoma may rarely appear first in the gonads (8). Particularly important is the occurrence of histiocytic lymphoma in the testicle. The prognosis for patients presenting with gonadal lymphoma has been poor.

#### REFERENCES:

1. Berard, C., et al.: Histopathological definition of Burkitt's tumor. W.H.O. Bull. 40, 601, 1969.
2. Dorfman, R.F.: Proposed classification of non-Hodgkin's lymphoma. To be published in Lancet.
3. Dorfman, R.F.: Diagnosis of Burkitt's tumor in the United States. Cancer 21:563, 1968.
4. Wright, D.H.: Burkitt's tumor and childhood lymphosarcoma. Clin. Pediat. 6:116, 1967.
5. Finkle, H.I and Goldman, R.L.: Burkitt's lymphoma, gynecologic considerations, Obstet. & Gynecol. 43:281, 1973.

6. Burkitt, D.P. and Wright, D.H.: Burkitt's lymphoma. London 1970. E. & S. Livingstone.
7. Cohen, M.H. et al.: Burkitt's tumor in the United States. Cancer 23: 1259, 1969.
8. Woodruff, J.D. et al.: Lymphoma of the ovary. A study of 35 cases. Am. J. Obstet. & Gynecol. 85:912, 1963.

APRIL 21, 1974 - CASE NO. 11

ACCESSION NO. 11497

MODERATOR'S DIAGNOSIS: Endometrial stromal sarcomaCLINICAL ABSTRACT:

This 51 year old female had a long history of dysmenorrhea with almost continuous vaginal bleeding for three months prior to admission to the hospital. Physical examination revealed vaginal bleeding and a polyp protruding from the cervical os. A D&C was done and large amount of yellow polypoid smooth material was obtained. Following this, a hysterectomy was done. The corpus and fundus were globular and on the serosal surface there was a reddish tan nodularity covering an area of 1.5 cm. The entire fundus of the uterus was expanded diffusely to form an ill-defined tumor, measuring 7 x 6 x 5 cm. Cut surface of the myometrium showed innumerable soft, yellowish, nodular, well demarcated masses extending to the serosa.

MICROSCOPIC DESCRIPTION:

The sections show masses of tumor infiltrating the myometrium. Some of these tumor masses are in vascular spaces while others are infiltrating the muscle fibers. The tumor is densely cellular and composed of closely packed uniform cells with scant cytoplasm and indistinct cell margins. The cells resemble endometrial stromal cells in the estrogenic phase of the cycle. Blood vessels are present within the tumor masses but are small and inconspicuous. No glandular differentiation is noted. Mitoses vary considerably but are easily found. In some areas of the tumor, I could count 15 to 20 mitoses per 10 high power fields. The tumor extends to the serosa of the uterus.

DISCUSSION:

Endometrial stromal neoplasms may be divided into three types as noted in Table 4 (1,2). These are stromal nodules, endolymphatic stromal myosis and stromal sarcoma. The criteria used to separate these three entities include pushing versus infiltrating margins and the number of mitoses per 10 high power fields. Tumors with pushing margins are considered stromal nodules while those with infiltrating margins are considered to be endolymphatic stromal myosis or stromal sarcoma. Stromal sarcomas are those infiltrating stromal neoplasms with more than 10 mitoses per 10 high power fields while endolymphatic myosis is an infiltrating tumor with less than 10 mitoses/10 HPF. Endometrial stromal tumors may be present in vascular spaces but this is particularly frequent in endolymphatic stromal myosis. Pleomorphism of tumor cells is of little value in separating stromal neoplasms. The same precautions and care to obtain representative and sufficient sections for mitotic counts as noted for smooth muscle tumors should be used for the

stromal tumors.

Infiltrating stromal tumors of the uterus are usually found in older patients but we have encountered them in children (3). Almost, invariably the patients present with abnormal vaginal bleeding and frequently there is a mass protruding from the cervix. Grossly stromal tumors are yellow white to gray with frequent areas of necrosis. Endolymphatic stromal myosis may present as worm like masses in vascular spaces which can be seen grossly. Sometimes these masses may extend beyond the uterus into the broad ligament and other structures. Endometrial stromal sarcomas frequently bulge into the endometrial cavity and infiltrate the myometrium widely. Endometrial stromal tumors are composed of rather uniform cells with scant cytoplasm.

Endolymphatic stromal myosis has two rather distinct forms. In the first of these, mitoses are very sparse or not found at all. The stromal is hyalinized and thick walled blood vessels are frequently present in the tumor masses. This form of the neoplasm is almost always confined to the uterus with involvement of vascular spaces being common. In the second form, mitoses are more easily found but do not exceed 10/10 HPF. Hyalinization is less marked, vascular involvement is not always present and thick walled blood vessels are inconspicuous. The prognosis for endolymphatic stromal myosis is directly related to the presence or absence of tumor outside of the uterus. It is very unusual for lesions which do not extend beyond the uterus to recur but recurrence is frequent when tumor extends outside the uterus. Recurrences of endolymphatic stromal myosis is almost always locally in the pelvis. Although metastases may occur, they usually do so only after local recurrence. Recrudescence of the tumor may occur long periods after the uterus has been removed; up to 25 and 30 years in some instances. There is some tendency for tumors with more mitoses to have a higher recurrence rate.

Endometrial stromal sarcoma is a much more aggressive tumor and metastases are more common. The overall survival in stromal sarcoma is between 30 and 40%. Both endolymphatic stromal myosis and stromal sarcoma may arise outside the uterus, most commonly in the fallopian tube, the peritoneum or in the bowel (4,5). Often, but not always, these extrauterine tumors are associated with endometriosis.

The differential diagnosis of endometrial stromal tumors should include lymphoma and leukemia, particularly histiocytic lymphoma. The sheet like arrangement of the tumor cells, the vascular involvement and the cohesiveness of the cells plus the lack of the distinct cytoplasmic borders in stromal tumors usually help to rule out the possibility of lymphoma or leukemia. Nucleoli are prominent in histiocytic lymphoma and are unusual in most stromal tumors. However, at times the differentiation between lymphoma and stromal

sarcoma can be extremely difficult. Undifferentiated endometrial carcinoma can also resemble stromal sarcoma. Glandular structures can be found in stromal tumors as well as in carcinoma. However, the glands and tumor cells in carcinoma are more pleomorphic than in stromal sarcoma. A reticulin stain can be very useful. Since carcinoma is characterized by large clusters of cells surrounded by reticulum whereas in stromal sarcoma single cells or at most, very small groups of cells, are surrounded by reticulum fibers. Intravenous leiomyomatosis involves the uterine vessels in the same manner as endolymphatic stromal myosis and differentiation depends upon the demonstration of smooth muscle in the former condition. The tumor cells in leiomyomatosis are spindle and stain as smooth muscle with the trichrome stain. Malignant mixed Mullerian tumors may contain stromal sarcoma as one of the sarcomatous elements and can cause confusion with stromal sarcoma. When glands occur in stromal sarcoma they are not histologically malignant as they are in malignant mixed Mullerian tumors. Stromal sarcomas have often been confused with hemangiopericytoma. However, stromal sarcomas do not have the vascular pattern of that tumor and do not show the tuft and weave pattern which is characteristic of pericytoma. Hemangiopericytoma of the uterus does occur but it is very rare and usually is easily distinguished from the stromal neoplasms (6). Metastatic undifferentiated carcinoma can also resemble the infiltrating stromal tumors but the carcinoma cells are usually more pleomorphic than the cells in the stromal sarcoma.

#### REFERENCES:

1. Norris, H.J. and Taylor, H.B.: A clinical and pathological study of 53 endometrial stromal tumors. Cancer 19:755, 1966.
2. Kempson, R.L.: Uterine Sarcomas. In: Norris, H.J., Hertig, A. and Abell, M.R.: The Uterus, IAP monograph #14. Baltimore, 1973. The Williams and Wilkins Co. p. 298.
3. Kempson, R.L. and Bari, W.: Uterine Sarcomas. Hum. Pathol. 1:331, 1970.
4. Palladino, V.S. & Trousdell, M.: Extra-uterine Mullerian tumors. Cancer 23:1413, 1964.
5. Gerber, M.A. and Toker, C.: Primary extrauterine endometrial stromal sarcoma. Arch. Path. 89:477, 1970.
6. Silverberg, S.C. et al.: Hemangiopericytoma of the uterus; an ultra-structural study, Am. J. Obstet. & Gynecol. 110:397, 1971.

Table 6

Pathologic Characteristics of Endometrial Stromal Tumors

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## I. Stromal nodule

- A. Pushing margins
- B. Less than 10 mitoses in 10 HPF
- C. Confined to the uterus
- D. No lymphatic or vascular invasion

## II. Endolymphatic stromal myosis

- A. Infiltration of myometrium
- B. Less than 10 mitoses in 10 HPF
- C. Vascular and lymphatic invasion common which may be massive giving rise to distinctive gross and microscopic patterns
- D. May extend beyond the uterus and can metastasize

## III. Stromal sarcoma

- A. Infiltrating margins, usually with extensive myometrial infiltration
- B. Greater than 10 mitoses in 10 HPF
- C. Vascular and lymphatic invasion common
- D. Frequently extends beyond the uterus and metastases are common

APRIL 21, 1974 - CASE NO. 12

ACCESSION NO. 19913

MODERATOR'S DIAGNOSIS: Malignant Brenner tumor of the ovary.CLINICAL ABSTRACT:

This 62 year old female presented with dull pain and pressure in the left lower quadrant. She had previously had a mucinous cystadenoma of the ovary removed. At laporatomy there was a cystic left ovarian tumor measuring 7 cm. in diameter. The inside of the cyst was lined with purple, friable, papillary material and in one portion of the wall there was a lobulated, multicystic, white and yellow mass.

MICROSCOPIC DESCRIPTION:

The tumor is composed of proliferating masses of transitional like epithelium which are many cell layers thick. The cells are present over fibrous cores giving a papillary appearance to most of the tumor. In other areas solid nests of tumors are present with a dense fibrous stroma. The tumor nests in the fibrous stroma are frequently cystic and many of the proliferating masses are lining cystic spaces. Mucin filled spaces are frequent within the epithelium and many of the cells contain cytoplasmic mucin, particularly those near the surface of the cystic spaces. Mitoses are numerous throughout the tumor and some mitoses are bizarre and abnormal. There is marked cellular atypia and anaplasia in focal areas. In some areas of the stroma, islands of the cells are irregular and atypical, and appear to represent invasive malignant neoplasm.

DISCUSSION:

The differential diagnosis in this case would include endometrioid carcinoma with squamous metaplasia. However, I think the cytologic features of the tumor cells suggest a resemblance to transitional cells of the bladder and this then would be a Brenner tumor. Whenever one diagnoses Brenner tumor, particularly one with this degree of atypia and number of mitoses, the possibility of metastatic bladder carcinoma to the ovary has to be excluded. Granulosa cell tumor is also a consideration when a Brenner tumor is considered. However, Call-Exner bodies are not identified in this tumor, pleomorphism is much more marked than in the most granulosa cell tumors, and granulosa cell tumors do not contain PAS positive material. In addition, granulosa cells often contain cytoplasmic lipid.

