Bulletin of

Staff Meeting

University of Minnesota Hospitals
University of Minnesota

Vol. V
No. 9
12-7-33

Ovarian Tumors

INDEX

I. LAST WEEK'S MEETING

Date: November 23, 1933.

Place: Recreation Room, Nurses' Hall.

Time: 12:15 to 1:15 P.M.

Program: Primary Liver Carcinoma. Amebic Dysentery.

Present: 115

Discussion: R. W. Koucky
L. G. Rigler
W. A. Riley
H. L. Ulrich
W. L. Boyd
K. W. Stenstrom
I. McQuarrie
H. W. Christianson

Theme: R.W.K.: The microscopic sections from the first case are rather difficult to interpret because of high differentiation. In many places, it is practically impossible to tell the difference between normal liver, adenoma and tumor. The study of the sinusoids, however, will reveal the difference as the endothelial cells are not well developed or absent in the adenomas and malignant changes. In the lungs, a typical nodule is seen which resembles those shown in the liver (made bile).

L.G.R.: Slides show tumor nodules in liver as mottled density. The spleen is well shown with thorotrast. The kidney pelvis on the right is grossly normal, left not well visualized. My impression was that the child had a very massive tumor of the liver and metastasis to the lungs.

R.W.K.: (2nd case). This tumor is very different from the first. The cells are small, cuboidal, with dense nuclei. There is a great deal of fibrous tissue. The cells seem to arrange themselves in very slender cords, apparently trying to form tubules. This is difficult to interpret from trophic liver cord cells or compressed bile ducts. The tumor may have arisen from the bile ducts, hence the designation cholangioma. The tumors of the other organs present the same appearance. The third type of tumor is not illustrated today but is shown in this slide. There is formation of very large giant cells along the sinuses. Some of these cells contain from 15 to 20 nuclei. Note the peculiar character of the attempted formation of the sinusoidal endothelium here. There is apparently only a free cell in the sinus rather than a reproduction of this tissue.

L.G.R.: Great difficulty encountered in making the diagnosis. The left lobe is fairly well visualized but appears somewhat larger than normal. The spleen is moderately enlarged. Examination of the liver shows multiple small metastases. The question of whether the entire left lobe is involved by tumor was discussed. Other slides were shown of various changes in liver carcinoma. In this one, there is marked destruction of bone (metastatic). The general appearance is that of hypernephroma. It was apparently due to a primary tumor of the liver. Unfortunately, films in next case are not made with as heavy an exposure as we are accustomed to make. In any event, there was no evidence whatever of tumors or areas of destruction. It looked just like enlarged liver such as might be seen in the early stage of cirrhosis. However, autopsy showed the liver riddled with tumors. Microscopic examination of the tumor revealed reason. The tumor had picked up thorotrast because of its high degree of functional differentiation.

W.A.R.: Here are a few slides I would like to show here of infestation of the rat liver with tapeworm. This is the type in which cancer has been described. Liver fluke infestation is very common in China. Slides were shown illustrating how each village with its pond collected human excreta. The ponds are drained, the fish eaten and the human excreta used as fertilizer. The chances of cross infestation because of this method of living are very great. A small snail is necessary to perpetuate the liver fluke. This snail is in the

stream and infects the fish. Practically all fish are infected with this stage. Parasite bores into the skin of the fish and comes to lie just under the outer layer. Here are some cysts on cross section.

Bullheads in China are very commonly infested. Almost every fish in the infected water shows the disease. It is very common practice for the Chinese to eat uncooked fish. I saw thousands of fluke infestations in these people during my stay in China. I was interested, however, to learn that most physicians did not think cancer was very common in the Chinese. The statements today are rather interesting in this regard.