Brenner tumors represent 1-2% of all ovarian tumors and occur at a mean age of 50 years (1,2). They have never been reported in children. Approximately 80 to 90% of them are found as incidental findings subsequent to an oophorectomy done for other reasons. Brenner tumors may become large

and when they do, they can cause symptoms of abdominal pain and menstrual irregularities. Grossly, they are firm, gray white, sometimes yellow tumors which are usually unilateral but approximately 6 to 8% are bilateral. Microscopically they are composed of sheets and cords of epithelial cells embedded in a proliferative stroma, either ovarian stroma or fibrous tissue. The tumor cells are uniform with few mitoses. Epithelium and stroma are usually distinct but may appear to merge. The nuclei of the tumor cells characteristically have a longitudinal notch or groove similar to the grooves found in sex cord cells. Cells containing cytoplasmic mucin are frequently found, and cyst formation, calcification and hyalinization are common. Cortical inclusion cysts are associated with Brenner tumors in many cases and about 10% of Brenner tumors are associated with mucinous cyst adenomas, 5% with serous cyst adenomas and 5% with cystic teratomas. These other neoplasms are usually on the same side as the Brenner tumor, but not exclusively.

The histogenesis of the Brenner tumor is unknown but most authorities agree that it arises from the surface (coelomic) epithelium of the ovary as suggested by Arey from serial studies (3). The surface epithelium of the ovary is capable of differentiating into Mullerian structures such as mucinous and serous epithelium and urothelial epithelium such as that seen in the Brenner tumors and in Walthard's cell rests (4). Other origins of the Brenner tumor such as from the follicle, the undifferentiated sex cord cells, and the rete ovarii have also been suggested but not substantiated. Occasional Brenner tumors may be associated with hormone production, usually estrogen, and endometrial hyperplasia may be associated with these tumors.

Almost all Brenner tumors are benign; however, some Brenner tumors may have an unusual degree of epithelial proliferation, often papillary, resulting in a tumor which resembles a transitional cell carcinoma of the bladder (5). As long as the tumor cells do not invade, and as long as there are not cytologic features of malignancy, these tumors have a benign course and have been designated as proliferating Brenner tumors. Most proliferating Brenner tumors have no or minimal atypia, but mitoses may be found. Malignant Brenner tumors also occur and separation from the proliferating type may be difficult. Any Brenner tumor in which stromal invasion is present is malignant, however, determining whether the nests in the stroma in Brenner tumor are actually invasive or not is difficult. Miles and Norris have stated that if the proliferating epithelial nests contain cells which are cytologically malignant, the tumor should be considered a malignant Brenner tumor (6). On the other hand, Scully will accept a Brenner tumor as malignant only if invasion can be demonstrated and thinks that lesions with carcinoma-in-situ should be considered within the realm of the proliferating Brenner tumor (7). (See Table 5) In the present case, there is certainly cytologic evidence

of malignancy and in certain areas I have interpreted the nests as invasive rather than just Brenner nests within the stroma. I would thus consider this case to represent a malignant Brenner tumor.

Clinically the proliferating Brenner tumor usually occurs in an older patient than the benign type by about 10 years (5). Most patients with proliferating Brenner tumors present with symptoms of pain, backache and/or abnormal vaginal bleeding. The average size of the tumor is 16 cm. and it is almost invariably cystic. The cysts may be single or multilocular, are usually smooth on the external surface, are lined by velvety protrusions and contain a multilocular watery brown fluid. Solid masses within the cyst are rather common. In most proliferating Brenner tumors, the cystic spaces are lined by transitional papillary epithelium which is orderly and shows only focal or minimal atypia and variable numbers of mitoses. Patients with malignant Brenner tumors are usually older than those with proliferating tumors but malignant Brenner tumors have been detected in premenopausal women (8). Patients with malignant Brenner tumors have the same symptoms as those with the proliferating type and the gross tumor is also similar except that hard nodules or masses are more frequent in the malignant form. As noted above, malignant Brenner tumors contain transitional carcinoma cells which invade the stroma. Whether or not, the in-situ-carcinoma form should be considered malignant or a proliferating type is disputed at the present time. Mucin containing cells are frequent in both the proliferating and the malignant types of tumors and mucin is frequently present in the lumens of the cell nests.

#### REFERENCES:

1. Ehrlich, C.E. and Roth, L.M.: The Brenner tumor. *Cancer* 27:332, 1971.
2. Silverberg, S.G.: Brenner tumor of the ovary. A clinico-pathologic study of 60 tumors in 54 women. *Cancer* 28:583, 1971.
3. Arey, L.B.: The origin and form of the Brenner tumor. *Am. J. Obstet. & Gynecol.* 112:91, 1972.
4. Roth, L.M.: Fine structure of the Brenner tumor. *Cancer* 27:1482, 1971.
5. Roth, L.M. and Sternberg, W.H.: Proliferating Brenner tumors. *Cancer* 27:687, 1971.
6. Miles, P.A. and Norris, H.J.: Proliferative and malignant Brenner tumor of the ovary. *Cancer* 30:174, 1972.

7. Hallgrímsson, J. and Scully, R.E.: Borderline and malignant Brenner tumors of the ovary. Acta. Path. Suppl. 233:56, 1972.
8. Hull, M.G.R. and Campbell, G.R.: The malignant Brenner tumor. Obstet. & Gynecol. 42:527, 1973

## . Table 5

Criteria for Proliferating & Malignant Brenner Tumors  
(Hallgrímsson and Scully)

- I. Proliferating (Borderline) Brenner Tumors
  - Type A: Single or several large cysts are lined by proliferating epithelium often papillary ranging in atypicality from none or slight to carcinoma-in-situ. All abnormal epithelium is confined to the cysts and is not in the stroma and mitoses may be numerous.
  - (B) Solid nests or small cysts in the stroma in which the epithelial cells are atypical but are not malignant.
- II. Malignant Brenner Tumors
  - (A) Small cysts or solid nests are lined by or composed of cytologically malignant cells; large cysts may be present; invasion of the stroma by malignant transitional cell. Benign Brenner elements are associated with the malignant epithelium.
  - (B) Same as A except benign Brenner elements are not found.

APRIL 21, 1974 - CASE NO. 13

ACCESSION NO. 19739

MODERATOR'S DIAGNOSIS: Adenocarcinoma of the cervix, mucinous type.

CLINICAL ABSTRACT:

This 44 year old patient had an abnormal pap smear with cells present suspicious for malignancy. Examination revealed cervical erosions and a D&C and conization of the cervix were performed. The cone specimen showed multiple small cysts filled with mucinous material measuring up to .3 cm. The cervical stroma was firm. The endometrial curettings revealed proliferative phase endometrium with mild cystic changes. Following the conization the patient received radiotherapy.

MICROSCOPIC DESCRIPTION:

The overlying squamous epithelium in the cervix shows mild to moderate dysplasia. Beneath this epithelium are irregular gland spaces filled with mucin as well as large pools of mucin lined by cervical stroma and clusters of atypical cells. Many of these pools and lakes of mucin appear to be extruding from abnormal glandular spaces. The intact neoplastic glands are lined by atypical cells with numerous mitoses and enlarged hyperchromatic nuclei. The endocervical surface epithelium blends imperceptibly into enlarged gland spaces lined by neoplastic cells indicating the presence of adenocarcinoma-in-situ. Other glandular structures appear to be invasive. Several glands are lined by cells with red granules in the cytoplasm and goblet cell transformation is noted in several of the enlarged cystic glandular spaces. A mucin stain reveals abundant intracytoplasmic mucin as well as pools of mucin. An argentaffin stain is negative.

DISCUSSION:

The main diagnostic challenge in this case is to distinguish metastatic mucinous carcinoma from a primary mucinous carcinoma of the endocervix. The presence of adenocarcinoma-in-situ is extremely helpful because it proves that the tumor is primary in the cervix. Mucinous hypersecretion can occur in progestogen stimulation of the endocervix as well as in microglandular hyperplasia. However, the abnormal cells lining the glands clearly indicate this is carcinoma. The prognosis in mucinous carcinoma is not well known because of the rarity of the entity, however, in Abell's series 2 of 10 patients were alive at 5 years and 1 of 10 at 10 years (1). Thus, the tumor is rather aggressive as are mucinous carcinomas in other sites.

APRIL 21, 1974 - CASE NO. 14

ACCESSION NO. 20287

MODERATOR'S DIAGNOSIS: Moderately differentiated adenocarcinoma of the endocervix with scirrhous areas

CLINICAL ABSTRACT:

The 58 year old patient was noted to have bleeding from the cervix during examination and a biopsy was obtained. Following the biopsy a total hysterectomy and bilateral salpingo-oophorectomy were performed. The cervix was hard up to the endometrial junction and apparently infiltrated by tumor. Following surgery the patient had cobalt radiotherapy and was seen a few months following the radiation therapy with no evidence of tumor.

MICROSCOPIC DESCRIPTION:

This adenocarcinoma shows several different histologic patterns. In most areas the tumor is a moderately to poorly differentiated adenocarcinoma infiltrating the cervical stroma. In these areas the tumor is composed of poorly formed glands lined by moderately pleomorphic cells with mitoses. There is some crowding and in areas a cribriform pattern is noted. In other areas, the tumor is growing as solid sheets of cells with focal gland formation. The PAS with diastase stain shows abundant mucin both intracellularly and within the glandular spaces. Other areas of the tumor, particularly at the base, show neoplastic cells infiltrating the stroma in an Indian file pattern without apparent glandular formation. In these latter areas there is considerable fibrous response to the tumor cells with little evidence of glandular differentiation. The tumor is deeply invasive and extends to the edge of the sections.

DISCUSSION:

One of the major problems in diagnosing adenocarcinoma of the cervix is to differentiate primary endocervical adenocarcinoma from primary endometrial adenocarcinoma. This can be very difficult but several features may be helpful.

1. Differential curettage to determine the location of the tumor is essential. The presence of carcinoma and benign non neoplastic tissue mixed together does not indicate actual invasion. Before deciding carcinoma is present in either the endometrium or the endocervix, invasion of the stroma of these tissues should be demonstrated. It is common to contaminate the specimen with the tumor during a differential curettage. While differential curettage is extremely helpful in many cases, it does not aid in the situation in which adenocarcinoma is

arising in one place and invading the other secondarily. In this circumstance, search for carcinoma-in-situ can be extremely helpful. Abell has reported that approximately 40% of primary adenocarcinomas of the endocervix will be associated with adenocarcinoma-in-situ in the surrounding glands. Likewise atypical hyperplasia and in-situ in the changes in the endometrium can be helpful if the tumor is a primary endometrial carcinoma.

2. Histochemical staining may be useful (1). Characteristically, adenocarcinoma of the endocervix produces both intracytoplasmic and intraglandular mucin while adenocarcinoma of the endometrium produces mucin within the glandular lumens and on the terminal bars of the cell. Intracytoplasmic mucin is unusual. However, it must be remembered that the entire spectrum of adenocarcinomas found in the cervix can also be found in the endometrium and vice versa.
3. The cell type of the carcinoma (2). It is very unusual to have a primary endometrial carcinoma of the well differentiated endocervical type while it is also unusual to have endometrioid carcinomas primary in the endocervix.

Definition of the primary site of the adenocarcinoma can be achieved in most instances by using the results of the differential curettage, carefully searching the histologic sections for carcinoma-in-situ; determining the cell type of the carcinoma and doing mucin stains. Accurate determination of the primary site is of importance since primary endometrial carcinomas will be treated by surgery and possibly radiation whereas primary endocervical carcinomas are usually treated by radiation alone. If after the above procedures one is still uncertain as to the primary site, and there is definitely tumor in the endocervix, the best course is to treat the patient as if she had a primary adenocarcinoma of the endocervix, since endometrial adenocarcinoma secondarily invading the endocervix will metastasize to the regional lymph nodes in a pattern similar to that of primary endocervical carcinoma.

In summary, this is a moderately differentiated cervical cell type of adenocarcinoma with areas of scirrhous differentiation. The tumor demonstrates the admixing of cell types frequently found in endocervical adenocarcinoma which makes classification somewhat difficult. The prognosis in this case is guarded because of the poor differentiation of the tumor and the extensive infiltration noted in the histologic sections.

REFERENCES:

1. Sorvari, T.E.: A histochemical study of epithelial muco-substances in endometrial and cervical adenocarcinomas. *Acta Pathol. Microbiol. Scand.* 207 (Suppl):1, 1969.
2. Abell, M.R.: Invasive Carcinomas of the Uterine Cervix. In Norris, H.J., Hertig, A.T. and Abell, M.R. Eds: The Uterus IAP monograph #14, Baltimore 1973. The Williams & Wilkins Co. p. 437.

APRIL 21, 1974 - CASE NO. 15

ACCESSION NO. 20304

MODERATOR'S DIAGNOSIS: Metastatic malignant neoplasm, primary undetermined  
(A likely primary is breast)

CLINICAL ABSTRACT:

This patient presented with menometrorrhagia of one year's duration. Pelvic examination revealed a mass in the uterus consistent with a leiomyoma. X-rays showed numerous radiolucent bony lesions suggestive of metastatic carcinoma. Some examiners felt a mass in the breast, others did not. Mammography was negative. Serum calcium, phosphorus and alkaline phosphatase were normal as was the serum electrophoresis. A 5HIAA determination was within normal limits. The uterus was removed and weighed 410 grams. There were numerous small leiomyomas and one large intramural mass thought to be a smooth muscle tumor located in the fundus which was tan and had areas of hemorrhage and central cystic degeneration.

MICROSCOPIC DESCRIPTION:

Infiltrating the myometrium are groups and nests of cells with uniform nuclei and indistinct cytoplasmic borders. Some of the tumor cells are arranged in large sheets while in other areas the tumor cells are in small clusters and groups. The tumor cell nuclei have delicate chromatin and some contain longitudinal grooves or notches. In some areas, the tumor cells are arranged in an acinar like arrangement but definitive Call-Exner bodies are not seen. Vessel invasion is prominent. Examination of the right ovary shows similar neoplastic cells arranged in cords, as single files, and as individual cells mixed with stromal cells. The tumor cells are not forming Call-Exner bodies nor follicle like structures. In focal areas, the tumor cells are arranged in a pattern reminiscent of breast carcinoma.

DISCUSSION:

This malignant neoplasm metastatic to the uterus is difficult to classify. One of the major considerations is whether or not it represents metastatic granulosa cell tumor. I seriously doubt this is granulosa cell tumor because I do not see definitive Call-Exner bodies nor can I find the peripheral palisading of cells at the edges of the tumor nests which I associate with granulosa cell tumors. There is a tendency to diagnose poorly differentiated malignant neoplasms which vaguely resemble granulosa cell tumor as the neoplasm. Many different types of malignant neoplasms have patterns suggestive of granulosa cell tumors and to cause further confusion at least 11 different types of histologic patterns have been described for granulosa cell tumor itself (1). These include the so-called cylindroid, sarcomatous, pseudo-adenomatous, folliculoid and others. Tumors which resemble granulosa cell tumors, but which do not have definitive histologic criteria, should be

designated simply as tumor unclassified or sex cord tumors unclassified.

Granulosa cell tumors have little variation in microscopic appearance and are composed of monotonous uniform round cells with slightly granular eosinophilic cytoplasm and indefinite cellular margins. The nuclei are small without atypia and frequently contain a longitudinal groove. Call-Exner bodies are found in granulosa cell tumors and are an important diagnostic feature. Call-Exner bodies should not be confused with the acinar structures of adenocarcinoma. They are formed by granulosa cells with the nuclei toward the center of the Call-Exner body and the bulk of the cytoplasm more peripheral (2). In the center is pink material or a degenerating cell but not a blood vessel. This central material is basement membrane matrix. Call-Exner bodies, as opposed to acini of adenocarcinoma, have an indefinite central cytoplasmic margin which is fuzzy rather than sharp. Acini are not formed. Granulosa cells are negative for glycogen and mucin and mitoses are very rare and difficult to find. Tumors which do not conform to these histologic criteria should not, in my opinion, be diagnosed as granulosa cell tumors.

Granulosa cell tumors are rarely malignant or aggressive. A study at the Armed Forces Institute by Norris and Taylor, using life table survival statistics, showed patient survival for granulosa cell tumor to be 97% at five years and 93% at ten years (2). Very few patients die from granulosa cell tumors and aggressive tumors almost always involve pelvic recurrences or metastases to the pelvis rather than widespread distant metastases. I have never heard of a granulosa cell tumor with extensive bone metastases as are apparently present in this case.

In summary, strict criteria should be used to diagnose granulosa cell tumors and tumors which do not meet the histologic criteria should not be classified as granulosa cell tumors or granulosa cell carcinomas. Widely metastasizing tumors are unlikely to be granulosa cell tumors. On the basis of the above criteria, I do not think that the tumor in this patient's uterus is a granulosa cell tumor.

The second consideration in the differential diagnosis is metastatic breast carcinoma. The tumor nests are similar to those found in metastatic breast carcinoma and nuclear grooves can be found in breast carcinoma cells. In addition, a low mitotic rate is rather characteristic of some types of ductal and lobular carcinoma. The negative mammogram is of course, interesting but I think it probably should be repeated and other techniques such as thermography or xerography considered. On the basis of the histologic findings, the extensive bony metastases, and the difficulty of detecting primary breast carcinoma, I think the primary is most likely in the breast.

The third possibility is a carcinoid. The cords and ribbon like arrangement of the tumor as well as the nuclear uniformity suggest carcinoid. However, the argentaffin stain is negative, as is the 5HIAA determination, and the patient does not have the carcinoid syndrome. The histologic pattern of the tumor in the ovary does not particularly resemble carcinoid although carcinoid is very difficult to absolutely exclude. Ovarian carcinoids arise most often from respiratory and gastrointestinal epithelium in cystic teratomas but can arise in other types of teratomas, in mucinous tumors, and can occur as primary tumors in the ovary. They may also be metastatic from other sites. Small intestinal carcinoids are particularly notorious for giving rise to large ovarian metastases. All the primary ovarian carcinoids thus far reported have been unilateral and only one has metastasized. Approximately a third of primary ovarian carcinoid are associated with the carcinoid syndrome in the absence of metastases (3).

Other considerations in the differential diagnosis would be myeloma but the tumor cells do not resemble plasma cells and the MGP stain was negative. Another consideration is metastatic paraganglioma because of the ball arrangement of some of the tumor cell mass (4). However, these are not well formed zell-ballen and the histologic pattern does not particularly resemble paraganglioma to me.

REFERENCES:

1. Novak, E.R.: Feminizing gonadal stromal tumors. *Obstet. & Gynecol.* 38: 701, 1971.
2. Norris, H.J. and Taylor, H.B.: Prognosis of granulosa-theca tumors of the ovary. *Cancer* 21:255, 1968.
3. Scully, R.E.: Recent progress in ovarian cancer. *Hum. Pathol.* 1:73, 1970.
4. Abell, M.R., et al.: Tumors of the peripheral nervous system. *Hum. Pathol.* 1:503, 1970.

FOLLOW-UP: (Dr. Charles Haskell)

Most recent information which was unavailable to Dr. Richard Kempson at the time of the seminar is as follows: "Examination of bone marrow at UCLA in September 1973 revealed tumor cells and radiograph exhibited multiple destructive bone lesions. The patient was treated with alkeran and is reported to be relatively stable with good clinical response to treatment as of September 1974. The primary site of the neoplasm has not yet been clearly delineated."

APRIL 21, 1974 - CASE NO. 16

ACCESSION NO. 11830

MODERATOR'S DIAGNOSIS: Papillary adenofibroma of the endometrium.

CLINICAL ABSTRACT:

This 71 year old female presented with a history of intermittent vaginal bleeding of 8 months' duration. A hysterectomy was done. Within the endometrial cavity there was a 4.0 x 2.5 cm. mass of cystic, papillary and nodular tissue attached to the posterior and lateral walls of the uterus.

MICROSCOPIC DESCRIPTION:

Present in the endometrial cavity is a mass containing stroma and epithelium thrown up into polypoid branching masses with prominent cleft formation. The cystic spaces and clefts form blunt papillary folds which protrude into the cystic spaces. Endocervical, endometrial and squamous epithelium are all focally present lining the papillae. Some of the papillae are denuded of epithelium. The stroma is hyalinized and focally myxoid with spindle cells in a whorled pattern. Mitoses are very rare and there is no evidence of atypia or malignancy.

DISCUSSION:

Papillary adenofibroma appears to be the benign counterpart of the malignant mixed Mullerian tumor. It might conceivably be called a benign mixed Mullerian tumor but such terminology could lead to confusion with malignant mixed Mullerian tumor. Since the lesion has many similarities to the adenofibroma of the ovary, it is best designated as a papillary adenofibroma, as suggested by Abell who described 3 cases arising in the cervix (1). Papillary adenofibroma is a lesion in which there is both mesenchymal and epithelial proliferation and both elements are histologically benign. Clinically, patients with this lesion present with vaginal bleeding and are usually in an older age group. The mass may protrude from the cervix. All adenofibromas thus far reported have been benign with the exception of one of the cases reported by Vellios, et al. which contained focal adenocarcinoma in one portion of the lesion (2).

The differential diagnosis must include endometrial polyps but the polypoid masses within cystic spaces, the clefting, the hyalinized stroma and the club shaped papillae should serve to separate this lesion from the usual endometrial polyp. In addition, papillary adenofibromas contain endocervical as well as squamous and endometrial epithelium. Malignant mixed Mullerian tumors have a similar proliferation of epithelial and mesenchymal elements. However, both the epithelium and the mesenchyme are malignant in malignant Mullerian tumors while both elements are benign in the papillary adenofibroma. Submucous adenomyoma contains both smooth muscle and endometrial glands and has some

resemblance to the papillary adenofibroma. However, it does not show the intracystic papillary clubbing and the clefting which are characteristic features of papillary adenofibroma. The stroma of papillary adenofibroma can be cellular and myxoid and care must be taken not to confuse it with embryonal rhabdomyosarcoma or the other sarcomas.

REFERENCES:

1. Abell, M. R.: Papillary adenofibroma of the uterine cervix. Am. J. Obstet. and Gynec. 110:990, 1971.
2. Vellios, F., et al.: Papillary adenofibroma of the uterus. Am. J. Clin. Path. 60:543, 1973.

APRIL 21, 1974 - CASE NO. 17

ACCESSION NO. 20565

MODERATOR'S DIAGNOSIS: Sex cord mesenchymal tumor with annular tubules

CLINICAL ABSTRACT:

This 25 year old female had a 4 year history of irregular menses with periods of amenorrhea. A dilatation and curettage revealed mild hyperplasia of the endometrium. Three years prior to admission a left adnexal mass was noted which slowly increased in size. At the time of operation there was a 6 cm. mass replacing the left ovary and involving the posterior leaf of the broad ligament. The right ovary was unremarkable. The tumor was solid, bosselated, tan-yellow, and measured 6 cm. in diameter.