Question: How about amebic dysentery? You will find this rather well cogered in the last issue of the J.A.M.A. My attention was directed to it about a month ago when a Philadelphia physician on vacation in Chicago came through here and stopped off on account of intestinal upset. Diagnosis of amebic dysentery was made at the Miller Hospital. It was a perfectly typical acute case. I had a letter from him yesterday in which he stated that he is improving. You all are familiar with the origin of this epidemic in the two large Chicago hotels during the fair. The guests have now scattered throughout the country and will be spreaders of this infection. The acute stage is apparently not infectious. It is during the cystic stage that carriers are most dangerous.

The figures, stating that 10% of the population are carriers is not borne out by facts. This exaggerated figure was obtained from surveys made in insane asylums, etc. At Johns Hopkins a survey of outpatient cases with symptoms of gastro-intestinal trouble revealed on rigid examination that less than .5 to 1% were amebic infestations. I do not want to minimize the degree of this epidemic but I would like to call your attention to this figure which is apparently too high.

Question: Is there any danger of liver fluke infestation in this country? Apparently not because a special form of snail is necessary to perpetuate the fluke. We must have great carelessness in the disposal of human excreta, infected fish and this snail before the disease can develop in man.

H.L.U.: I recently saw a patient who contracted her disease at the Congress Hotel. In fact, I have seen 4 up to the present. Following her return from Chicago, she had diarrhea and later constipation. We hunted for ameba at this time but could not find them. Later she developed herpes zoster and we explained all of her symptoms on this basis. She also had some hemorrhoids and tendency to bleed. During the next exacerbation, amebae were found in the stools. We used emetin on this case. Emetin is specific for the acute stage. It is a rather dangerous drug to use however and warning should be issued at this time. The last issue of the Journal of the American Medical Association shows that there are many other remedies which are apparently equally effective. Emetin is given just under the skin and by mouth.

W.L.B.: I am rather interested in the question of liver fluke disease. We have examined many domestic animals of this state in the past 7 years and only few have shown infestation (cattle). They came from the northern section. Since then, we have seen it in moose and deer. In the western part of the U.S., liver fluke disease is quite a problem. This is especially true in areas in which the rainfall is scanty. Apparently the dew on the grass is all that is needed to perpetuate the parasite. They are attempting to combat infestation in animals by spraying the pasture lands with a solution of copper sulphate.

W.K.S.: We treated the first patient recorded here today. We assumed that it was a primary liver tumor or lympho-sarcoma. There was no response during the short course we tried. Looking at the slides today, one would not expect very much response from radiation in a tumor which was so well differentiated. We have occasionally had Hodgkin's disease in the liver which has responded fairly well. At one time,

it was considered rather dangerous to radiate the liver and everyone was warned about the possibility of destroying liver substance with a heavy dose. However, one can apparently give quite a heavy dose over the liver without severe reaction. It cannot be continued indefinitely however.

I.M.: We have seen 2 patients (infants) with primary liver carcinoma. We found large liver in both cases. At the time they were recognized, it was too late to do anything. I saw a liver tumor in a girl about 13 years of age which apparently originated in the region of the gall-bladder.

O.H.W.: We had a case here about 2 years ago in which a liver cyst was successfully operated.

H.L.U.: I would like to call your attention to the fact that one can occasionally pick up carcinomatous nodules on the posterior edge of the liver.

H.W.C.: Mention has been made of the large number of preparations on the market for the treatment of amebic dysentery. I would like to call your attention to tryparsol which apparently is the least toxic of the group.

Question: Some time ago, we had a patient here on whom a diagnosis of carcinoma of the stomach with metastasis to the liver was made. After 2 years, this patient shows no sign of the disease progressing. Re-examination of the section of the liver nodule (at the edge) revealed that at that time the pathologists were rather in doubt as to its nature and suggested some kind of liver tumor. This may represent one of the more benign types of liver adenomas or low grade carcinoma which may respond to surgery.

Gertrude Gunn,
Record Librarian.

II. CASE REPORT

MALIGNANT MULTILOCULAR CYST OF OVARY.