MICROSCOPIC DISCUSSION:

The tumor is composed of rounded epithelial nests of varying size containing eosinophilic hyaline bodies with barely perceptible lamination. These hyaline bodies coalesce to form complex networks within some of the nests and are continuous with the basement membrane material outside the nests. This matrix also separates many of the nests of cells. Most of the nuclei of the tumor cells are arranged at the base of the cells and have small inconspicuous nucleoli. Two patterns can be discerned in the epithelial masses: Firstly, closed tubules with hyaline bodies at the center, and secondly, a network of continuous tubules arranged about numerous hyaline bodies. Longitudinal solid tubules are also noted. Between some of the nest there is ovarian stroma, and foci of calcification are scattered about the tumor. The hyaline material is PAS positive and congo red negative.

DISCUSSION:

Sex cord mesenchymal tumor with annular tubules is a distinctive and rare ovarian tumor which should be separated from granulosa cell tumor and Sertoli cell tumor (1). The tumor has been reported to occur in patients from 11 - 64 years of age, and some, but not all, of the patients with this tumor also have the Peutz-Jegher syndrome with oral melanosis and gastrointestinal hamartomatous polyps. Sex cord mesenchymal tumor with annular tubules is also the most common ovarian tumor encountered in patients with the Peutz-Jegher syndrome. Four patients in Scully's series (1) had endometrial cystic hyperplasia associated with sex cord tumor and one patient was sterile. Grossly, sex cord mesenchymal tumors with annular tubules are soft to firm, yellow, and solid. Bilateral involvement occurs in about 20% of the cases. A germinoma has been found in the opposite ovary in one patient with an XY genotype. The tumors range from microscopic up to 17 cm. and may be multiple.

The neoplasm that sex cord mesenchymal tumor most resembles is granulosa cell tumor, which may rarely have tubules and can contain hyaline bodies and plaques of basement material, although these structures are unusual (1,2). However, granulosa cell tumors do not undergo calcification and the nuclei in the sex cord tumor do not have the prominent nuclear grooves which are seen in granulosa cell tumors. Sertoli cell tumors are not calcified but do contain tubules which look similar to those in the annular tumor. However, hyaline plaques are most unusual in pure Sertoli cell tumors. Topographically sex cord mesenchymal tumor appears to be a granulosa cell tumor which is growing in a tubular fashion similar to the Sertoli cell tumor. Sex cord mesenchymal tumor is not a gynandroblastoma which has mature granulosa cells with Call-Exner bodies and typical Sertoli tubules with Leydig cells containing Reinke crystalloids. Leydig cells are not found in the sex cord mesenchymal tumor. Some areas of the sex cord tumor resemble a Brenner tumor, however, the mucin producing cells characteristic of Brenner tumor are not present. In addition, the tumor cells do not look like transitional cells, tubular structures with peripheral nuclei are not seen in the Brenner tumor, and nuclear grooves not found in the sex cord tumor, are characteristic of the Brenner tumor.

Sex cord mesenchymal tumor with annular tubules resembles gonadoblastoma since both tumors contain calcium and have PAS positive hyaline material between the cells and around the tumor cell nests and tubules (3). However, germ cells are always present within the nests in gonadoblastoma and are not found in sex cord tumors, this feature allows easy separation of the two tumors. Gonadoblastoma frequently contains Leydig-like cells in the stroma. We have recently completed an ultrastructural study of gonadoblastoma and are finishing a similar study of sex cord tumors (4). The hyaline material in both tumors is similar and appears to be formed by the Sertoli/granulosa type cells in the nests and tubules.

Thus far, all sex cord mesenchymal tumors have been benign. Although many of the patients who have sex cord mesenchymal tumor also have the Peutz-Jegher syndrome, it is not found exclusively in such patients. The present patient apparently does not have the Peutz-Jegher syndrome. Approximately 5% of females with the Peutz-Jegher syndrome have ovarian tumors, which are of a wide variety of types, but the most common type is sex cord tumor with annular tubules.

Reproduced in Table 6 is our working classification of the sex cord stromal tumors of the ovary. This is based on the recent WHO classification as well as the FIGO classification (5). It is hoped this international classification will be universally used. Sex cord tumor is placed with the unclassified tumors since its histogenesis is obscure. The sclerosing stromal

tumor is a benign sex cord tumor recently described by Chalvardjian and Scully (6). It is similar to the fibromas and thecomas but differs from them by having marked vascularity, cellular pleomorphism, and a prominent tendency to undergo sclerosis. The category of lipid cell tumor is reserved for those tumors composed of cells with clear to eosinophilic cytoplasm in which crystalloids of Reinke cannot be found and which are not luteomas. Interestingly, Sternberg and Roth have recently described sex cord tumors arising from the stroma which contain neoplastic Leydig cells with cytoplasmic crystalloids of Reinke (7,8). We agree that these latter tumors should be classified separately as stromal Leydig cell tumors or pure Leydig cell tumors, non hilar type, and the term lipid cell tumor should be used only for neoplasms whose histogenesis is uncertain.

REFERENCES:

1. Scully, R. E.: Sex cord tumor with annular tubules. A distinctive ovarian tumor of the Peutz-Jeghers syndrome. *Cancer* 25:1107, 1970.
2. Norris, H. J. and Taylor, H. B.: Prognosis of granulosa-theca tumors of the ovary. *Cancer* 21:255, 1968.
3. Scully, R. E.: Gonadoblastoma. A review of 74 cases. *Cancer* 25: 1340, 1970.
4. Hou-Jensen, K. and Kempson, R. L.: The ultrastructure of gonadoblastoma and dysgerminoma. *Hum. Path.* 5:79, 1974.
5. Serov, S. F. and Scully, R. E.: Histologic typing of ovarian tumors. Geneva 1973 World Health Organization.
6. Chalvardjian, A. and Scully R. E.: Sclerosing stromal tumors of the ovary. *Cancer* 31:664, 1973.
7. Sternberg, W. H. and Roth, L. M.: Stromal-Leydig cell tumor and non-neoplastic transformation of ovarian stroma to Leydig cells. *Cancer* 32: 940, 1973.
8. Roth, L. M. and Sternberg, W. H.: Pure Leydig cell tumor, non hilar type. *Cancer* 32:952, 1973.

TABLE 6

CLASSIFICATION OF SEX CORD TUMORS OF THE OVARY  
(WORLD HEALTH ORGANIZATION) (5)

## Sex Cord Stromal Tumors

- A. Granulosa-stromal cell tumors
  - 1. Granulosa cell tumor
  - 2. Thecoma fibroma group
  - 3. Stromal luteoma
  - 4. Sclerosing stromal tumor
- B. Sertoli-Leydig cell tumors (Androblastoma)
  - 1. Well differentiated
    - a) Tubular adenoma (pure Sertoli cell tumor)
    - b) Tubular adenoma with lipid storage (Sertoli cell tumor with lipid storage)
    - c) Tubular adenoma with Leydig cells (Sertoli-Leydig cell tumor)
    - d) Leydig cell tumor; Hilar cell tumor
  - 2. Intermediate differentiation
  - 3. Poorly differentiated
- C. Lipid (lipoid) cell tumor (of indeterminate cell type)
- D. Gynandroblastoma
- E. Unclassified
  - 1. Tumor with annular tubules
  - 2. Too poorly differentiated to identify cell types

APRIL 21, 1974 - CASE NO. 18

ACCESSION NO. 20562

MODERATOR'S DIAGNOSIS: Mullerian adenosarcoma of the uterus (heterologous element of rhabdomyosarcoma)

CLINICAL ABSTRACT:

This 43 year old female had regular menses until 6 weeks prior to admission when she developed continuous vaginal bleeding. Examination revealed a fungating, friable, soft mass which filled the upper vagina. The hysterectomy specimen showed the cervix to be replaced by a 6.0 x 6.0 x 5.0 cm. fungating, necrotic, papillary tumor. On opening the endocervical canal, the tumor tissue extended up into the uterine cavity.

MICROSCOPIC DESCRIPTION:

This tumor is infiltrating and replacing portions of the endometrium. The tumor cells are spindle to cuboidal and contain numerous mitoses which in some areas exceed 10 per 10 high power fields. Some of the neoplastic cells have elongate eosinophilic cytoplasm and definite cross striations can be identified in most of these tumor cells. Other tumor cells have rather clear cytoplasm with indistinct margins. Focally, there is edema with a more myxoid appearance to the stromal cells. These cells appear to be mesenchymal and are histologically malignant. Embedded within the mesenchymal portion of the tumor are glandular structures which are lined by histologically benign cells. Surrounding these glands is a collar of edematous spindle stroma. Histologically, the mesenchymal element of the tumor appears to be a combination of rhabdomyosarcoma, leiomyosarcoma and undifferentiated sarcoma. The sarcomatous portion of the tumor also infiltrates the myometrium superficially in one area.

DISCUSSION:

The differential diagnosis of this neoplasm would include pure rhabdomyosarcoma of the uterus. Rhabdomyosarcomas do occur in the uterus, most often in association with malignant mixed Mullerian tumors, but they may be pure as in embryonal rhabdomyosarcoma of the cervix seen most frequently in childhood and in the pleomorphic rhabdomyosarcoma occasionally encountered in adults (1,2). However, it is not entirely clear that all of the mesenchymal elements in this tumor are rhabdomyosarcoma and this could be a mixed leiomyosarcoma and rhabdomyosarcoma. In any case, the presence of glands in the tumor makes the diagnosis of pure sarcoma difficult. One could conclude that the glands are normal endometrium which has been surrounded by the mesenchymal proliferation but it would be most unusual for a malignant mesenchymal tumor to surround rather than obliterate normal endometrial glands. Malignant mixed Mullerian tumor also has to be considered but the epithelial

elements in malignant mixed Mullerian tumor are always malignant. This neoplasm, then, does not fit well into any of the previously described types of uterine sarcomas. I have observed neoplasms of this type and have been puzzled as to what terminology to use for them.

Recently, Clement and Scully have collected seven or eight tumors of this type and have coined the term Mullerian adenosarcoma of the uterus to describe them (3). The term encompasses the Mullerian origin of the neoplasm, the sarcomatous nature of the mesenchymal portion and the benign nature of the epithelial elements. Characteristically, Mullerian adenosarcoma of the uterus occurs as large masses in the uterus of older women. The most common presenting symptom is abnormal vaginal bleeding. The benign glandular elements are surrounded by a collar of compressed cells while the malignant stromal elements may be any of a number of different sarcomas including both heterologous and/or homologous types. Rhabdomyosarcoma has been observed in these neoplasms by Clement and Scully. It is important to separate Mullerian adenosarcoma from the pure sarcomas and from malignant mixed Mullerian tumors since Mullerian adenosarcoma has a better prognosis. Most of the patients with this neoplasm do well and apparently the only patients to develop metastases are those who have deeply invasive and extensive neoplasms at the time of hysterectomy. Tumors which are only superficially invasive rarely ever metastasize. This is in contrast to malignant mixed Mullerian tumor which may develop metastases even though the tumor is only superficially invasive. If the sections are representative of the extent of invasion, I would expect a good prognosis for this patient. However, the gross photographs suggest rather extensive invasion.