Case is that of white female, 59 years of age, admitted to the Minnesota General Hospital 8-12-32 and discharged 8-28-32: readmitted 12-16-32 and expired 1-7-33. Total stay - 48 days.

Menopause - spotting

1924 - Menopause. Six months thereafter patient observed spotting.

1932 (January ?) - Spotting recurred. In interval, has had no symptoms of note.

Enlargement of Abdomen - spotting

8-12-32 - Admitted. In interval, spotting recurred 5 or 6 times. In addition, noted abdomen becoming larger, particularly on right side. Not associated with pain but there was dragging sensation in pelvis. 15 lbs. weight loss.

Physical examination

Positive findings as follows: Mouth - carious teeth. Heart - blood pressure 140/90. Abdomen - enlarged; mass present in midline extending left reaching up to umbilicus. Pelvic - external genitalia normal; lacerated perineum; second degree cystocele and rectocele; cervix points backward and to left and hypertrophied; corpus of uterus enlarged and points to right; adnexae show no palpable masses but there is large mass in abdomen arising from pelvis and going up 2 or 3 fingers above umbilicus, this mass firm, nodular and irregular but not especially tender. Clinical diagnoses: Multilocular cyst of ovary. Possible pedunculated myoma with small myomatous uterus. Laboratory: Urine - negative. Blood - Hb. 82%, wbc's 8,350, Pmn's 60%. Blood Wassermann - negative. X-ray of abdomen - visualized a large soft tissue pelvic tumor displacing the colon.

Operation: Cystadenoma

8-16-32 - Operated upon; curettage, biopsy of cervix and laparotomy. Very large cystadenoma (multilocular) of right ovary removed. During delivery of tumor, its thin wall was ruptured. Cystic fluid left free in peritoneal cavity.

Pathology

Tumor is a cystic mass weighing 2.7 kilos. Interior of mass composed of

cysts ranging from 1 cm. to 7 or 8 cm. in diameter, separated from each other by thin partitions. The cyst content serous, in some areas pseudomucinous and in others milky. In one area, a small papillary projection found in a cyst wall. Microscopic examination shows pseudostratified, columnar, and folded, tall, columnar epithelium. Mucus being secreted by tall columnar cells. Papillary projection described is very cellular but apparently not malignant as far as can be determined.

8-19-32 - Slight upper respiratory infection.

8-21-32 - Temperature down to 98.

8-23-32 - Temperature normal. Wound in good condition.

8-28-32 - Discharged.

8-31-32 - Letter from husband received, stating that small opening occurred in incision discharging bloody mucus.

Generalized Abdominal Pain, Enlargement

12-16-32 - Readmitted. During interval, felt well up to latter part of October. All teeth extracted because of infection. About November 15th was awakened by severe sharp pain in right lower quadrant of abdomen. Pain gradually developed in entire abdomen. Became conscious of mass in abdomen, slightly to right of midline. About November 25th, noticed abdomen was enlarging. Enlargement continued rapidly. Dyspnea developed.

Ascites

Physical examination - abdomen greatly enlarged, distended and bulging at flanks. Tender to pressure, feels firm and hard. Tympany reduced throughout abdomen. Laboratory: Urine - negative. Blood - Hb. 75%, rbc's 3,500,000, wbc's 9,000. P.S.P. - total 47%.

Paracenthesis

12-22-32 - Paracentesis of abdomen done, 8,000 cc. yellow fluid removed. Cultures of this - negative except for a diphtheroid organism.

Operation: Generalized Carcinomatosis

12-30-32 - Abdomen explored. Entire peritoneal cavity obliterated by extensive hard, irregular masses.

Pulmonic Signs

1-2-33 - Coughing. Few fine rales in left base.

Pleural Effusion - Aspiration

1-5-33 - Large pleural effusion on left side. X-ray confirms this diagnosis. 500 cc. clear fluid withdrawn.