Three different types of uterine mixed Mullerian tumors have now been described. Firstly, the tumor in which both sarcoma and carcinoma are present, i.e. glandular and mesenchymal elements are both malignant, is designated as malignant mixed Mullerian tumor. A second type, composed of sarcoma with benign glands, is designated as Mullerian adenosarcoma. A third type, in which both the stroma and the glands are benign, is designated as papillary adenofibroma. Theoretically, there should be a neoplasm with carcinoma and benign stromal elements. Although this probably occurs, it is obvious that separation from ordinary carcinoma is almost impossible and such a tumor would be difficult to recognize.

REFERENCES:

1. Donkers, B. et al.: Rhabdomyosarcoma of the corpus uteri, Am. J. Obstet. & Gynecol. 114:1025, 1972.
2. Hilgers, R.D.: Embryonal rhabdomyosarcoma (botryoid type) of the vagina, Am. J. Obstet. & Gynecol. 107:484, 1970.
3. Clement, R. and Scully, R.E.: Mullerian adenofibroma. To be published Cancer 1974.

APRIL 21, 1974 - CASE NO. 19

ACCESSION NO. 12141

MODERATOR'S DIAGNOSIS: Plexiform tumor (tumorlet) of the uterus.

CLINICAL ABSTRACT:

This 44 year old patient had complained of irregular menstrual periods and prolonged heavy flow for many years. She stated that she never had a regular menstrual cycle. A hysterectomy and bilateral salpingo-oophorectomy was done. Serosal nodules, measuring up to 0.6 cm. were present on the uterus and there was a bulging pink-tan 2 cm. mass present in the fundus. The entire myometrium was speckled with innumerable slightly raised, gray-white areas, measuring 0.2-0.6 cm. in diameter. Both ovaries contained endometriosis.

MICROSCOPIC DESCRIPTION:

Within the endometrium and the myometrium are nodular masses of cells which tend to be sharply demarcated from the surrounding tissues. In the endometrium, the masses appear to be infiltrating the endometrium while they are more circumscribed in the myometrium. Within the groups, the individual cells have indistinct cytoplasm and crumpled but bland nuclei. In most groups, the nuclei are arranged in elongated cords and tend to be crowded together and separated by hyaline material. Nucleoli are inconspicuous and mitoses are not found. Blood vessels and capillaries are not prominent. Overall, the histologic pattern is distinctive and not indicative of malignancy. By trichrome stain, the tumor cell cytoplasm is red and reticulin staining shows groups of cells surrounded by reticulin.

DISCUSSION:

Plexiform tumors of the uterus are benign lesions, usually found incidentally in hysterectomy specimens. There have been approximately thirty-five cases reported (1,2,3,4,5). Characteristically, plexiform tumors are present at the endometrial-myometrial junction and occasionally are found in both the endometrium and the myometrium. It is most unusual for them to be as large and diffuse as in this case, and I know of only one other instance with this degree of involvement and apparent multicentric pattern. There are no known symptoms from the lesion and it seems to occur most commonly in women older than age forty. All except one of the reported patients have had leiomyomas as well as the plexiform tumor (6). The histogenesis of plexiform tumors is uncertain; it has been suggested that they are vascular tumors, either glomus type or capillary hemangiomas. In one of the cases reported from Memorial Hospital, a plexiform tumorlet developed in a focus of adenomyosis suggesting endometrial stromal origin (5). The tumor cells closely resemble normal endometrial stromal cells and their frequent occurrence at

the junction between the endometrium and myometrium also supports a stromal origin. However, there is no proof that these are indeed stromal cells. The paucity of vascular spaces and the lack of resemblance to other vascular tumors as well as the pattern of reticulin fibers makes it extremely unlikely that these are hemangiomas, glomus tumors or hemangiopericytomas. A recent ultrastructural study suggests smooth muscle origin because of fibrils in the cytoplasm of the tumor cells (6). However, basement membranes, a feature of normal smooth muscle, were not found. Fixation for the ultrastructural studies was not ideal, and confirmation of the findings should be obtained. There is some resemblance between plexiform tumors and the so-called "bizarre" smooth muscle tumors. We think plexiform tumor is a better name than plexiform tumorlet because the lesions can be large as in this case.

The differential diagnosis of plexiform tumor would include the bizarre leiomyomas since this form of smooth muscle tumors may have a variety of different histologic patterns and, indeed, plexiform tumor may be derived from smooth muscle. Another lesion to be considered in the differential diagnosis is adenomatoid tumor which can involve the uterus. When it does, it most commonly occurs near the serosa, but can be located deeper in the myometrium. Plexiform tumor has an entirely different histologic pattern than the glandular structures embedded in connective tissue and smooth muscle characteristic of adenomatoid tumor. The importance of recognizing plexiform tumors is not to confuse them with malignant neoplasms particularly metastatic carcinoma, and to recognize them as benign harmless lesions.

#### REFERENCES:

1. Bader, L.V.: Multicentric plexiform tumorlets of the uterus, *Pathology* 3: 167, 1971.
2. Cera, P.J.: Plexiform tumorlet of the uterus. *Am. J. Clin. Path.* 59: 263, 1973.
3. Budinger, J.M. and Greene, R.R.: A distinctive tumor of undetermined origin. *Cancer* 17:1155, 1964.
4. Patchefsky, A.S.: Plexiform tumorlet of the uterus. Report of a case. *Obstet. & Gynecol.* 35:592, 1970.
5. Larlig, G.G. et al.: Plexiform tumorlets of endometrial stromal origin. *Amer. J. Clin. Pathol.* 44:32, 1965.
6. Goodhue, W.W. et al.: Smooth muscle origin of uterine plexiform tumors. *Arch. Pathol.* 97:263, 1974.

APRIL 21, 1974 - CASE NO. 20

ACCESSION NO. 20056

MODERATOR'S DIAGNOSIS: Extramedullary myeloblastoma (granulocytic sarcoma, chloroma).

CLINICAL ABSTRACT:

This 27 year old Caucasian female presented with a pelvic mass of five months' duration. Some years prior to admission she had had bilateral mastectomies for malignant tumors. A blood count on admission showed a white count of 10,400 with 25% blast forms. At laparotomy, there was a large firm pelvic mass arising from the uterus and involving loops of small bowel, the colon, and the side walls of the pelvis. The liver and spleen appeared normal, although both were slightly enlarged. There were numerous tumor implants over the omentum. Grossly, the tumor was green and involved, and markedly distorted, the uterus and both adnexa so that the ovaries could not be recognized. It was irregular, focally friable, necrotic, and contained gelatinous thick material.

MICROSCOPIC DESCRIPTION:

The myometrium and endometrium are infiltrated by cords and files of cells which do not form cohesive masses. The nuclei are vesicular, irregular, and frequently indented with overlapping nuclear segments. Nuclear moulding is prominent and nucleoli are inconspicuous. Mitoses are easily found. In some cells the cytoplasm is indistinct, while in others it is more abundant and eosinophilic. Eosinophilic myelocytes are mixed amongst the tumor cells. The naphthol-ASD-chloroacetate esterase stain is positive in many of the tumor cells and characterized by bright red cytoplasmic staining. The MGP stain is negative.

DISCUSSION:

One of the most important considerations in the differential diagnosis of extramedullary myeloblastoma involving the uterus is stromal sarcoma. In stromal sarcoma, however, the nuclei are more regular, the chromatin pattern is not as coarse, the ASD-chloroacetate stain (esterase stain) is negative, eosinophils are rarely found, and the tumor cells are cohesive with scant cytoplasm. Histiocytic lymphoma is also a consideration. However, the tumor cells in this case have too little cytoplasm for the usual histiocytic lymphoma, the nucleoli are not prominent as would be expected, and the naphthol-ASD-chloroacetate stain is negative in histiocytic lymphoma. Plasma cell myeloma is unlikely since the morphology of the tumor cells does not resemble that of plasma cells, the esterase is positive, and the MGP stain is negative, which is exactly the reverse of the histochemical reactions characteristics

expected in plasma cell myeloma. Undifferentiated carcinoma must also be considered but can be ruled out with the histochemical stains. In addition, eosinophils are present in this tumor in large numbers, a feature which would be most unusual for all the tumors discussed above. Therefore, the combination of the morphology, the positive ASD-chloroacetate esterase stain, and the negative MGP stain indicate this is extramedullary myeloblastoma.

Extramedullary tumors of myelogenous origin are often designated as granulocytic sarcoma although extramedullary myeloblastoma is a preferable term (1,2,3). When the tumor masses are green, they are often designated as chloromas. The green color present in some extramedullary myeloblastomas is due to the presence of the enzyme myeloperoxidase which occurs in myelogenous cells (1). The fact that some extramedullary myeloblastomas are green and others are not, is probably due to the amount of this heme enzyme present and/or its oxidation state. The green color fades on exposure to air and may be re-induced by hydrogen peroxide. Myeloblastomas are not all that rare. A recent series from Harvard contained fifteen cases in a series of 478 cases of leukemia (1). They may occur in chronic myelocytic leukemia as well as in acute myelocytic leukemia and the presence or absence of the green color has nothing to do with the cell type. Myeloblastomas may be found within any organ and are usually discovered in patients with known myelogenous leukemia, but rarely they may precede the leukemic manifestations in the peripheral smear and marrow by as long as twenty-five months, thereby causing diagnostic problems (4,5). However, the time interval is usually shorter. They usually occur in young patients. Myeloblastomas are most frequently found in close proximity to bone, particularly the vertebral column and in epidural structures. This frequently results in cord involvement by the tumor. Ovarian involvement is also common in myeloblastoma, and in one series six of eight females with myeloblastoma had involvement of the gonads (3). Other common sites for myeloblastoma to occur are the mediastinum, the breast lymph nodes and soft tissue.

Diagnostic problems arise for the pathologist when extramedullary myeloblastomas develop in extramedullary tissues concurrent with or preceding the leukemic manifestations in the peripheral smear and bone marrow (6,7,8,9). This can be a particularly acute problem in lymph nodes and breast, where errors in classification of the malignant process can easily be made. The most common tumors to be confused with myeloblastomas are histiocytic lymphoma and undifferentiated carcinoma, particularly carcinomas in which the tumor cells are arranged in an "indian file" pattern (6,7).

Some tips to help avoid errors in diagnosis in conjunction with myeloblastomas are as follows:

1. Think of the possibility of extramedullary myeloblastoma in all undifferentiated malignancies; particularly look for eosinophils in all undifferentiated neoplasms and in neoplasms in which the diagnosis of histiocytic lymphoma is considered.
2. Always do imprints when lymph node biopsies are performed. Imprints stained with Romanofsky's stain will help identify myelocytic differentiation.
3. Utilize the ASD-chloroacetate stain for esterase whenever the possibility of myeloblastoma is considered. The stain can be done on paraffin sections and visualizes esterase specific for neutrophils, neutrophil precursors, and mast cells. We use the Leder modification of the procedure originally described by Maloney et al. (10). Cells containing the esterase show bright red cytoplasmic staining with this technique. The enzyme is resistant to histologic procedures and will persist after prolonged storage in paraffin.
4. Electron microscopy can be helpful in identifying characteristic myelocytic granules in tumor cells.

In summary, extramedullary myeloblastoma can be accurately diagnosed by careful histologic examination, histochemical techniques, and imprints. Although rare, it must be considered whenever undifferentiated neoplasms are encountered.

#### REFERENCES:

1. Muss, H.B. and Moloney, W.C.: Chloroma and other myeloblastic tumors. Blood 42:721, 1973.
2. Wiernik, P.H. and Seyrick, A.A.: Granulocytic sarcoma (chloroma). Blood 35:361, 1970.
3. Liu, P.E. et al.: Autopsy study of granulocytic sarcoma (chloroma) in patients with myelogenous leukemia, Hiroshima-Nagasaki 1949-1969. Cancer 31:948, 1973.
4. Mason, T.E. et al.: Granulocytic sarcoma (chloroma) two years preceding myelogenous leukemia. Cancer 31:423, 1973.

5. Lusher, J.M.: Chloroma as a presenting feature of acute leukemia. *Am. J. Dis. Child.* 108:62, 1964.
6. Pascoe, H.R.: Tumors composed of immature granulocytes occurring in the breast in chronic granulocytic leukemia. *Cancer* 25:697, 1970.
7. Garfinckle, R.S. and Bennett, D.E.: Extramedullary myeloblastic transformation in chronic myelocytic leukemia simulating a co-existent malignant lymphoma. *Amer. J. Clin. Pathol.* 51:638, 1969.
8. Gralnick, H.R. and Dettman, K.: Development of myeloblastoma with massive breast and ovarian involvement during remission in acute leukemia. *Cancer* 24:746, 1969.
9. Lancet editorial: Chloroma confusion. May 19, 1973, p. 1099.
10. Leder, L.D.: The selective enzymocyto-chemical demonstration of neutrophil myeloid cells and tissue mast cells in paraffin sections. *Klinische Wochenschrift* 42:553, 1964.

APRIL 21, 1974 - CASE NO. 21

ACCESSION NO. 20542

MODERATOR'S DIAGNOSIS: Endometrial hyperplasia with intraglandular morules (metaplastic change).

CLINICAL ABSTRACT:

This 32 year old female presented with uterine bleeding of three months' duration. A D&C and then a total hysterectomy were performed. The endocervical lining and the endometrial mucosa appeared diffusely hemorrhagic and focally roughened.

MICROSCOPIC DESCRIPTION:

Some of the tissue fragments in the curettings are normal proliferative endometrium, while other fragments contain increased numbers of glands with focal budding and crowding. In these latter areas, there are sheets of bland cells with regular nuclei and abundant cytoplasm replacing portions of the glands and extending out from the glands into the stroma. Necrosis is present in some of these sheets of cells but mitoses are very rare. No malignant criteria can be found. Some of the cells are spindled, but no intercellular bridges and no keratin can be identified. The overall appearance of these sheets of cell suggest they originate from the glands and grow outward into the stroma, resulting in fusion of the masses. In the hysterectomy specimen, the endometrium shows less active hyperplasia, but the morules are still present.

DISCUSSION:

Intraglandular morules are an important lesion because they may be misdiagnosed as carcinoma. The sheetlike arrangement of these metaplastic cells can cause obliteration of the endometrial architecture similar to that seen in well differentiated adenocarcinoma with squamous metaplasia. However, the cells are cytologically bland and do not demonstrate malignant criteria. The glands associated with the morules are also benign. The cells in the morules do not contain mitoses, there is no pleomorphism, and the cells are uniform with abundant cytoplasm. Although well differentiated adenocarcinoma may have bland metaplastic areas such as is seen in squamous metaplasia, the glandular structures in adenocarcinoma are malignant, unlike those seen in association with morules.

Another malignant neoplasm which may be confused with morule formation is mixed adenocarcinoma and squamous cell carcinoma. In that entity, both elements are neoplastic and there are malignant criteria in both the adenomatous and squamous cells. Such features are not found in this case. Pure squamous cell carcinoma may also occur in the endometrium but intercellular

bridges and/or keratin must be demonstrated before diagnosing a malignant neoplasm as squamous cell carcinoma (1).

Other types of metaplasia can occur in the endometrium and resemble morules (2). One of these is the so-called papillary surface metaplasia in which the cell cytoplasm is eosinophilic and abundant, and the nuclei are large, regular, and vesicular without atypia. Such eosinophilic surface metaplasia may be papillary and can be confused with so-called carcinoma-in-situ of the endometrium. However, there is no nuclear atypia as would be present in carcinoma-in-situ. Surface eosinophilic metaplasia probably represents a regenerative phenomenon and is often seen in patients receiving estrogens. Tubal metaplasia may also be found in the endometrium. It is characterized by cells which have abundant eosinophilic cytoplasm, bland vesicular nuclei, and cilia. These cells line glands. Benign squamous metaplasia may also occur in the endometrium, either in association with estrogen effect or in hyperplasia (3). Benign squamous metaplasia has histologic similarities to morules except that intercellular bridges and/or keratin are present, which identify the cells as squamous. Lastly, since sheets of cells are present in morules, confusion with undifferentiated carcinoma of the endometrium is possible. Close examination of the process at high power should allow easy separation between morules and undifferentiated carcinoma.

The etiology of morules is not known. We have observed the process more frequently in women receiving exogenous estrogen therapy and there may be a relationship to hormone therapy. Morules have been designated as squamous metaplasia because of the resemblance of the cells to squamous cells. However, we think the term squamous metaplasia should be limited to those processes in which the cells demonstrate keratin production and/or intercellular bridges. These are not found in intraglandular morules. The relationship of morules to squamous metaplasia is unknown. The term adenocanthosis has also been suggested, but we do not like this term because of its similarity to adenocanthoma (4).

Dutra has clearly described morules arising from the columnar cells of the endothelial glands and suggested that the process represents a manifestation of the metaplastic potential of the Mullerian epithelium of the endometrium (5). We also think this is most likely a metaplastic process and do not think it is related to neoplasia. There is no evidence that it is a pre-malignant process.

The terminology for carcinomas in the endometrium containing squamous epithelium is somewhat confused. The term adenocanthoma, in my opinion, should not be used since it has been used both for those adenocarcinomas in which there is bland or benign squamous metaplasia in association with the adenocarcinoma, and for mixed adeno and squamous carcinoma. We prefer

to label such tumors as adenocarcinoma with squamous metaplasia. Mixed carcinomas are composed of a combination of adenocarcinoma and squamous cell carcinoma (6). It is important to separate adenocarcinoma with squamous metaplasia and mixed carcinomas, because the prognosis is considerably different. In a recent study by Silverberg of 148 cases of malignancy involving the endometrium, 48% were pure adenocarcinoma, 30% were adenocarcinoma with squamous metaplasia, 17% were mixed adeno- and squamous carcinoma, and 5% were clear cell carcinoma (7). The prognosis for pure adenocarcinoma was 57% at five years, 83% at five years for adenocarcinoma with squamous metaplasia, and only 35% at five years for mixed carcinomas. Mixed carcinomas have a poor prognosis, a greater incidence of invasion, and are seen in somewhat older women. They have roughly the same prognosis as the poorly differentiated and anaplastic carcinomas of the endometrium. For these reasons, adenocarcinoma with squamous metaplasia, which has an excellent prognosis should be carefully and sharply separated from the mixed carcinomas. Both types of carcinoma should be separated from morules which are benign and associated with benign endometrium.

#### REFERENCES:

1. White, A.J. et al.: Primary squamous cell carcinoma of the endometrium. *Obstet. & Gynecol.* 41:912, 1972.
2. Vellios, F.: Endometrial hyperplasias, precursors of endometrial carcinoma. *Pathol. Ann.* 7:201, 1972.
3. Baggish, M.S. and Woodruff, J.D.: The occurrence of squamous epithelium in the endometrium. *Obstet. & Gynecol. Survey* 22:69, 1967.
4. Bomze, E.J. and Friedman, N.B.: Squamous metaplasia and adenoacanthosis of the endometrium. *Obstet. & Gynecol.* 30:619, 1967.
5. Dutra, F.R.: Intraglandular morules of the endometrium. *Am.J. Clin. Path.* 31:60, 1959.
6. Ng, A.B.P., et al.: Mixed adenosquamous carcinoma of the endometrium. *Am. J. Clin. Pathol.* 59:765, 1973.
7. Silverberg, S.G., et al.: Adenoacanthoma and mixed adenosquamous carcinoma of the endometrium. A clinicopathologic study. *Cancer* 30:1307, 1972.

APRIL 21, 1974 - CASE NO. 22

ACCESSION NO. 20525

MODERATOR'S DIAGNOSIS: Clear cell adenocarcinoma of the vagina.

CLINICAL ABSTRACT:

This 18 year old female presented with an 8 month history of premenstrual spotting followed by profuse vaginal bleeding. The patient's mother had received large doses of diethylstilbestrol for the treatment of a threatened miscarriage at 13 weeks' gestation. Physical examination revealed a papillary mass with superficial necrosis in the upper third of the vagina on the right lateral wall. A total hysterectomy, partial vaginectomy, and lymph node dissection were performed. The vaginal tumor was dome-shaped measuring 1.5 x 1.5 cm. and contained multiple cystic spaces. The lesion appeared limited to the superficial portion of the vagina. The remainder of the specimen was negative including the resected lymph nodes.

MICROSCOPIC DESCRIPTION:

The tumor is composed of a network of tubular structures lined by square to cuboidal cells with irregular prominent nuclei, many of which apparently are being extruded from the cells. Some of the cells are clear while others have pale eosinophilic cytoplasm. The tumor invades into the underlying stroma. Mitoses are frequent and the nuclei are hyperchromatic, irregular and cytologically atypical. Mucin is present in the spaces and in the cytoplasm of many of the tumor cells. Adjacent to the tumor, in some sections, are bland endocervical type glands consistent with adenosis vaginae.

DISCUSSION:

The tumor now known as clear cell adenocarcinoma was originally described by Schiller as mesonephroma or mesonephric carcinoma and was generally diagnosed as such until 1967 when Scully demonstrated the probable origin of the tumor from the coelomic epithelium of the ovary and suggested the term clear cell adenocarcinoma (1). Following publication of Scully's study, it was recognized that the clear cell carcinomas arising in the vagina, the cervix and the endometrium were almost all of Mullerian origin rather than being derived from the mesonephros. The term clear cell carcinoma has also been applied to these carcinomas. Schiller also described another tumor as mesonephroma, namely the endodermal sinus tumor, which as mentioned in Case 4 has a different histologic appearance. These tumors originally described by Schiller as mesonephromas are now thought to have another origin. Both endodermal sinus tumor and clear cell carcinoma occur in the vagina and in the ovary and care should be taken to keep them separate (2,3).

Clear cell adenocarcinoma may have 3 different histologic patterns. One is tubular (parvolocular) in which the tumor looks like renal tubules, the second is papillary and the third is solid sheets of tumor cells. Within each of these three basic patterns there may be two cell types: clear cells similar to those in renal cell carcinoma and cells with eosinophilic cytoplasm. The latter cells are the ones that most commonly demonstrate the extruded nuclei or hobnail appearance. These two cell types are almost always found mixed together in the same tumor but one may predominate. Some clear cell carcinomas, for example, may resemble renal cell carcinoma. The most common histologic pattern is tubular, as is found in this case, with the hobnail nuclei and scattered foci of clear cells. The cytoplasm of the tumor cells in the tubular form contain both glycogen and mucin and mucin is often present in the lumens of the tubular structures. The tumors predominantly composed of clear cells have a better prognosis than those with the tubular and papillary patterns.