Death

1-7-33 - More comfortable since paracentesis. Late in afternoon, became weak and dizzy. Complained of feeling strange. In few minutes, stopped breathing. Stimulants, etc. of no benefit.

Partial Autopsy

Permission for limited autopsy only. Body is that of an elderly, white female, 59 years of age, measuring 163 cm. in length and weighing approximately 160 lbs. Development and nourishment are good. Rigor is present. Hypostasis is beginning. Slight edema of ankles. No cyanosis or jaundice. Pupils equal, each measuring 4 mm. in diameter. 16 cm. incision in midline below umbilicus which drains a small amount of bloody fluid. Deeper near peritoneum, there is an extension of carcinoma into depth of wound. Manual exploration of abdominal and thoracic cavities done.

All of peritoneal spaces obliterated by adhesions and heavy, nodular, irregular masses. Nothing can be recognized within pelvis and it is impossible to separate organs. The liver and spleen are bound to diaphragm and adjacent structures. The gall-bladder contains a small stone, about 1-1/4 cm. in diameter, and wall is thick and contracted. The great omentum cannot be separated away from the underlying structures and in areas has to be torn away from abdominal wall. It is extremely thick, in areas measures 3 to 4 cm. in thickness. On cross section, it is composed of fat and white, fibrous, hard tissue. At no point can cysts be recognized. The diaphragm on both sides is punctured,

about 3 to 400 cc. fluid escapes from the left side. The lungs are compressed and almost entirely airless. No evidence of metastasis can be found in the lungs or mediastinum. Attempt is made to deliver the kidneys from their bed but this was impossible because of the extreme amount of hard tissue intervening.

Diagnoses:

1. Malignant, multilocular, serous and pseudomucinous cystadenoma of ovary.
2. Generalized abdominal metastases.
3. Chronic peritonitis.
4. Cholecystitis.
5. Gall-bladder stones.
6. Pelural effusion.
7. Collapse of left lung.

Microscopic Report

Only biopsies taken were those of the tumor. These show a very heavy fibrous tissue stroma in which are imbedded small cords and nests of malignant cells. These cells have no characteristics differentiating them from any other type of scirrhous carcinoma. No cysts are formed and there is no secretion within the cells. There is no resemblance between the cells in the peritoneal metastases and the cells of the papilloma within the cyst removed at operation.

III. ABSTRACT

OVARIAN CYSTS

References:

*1. McCarty, R. B.:
Histogenesis and tendency to bilaterality of papillary ovarian cysts.
Surg., Gyn. and Obst. 55: 188-192, '32.

*2. Green-Armytage, V. B.
Ovarian Tumors.
J. Obst. and Gyn. Brit. Emp. 38: 111-113, '31.

3. Frank, R. T.
Premature sexual development in children due to malignant ovarian tumors.
Am. J. Dis. Child. 43: 942-946, '32.

4. Weinstein, M.
The relation between appendicitis and right ovarian retention cysts.
Am. J. Surg. 13: 270-272 (Aug.) '31.

5. Jones, H.
Primitive methods in abdominal surgery.
M. J. & Rec. 133: 142-143, '31.

6. Lepper, E. H., Baker, A. H., Vaux, D. M.
Granulosal-cell tumors of the ovary.
Proc. Roy. Soc. Med. 25:1241-1244, (June) '32.

*7. Taylor, H. C. and Wilson, E. A.
Spontaneous regression of peritoneal implantation from ovarian cystadenoma.
Am. J. Ca. 16: 1305-1325, Nov. '32.

*8. Bell, W. B. and Datnow, M. M.
Ovarian Neoplasma.
Am. J. Ca. 16: 1-55 (Jan.) '32.
Am. J. Ca. 16: 439-459 (May) '32.

*9. Masson, J. C. and Hamrick, R. A.
Pseudomucinous cystadenoma.
Surg. Gyn. and Obst. 50: 752-756, (April) '30.