Clear cell adenocarcinoma occurs in the ovary, vagina, endometrium and cervix (4,5,6,7). The relationship between vaginal clear cell adenocarcinoma and stilbestrol therapy has become well known due to the work of Herbst and co-workers in Boston who explored the relationship between stilbestrol therapy in pregnant women and the development of clear cell adenocarcinoma of the vagina in their daughters (8). The initial publication by the clear cell adenocarcinoma registry in Boston concerned 91 patients, 53 with vaginal clear cell adenocarcinomas, and 38 with cervical carcinoma (9). A pregnancy history was available for 66 patients and the mothers of 49 patients had received stilbestrol during their pregnancy. The increased incidence of vaginal and cervical clear cell carcinomas in patients whose mothers received stilbestrol has not been reflected in an increase in ovarian or endometrial clear cell carcinomas. However, there are isolated reports to suggest that squamous cell carcinoma and possibly other types of adenocarcinomas of the cervix may also be increased in young women whose mothers received stilbestrol. Careful questioning of any patient who develops carcinoma of the cervix or vagina below the age of 25 as to maternal stilbestrol therapy may help to determine if other types of carcinoma are indeed associated with stilbestrol therapy.

Another feature noted in the study by the clear cell carcinoma registry was an increase in adenosis vaginae in young women whose mothers received stilbestrol. Adenosis vaginae is the presence of Mullerian glands in the vagina which may be lined by either endocervical or endometrial epithelium. The incidence of adenosis in young women whose mothers received stilbestrol is around 70% in most series and as high as 90% in one culpomicroscopic series (10). The common association of vaginal adenosis, and the occasional existence of transverse vaginal and cervical ridges in these young women,

provide morphologic evidence that stilbestrol causes disturbance of the development of the lower Mullerian tract. Whether the clear cell adenocarcinoma develops from foci of adenosis or de novo is not entirely clear. For practical purposes young women with adenosis must be followed carefully to be sure they do not develop carcinoma. Large areas of adenosis should be removed if possible and the smaller areas examined regularly. A recent update from the adenocarcinoma registry to include 170 total cases indicates that no asymptomatic patient with clear cell carcinoma has thus far died of tumor. This emphasizes the importance of regularly examining asymptomatic exposed patients, and identifying such patients in the population. In the registry cases, 80% of the patients who had vaginal adenocarcinoma are alive and 65% of those with cervical tumors are alive. The features which seem to be of most prognostic importance are the number of mitoses per 10 high power fields and the presence or absence of lymphatic invasion. A copy of the abstract from the registry, concerning the 170 cases to be published shortly, is attached following the references.

Adenosis vaginae may occur in women whose mothers have not been exposed to stilbestrol. In Sandberg's very careful autopsy study, adenosis was found in the vaginae of 9 of 35 women of all different ages after puberty (11). Sandberg did not find adenosis in the prepubertal vagina. A more recent study has indicated that adenosis may be found in the vagina of infants in the first month of life but then is not found again until after puberty. These studies suggest hormonal influence in the development of adenosis vaginae. Adenosis vaginae must be differentiated from the mesonephric ducts (Gartner's ducts) which can be found in the lateral wall of the vagina. The mesonephric ducts are mucin negative whereas adenosis is positive for mucin.

REFERENCES:

1. Scully, R.E. and Barlow, J.F.: "Mesonephroma" of the ovary. A tumor of Mullerian nature related to the endometrioid carcinoma. *Cancer* 20:1405, 1967.
2. Allyn, D.L., et al.: Endodermal sinus tumor of the vagina. *Cancer* 27: 1231, 1971.
3. Norris, H.S., Bagley, G.P. and Taylor, H.B.: Carcinoma of the infant vagina. *Arch. Pathol.* 90:473, 1970.
4. Fine, G., et al.: Mesonephroma of the ovary. *Cancer* 31:398, 1973.
5. Hameed, K., et al.: Clear cell carcinoma of the ovary. *Cancer* 24:452, 1969.

6. Tsukada, Y., et al.: Clear-cell adenocarcinoma of the vagina. Three cases associated with maternal synthetic nonsteroid estrogen therapy. *Cancer* 29:1208, 1972.
7. Silverberg, S.G. and DeGiorgi, L.S.: Clear cell carcinoma of the vagina. A clinical, pathologic and electron microscopic study. *Cancer* 29:1680, 1972.
8. Herbst, A.L. and Scully, R.E.: Adenocarcinoma of the vagina in adolescence. *Cancer* 25:745, 1970.
9. Herbst, A.L. et al.: Clear-cell adenocarcinoma of the genital tract in young females. Registry report. *N.E.J.M.* 287:1259, 1972.
10. Stofl, A., et al.: Clinical diagnosis of vaginal adenosis. *Obstet. & Gynecol.* 43:118, 1974.
11. Sandberg, E.C.: The incidence and distribution of occult vaginal adenosis. *Amer. J. Obstet. & Gynecol.* 101:324, 1968.

CLEAR-CELL ADENOCARCINOMA OF THE VAGINA AND CERVIX  
IN YOUNG FEMALES: AN ANALYSIS OF 170 REGISTRY CASES  
(By Herbst, A.L., Scully, R.E., and Robboy, S. to  
be published in Amer. J. Obstet. and Gynecol., 1974)

Abstract:

One hundred cases of vaginal and 70 cervical adenocarcinomas from the Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females have been analyzed. The age range of the patients was 7 to 29 years and the frequent association with prenatal exposure to diethylstilbestrol and similar non-steroidal estrogens was confirmed. The hormone administration began prior to the 18th week of pregnancy and was continued for periods ranging from 1 week to almost the entire length of the pregnancy. The total dosages ranged from 300 to 18,200 mg. Although most patients had vaginal bleeding or discharge, 16 percent were asymptomatic. Abnormal cytology was the first clue to the diagnosis of cancer in 11 patients, but 21 percent of the smears were negative. The larger and more deeply invasive tumors were often complicated by lymph node metastases, but these were also encountered in 1 case in which the tumor had an area of only 3 cm<sup>2</sup> and with another tumor that invaded less than 3 mm. These findings suggest that local treatment of the primary tumor alone may be inadequate in some cases. Recurrences have developed in 37 of the patients and 24 of them have died, although the follow-up in one-third of the cases has been less than two years. The recurrences frequently involved the lungs and supraclavicular lymph nodes as well as the pelvis. The very common association of vaginal adenosis and the occasional co-existence of transverse vaginal or cervical ridges provide morphologic evidence of a stilbestrol-related disturbance in the development of the lower Mullerian tract. The results of intravenous pyelography suggest that the development of the urinary tract is not affected. The fact that all the asymptomatic patients with carcinoma have been successfully treated thus far underscores the importance of screening exposed asymptomatic patients in search of early cases. The rarity (9 percent) of these cancers prior to the age of twelve years, suggests that the inclusion of a large population of girls in this age group in a screening program would uncover very few cases. Such individuals should certainly be examined, however, at any time abnormal vaginal bleeding or discharge develops.

APRIL 21, 1974 - CASE NO. 23

ACCESSION NO. 20528

MODERATOR'S DIAGNOSIS: Low grade fibrosarcoma of the ovary

CLINICAL ABSTRACT:

This 18 year old female was found to have a large pelvic mass displacing the uterus. At operation the right ovary was replaced by a solid tumor which demonstrated extensive hemorrhagic necrosis in all areas except the periphery. The viable peripheral portions were pale-gray to slightly yellow and semi-translucent.

MIRCOSCOPIC DESCRIPTION:

This is a fibrous tumor of variable cellularity composed of elongate cells with generally spindle nuclei and fine chromatin. There is minimal atypia, but up to 5 to 6 mitoses per 10 high power field can be found. Hyaline plaques are also present. Some of the tumor cells are more cuboidal with rather abundant cytoplasm. A reticulin stain shows reticulin around individual cells. The trichrome stain indicates large amounts of collagen without smooth muscle staining pattern. Longitudinal grooves are not noted in the nuclei. A mucin stain is negative.

DISCUSSION:

The differential diagnosis of this tumor included fibrosarcoma, atypical fibroma with large numbers of mitoses, thecoma, leiomyoma, Krukenberg tumor and massive edema of the ovary. The latter entity is characterized by marked enlargement of the ovary by edema: fluid with retention of follicular structures (1). These features are not present in this case. Mucin stains in this case are negative and there is no evidence of metastatic carcinoma. The trichrome stain does not indicate the presence of smooth muscle.

This tumor then brings up two problems in diagnosis, namely, what are the criteria for the diagnosis of thecoma versus fibroma, and what are the criteria for the determining malignancy in fibromas and thecomas? Thecomas are tumors derived from the undifferentiated ovarian sex cord mesenchyme (2). When sufficiently differentiated to blend with granulosa cell tumor or to show evidence of luteinization and estrogen production, they are easy to diagnose. On the other end of the spectrum the tumor cells may be spindle and have characteristics of fibrous tissue as stromal cells do in the normal ovary. Where thecoma ends and fibroma begins is difficult to determine for many tumors. It is probable that both thecoma and fibroma represent parts of a spectrum of sex cord stromal neoplasms and that thecoma is composed of stromal cells which are producing hormones (3). In the classic examples, fibroma contains interlacing whorls of thin spindle cells with small dark nuclei and

occasional hyaline formation whereas thecoma is most frequently composed of fusiform cells with pale cytoplasm, large pale nuclei and foci of luteinization. The cells in thecoma frequently contain lipid. However, there are many transitional forms between these two classic examples, and in some tumors, it is morphologically impossible to separate thecoma and fibroma. Evidence of function indicates the tumor is thecoma. When one of these tumors is non-functioning and histologically doubtful, it is our policy to diagnose it as a fibroma.

Determination of a malignant criteria is also difficult. For practical purposes, thecomas are benign and I think reports of malignant varieties are open to question (2,4). As far as I know there have been no reports of biologically malignant tumors containing lipid cells which produce estrogen and morphologically look like thecoma. However, there are malignant spindle tumors arising in the ovary which do not function and have been considered to be fibrosarcomas. Thus, in my opinion, thecoma is a benign tumor and there have been no acceptable reports of malignant varieties. On the other hand, there are rare malignant spindle celled neoplasms in the ovary which do not function, which should be considered to be fibrosarcomas.

It is also difficult to determine where to draw the line between an atypical fibroma and fibrosarcoma of the ovary. Unfortunately, criteria are not available for making this distinction. Whenever a fibrous neoplasm contains extensive necrosis and readily found mitoses, it has been customary to diagnose the tumor as fibrosarcoma. Occasionally, such a tumor has been aggressive. However, as long as the tumor is confined to the ovary and the cells cytologically bland, I do not expect aggressive behavior and I am unaware of such tumors metastasizing. I originally interpreted this present tumor as an atypical fibroma rather than a fibrosarcoma but on the basis of the extensive necrosis, the cellularity and the mitoses, I would consider this to be a low grade fibrosarcoma. However, I would not expect this tumor to metastasize.

#### REFERENCES:

1. Kalstone, C.E., et al.: Massive edema of the ovary simulating fibroma. *Obstet. & Gynecol.* 34:564, 1969.
2. Scully, R.E.: Recent progress in ovarian cancer. *Hum. Pathol.*, 1:73, 1970.
3. Amin, H.K., Okagaki, T. and Richart, R.: Classification of fibroma and thecoma of the ovary. An ultrastructural study. *Cancer* 27:438, 1971.
4. Norris, H.J. and Taylor, H.B.: Prognosis of granulosa-theca tumors of the ovary. *Cancer* 21:255, 1968.

APRIL 21, 1974 - CASE NO. 24

ACCESSION NO. 20526

MODERATOR'S DIAGNOSIS: Squamous papilloma ("Cockscomb polyp") of the cervix associated with pregnancy.

CLINICAL ABSTRACT:

This 20 year old gravida II, para I patient had a 5-6 month history of post-coital bleeding, and an atypical cytology early in her pregnancy. Pelvic examination revealed two discoid lesions over the cervix. A cone was performed and grossly the specimen revealed most of the epithelial surface to be replaced by a velvety, somewhat papillary, lesion which in some areas was plaque like. The tumor mass was rather granular, pale yellow and elevated to 1.5 cm. above the background of the smooth portion of the epithelium.

MICROSCOPIC DESCRIPTION:

The epithelium of the cervix has been thrown up into papillary fronds lined by multilayered but orderly squamous epithelium. Most of the cells are rather basaloid and somewhat immature, but more mature squamous epithelium is also present on the papillary stalks. Remnants of the endocervical glands can be seen between the squamous elements. The stalks of the papillary fronds are composed of delicate connective tissue containing blood vessels. Focal areas of chronic inflammation are present. Hyperkeratosis and parakeratosis are not conspicuous and vacuolated cells are not seen.

DISCUSSION:

The squamous papillomas of the cervix include, besides the cockscomb polyp, condyloma accuminata and the "true" papilloma of Hertig and Gore (1,2,3). Verrucous squamous carcinoma must also be included in the differential diagnosis (4,5). Cockscomb polyp is of unknown etiology and is found only during pregnancy. It is a warty, firm, usually single, lesion which grows rapidly during pregnancy but regresses spontaneously in the post partum period (1). It is not malignant or premalignant and has no relationship to squamous cell carcinoma. As soon as carcinoma is ruled out by biopsy, the lesion need not be further treated. The tumor cells are usually not vacuolated. Condyloma accuminata is composed of multiple soft elevated masses of squamous epithelium of variable size and shape. It can be small or quite massive. Microscopically there is a complicated papillary arrangement of well differentiated and usually orderly squamous epithelium supported by delicate vascular connective tissue stalks. Focally, there is vacuolization of the squamous cells and a lymphocytic infiltrate in the underlying dermis or submucosa is a regular feature. Condyloma accuminata may also contain atypical cells, but full thickness atypia is not seen and the degree of atypia found in carcinoma-in-situ is not present. Hertig and Gore described "true" squamous papilloma as occurring in non-pregnant women usually after the

menopause (3). It is a single small lesion 2 to 4 mm. broad based and composed of squamous cells. It grows progressively larger and may be premalignant. This is an extremely rare form of squamous papilloma of the cervix.

Verrucous carcinoma must be separated from the squamous papillary lesions of the cervix. On the one hand, verrucous carcinoma should be recognized as a carcinoma and not a papilloma since it is capable of local aggressive growth which can result in the death of the patient (4,5). On the other hand, it is also important not to confuse verrucous squamous carcinoma with invasive squamous carcinoma of the usual type since verrucous carcinoma may become more anaplastic and metastasize if irradiated (6). Verrucous carcinoma is a fungating verruciform lesion with bulbous rounded ends of squamous epithelium protruding into the underlying stroma. Hyperkeratosis and parakeratosis are prominent and the squamous cells have pale staining eosinophilic cytoplasm. Chronic inflammation is invariable and mitoses and atypia may be present. Verrucous carcinoma can easily be misdiagnosed as condyloma accuminata histologically, and one should never diagnose a benign squamous papilloma of the cervix without knowing the clinical appearance of the lesion. Verrucous carcinoma is recognizable clinically as a tumor mass which does not resemble the soft papillary appearance of a squamous papilloma. Verrucous carcinoma, although locally aggressive, does not usually metastasize unless it has been irradiated. With irradiation, approximately 30% will transform to anaplastic carcinoma with metastasizing capability (6). The treatment of verrucous carcinoma is surgical.

#### REFERENCES:

1. Simcock, M.J.: Papillomas of the uterine cervix. Aust. N.Z.J. Obstet. Gynecol. 4:174, 1964.
2. Gilbert, T.F. and Palladino, A.: Squamous papillomas of the uterine cervix. Amer. J. Clin. Pathol. 46:115, 1966.
3. Hertig, A.T. and Gore, H.: Tumors of the female sex organs, Part 2, Tumors of the vulva, vagina and uterus. A.F.I.P. Sec. 9, Fas. 33:90, 1960.
4. Kraus, F.T. and Perez-Mesa, C.: Verrucous carcinoma. Clinical and pathologic study of 105 cases involving oral cavity, larynx and genitalia. Cancer 19:26, 1966.
5. Jennings, R.H. and Barclay, D.L.: Verrucous carcinoma of the cervix. Cancer 30:430, 1972.
6. Demian, S.D.F., et al.: Perineural invasion and anaplastic transformation of verrucous carcinoma. Cancer 32:395, 1973.

APRIL 21, 1974 - CASE NO. 25

ACCESSION NO. 20527

MODERATOR'S DIAGNOSIS: Serous tumor of borderline malignancy (low malignant potential) of the ovary

CLINICAL ABSTRACT:

This 47 year old female was first noted to have an abdominal mass during an admission for replacement of aortic, mitral and tricuspid valves. Following her cardiac surgery she was referred to a gynecologist but did not go to him for a year. By that time the mass had grown considerably larger. At laparotomy there was a smooth cystic mass occupying the left adnexa. There was no evidence of tumor on the outside of the cyst and no evidence of tumor elsewhere in the pelvis or in the abdomen. On cut section, the interior of the cyst contained sticky thick fluid and was lined by innumerable yellow pink papillae varying from 0.5 to 2.0 cm. in height.

MICROSCOPIC DESCRIPTION:

This papillary tumor is composed of columnar to cuboidal cells lining club shaped and often edematous papillae. The tumor cells have rather abundant eosinophilic cytoplasm and in many areas the cells are stratified to a height of 4 or 5 nuclei. As many as 4 mitoses can be found in a single high power field. Most of the nuclei are rather vesicular and bland but occasional cells have prominent eosinophilic nucleoli. Nuclear outlines are slightly irregular. Many of the papillae are edematous and club shaped but there is no evidence of stromal invasion in any area.

DISCUSSION:

Included in the surface (coelomic) epithelial neoplasms of the ovary are the serous, mucinous, endometrioid, Brenner, clear cell and malignant mixed Mullerian tumors (1,2). For each of these tumor types, except the malignant mixed Mullerian tumor, there is a benign form, a borderline malignant form and a frankly malignant form (2,3). In practice, this classification of benign, borderline malignant and malignant works well for the serous neoplasms, reasonably well for the mucinous neoplasms and is somewhat difficult to apply to the clear cell carcinomas and endometrioid carcinoma (4,5). The borderline variety of Brenner tumors is the proliferating tumor which has been benign in all the cases thus far reported. For the serous and mucinous neoplasms, the three different grades of tumors should be recognized and diagnosed since prognosis and therapy will vary.

Histologic criteria for diagnosing serous cystadenoma and mucinous cystadenoma are well known. The borderline tumors are characterized by epithelial cell proliferative activity, nuclear atypia, mitoses and nuclear

stratification (1). Adenomas may have minor degrees of atypia and focal areas of minor stratification, but when stratification becomes extensive and more than 1 or 2 nuclei, the tumor should be considered to be borderline (low malignant potential). Borderline tumors may implant on the peritoneum and rarely metastases can occur, but both events are unusual. The borderline tumors must be evaluated exclusively on examination of the ovarian tumor and not on the basis of spread to the pelvis (2). The validity of this diagnostic approach has been demonstrated by the better survival of the patients with borderline serous tumors, even those that have spread beyond the ovary, as compared to patients with frank carcinoma.

The histologic criteria for diagnosing carcinoma is stromal invasion. This criteria works well in the serous group of neoplasms and serous carcinoma should not be diagnosed unless invasion of the stroma can be demonstrated. One must be cautious not to misdiagnose glandular extensions into the stroma and complex glandular growth patterns as stromal invasion. The criteria of invasion is less reliable for the mucinous tumors because of the complexity of their growth pattern. A recent study by Hart and Norris indicates that mucinous tumors with nuclear stratification greater than 3 nuclei should be considered carcinoma while those with less stratification are borderline or benign neoplasms (6). In our experience, this criteria is extremely helpful. For the endometrioid tumors the borderline category is extremely unusual and would be represented by markedly atypical adenomatous hyperplasia in endometriosis. Instead of using the borderline category, we grade the endometrioid carcinomas from 1 to 4 using the same histologic criteria we use for corpus carcinomas. We have not found the borderline category to be of value in the clear cell carcinomas and it is obviously not pertinent for the mixed Mullerian tumors.

The serous tumor of borderline malignancy represent an important, and rather large, group of ovarian tumors and they should be recognized diagnostically. Borderline tumors should be separated from carcinoma and strict criteria used for their diagnosis. Characteristically, borderline serous tumors are cystic and the cysts are lined by broad club shaped papillae with edematous stroma as demonstrated in this case. Nuclear stratification is usually marked and mitoses may be numerous but invasion is absent. In most series the survival of borderline serous carcinoma is more than 85% for five years whereas the survival in serous carcinoma is usually less than 20% in five years. Because of this difference in prognosis, we think that patients with borderline serous neoplasms confined to the ovary can be treated by surgery alone without post-operative irradiation (7). In addition, even if patients should have recurrence of a borderline tumor, it is usually limited to local pelvic spread which grows very slowly often after long periods of time. Pelvic extension of borderline tumors may spontaneously regress after

the primary is removed. For mucinous tumors, the difference in prognosis is less striking, particularly if one uses only the criteria of invasion to diagnose malignancy. However, we think the borderline category should be recognized and the criteria of Hart and Norris utilized.

In summary, borderline serous and mucinous neoplasms have biologic behavior and histologic patterns which are significantly different from frank carcinoma and from the adenomas to allow recognition and separation. We think it important for purposes of prognosis and future therapy to diagnose this group of neoplasms accurately. The separation into 3 types of tumors has been recognized by both FIGO and the World Health Organization in the new classification of ovarian neoplasms. Criteria are easily applied for the serous and most of the mucinous tumors, whereas it is less useful for the endometrioid and clear cell tumors.

#### REFERENCES:

1. Scully, R.E.: Recent progress in ovarian cancer. *Hum. Path.* 1:73, 1970.
2. Serov, S.F. and Scully, R.E.: *Histological typing of ovarian tumors.* Geneva, 1973. World Health Organization.
3. Gondos, B.: Electron microscopic study of papillary serous tumors of the ovary. *Cancer* 27:1455, 1971.
4. Czernobilsky, B., et al.: Clear cell carcinoma of the ovary. A clinicopathologic analysis of pure and mixed forms and comparison with endometrioid carcinoma. *Cancer* 25:762, 1970.
5. Czernobilsky, B., et al.: Endometrioid carcinoma of the ovary. *Cancer* 26:1141, 1970.
6. Hart, W.R. and Norris, H.J.: Borderline and malignant mucinous tumors of the ovary. *Cancer* 31:1031, 1973.
7. Hintz, B.L., Fuks, Z., Kempson, R.L., et al.: Results of postoperative megavoltage radiotherapy of malignant surface epithelial tumors of the ovary. In press: *Radiology*.