*10. Meyer, R.
The pathology of some special ovarian tumors and their relation to sex characteristics.
Tr. Am. Gynec. Soc. 56: 161-179, '31.

11. Wakely, C. P. G.
Ovarian teratomatous cysts occurring in children.
Surg., Gynec. and Obst. 56: 692-695, (March) '33.

*12. Popoff, N. W.
Testicular tubular adenoma of the ovary.
Arch. Path. 9: 31-53, '30.

13. Sedlis, E.
Geschlechtsumstimmung durch Ovarialtumor (Arrhenoblastoma).
Arch. & Gynak. 149: 225-256. '32.

14. Leob, M. J. and Levy, W.
Ovarian cysts and tumors in children

under 10 years of age.
Arch. Pediat. 49: 651-666, (Oct.) '32.

*15. Moench, M. L.
Clinical study of 403 cases of adenocarcinoma of the ovary.
Proc. Staff. Meet. Mayo Clinic 7: 506-507, (Aug. 31) '32.

Symposium:

16. Stevans, T. J.
Ovarian tumors from the pathological aspect.
Jr. Obst. & Gynec. Brit. Emp. 38: 256-263, '31.

17. Whitehouse, B.
Clinical aspects of ovarian tumors.
Ibid. p. 264-279.

18. Fleming, A. M.
Clinical survey of consecutive cases of ovarian enoplasms.
Ibid. p. 280-301.

19. McIntyre, D.
Consideration of malignancy in ovarian tumors.
Ibid. p. 302-313.

20. Lochrane, C. D. and Keatinge, G. F.
Survey of 180 cases treated at Derbyshire Hospital for women involving 210 neoplasms.
Ibid. p. 314-323.

21. Masson, J. C. and Mueller, S. C.
Ovarian tumors of thyroid tissue.
Surg., Gyn. and Obst. 56: 931-938, (May) '33.

*22. Taylor, J. M., Wolfermann, S. J. and Krock, F.
Arrhenoblastoma of the ovary.
Surg., Gyn. and Obst. 56: 1040-1046, (June) '33.

* Excellent.

Introduction:

There is a marked trend in all literature on tumors to insist on more accurate differentiation. The days of "round-cell," "carcinosarcoma," etc. are gone. The data on tumors becomes valuable in proportion to the efficiency of this differentiation. Tumors of the ovary particularly are in need of more exact classification. The various new tumor groups under discussion are confusing at present because of their multiplicity but the value in estimating prognosis is already apparent.

Historical:

Jones gives a highly interesting historical sketch. He graduated from medical school in 1876 and personally observed the development of surgery. Commenting on abdominal operations, he states that Numa Pompilius the second ruler of Rome passed a law that no woman dying in childbirth was to be buried without an attempt to deliver the child by means of abdominal incision. Scipio Africanus, Caesar and (according to mythology) the God of Physic and Bacchus were all born by section. The art of laparotomy was then forgotten.

William Hunter, 1762, and L'aumoneir dared to revive it in spite of a ban on abdominal operations. In 1809, a Dr. McDowell of Kentucky did the first operation in America for ovarian cyst. Lazars in 1823 did the first ovariotomy. Not until 1857 (Spencer Wells) did laparotomy become established but even in 1873 (Jones' school days) few abdominal operations were done. Jones, a few years after graduation, was called to assist a Dr. Dunlop (Ohio) in performing an ovariotomy for a cyst. He gave the anesthetic (chloroform). The patient was placed on the dining-room table. Two tubs were at the foot of the table; one contained water and sponges, such as were used to wash buggies; the other was empty, for waste.

Dr. Dunlop clamped the pedicle of the cyst with a hemostat which he had just invented but had never used before. It failed to hold securely. During the night after the operation, Jones was awakened by a messenger who stated that the patient's "guts were all in the bed." In the morning, he and Dunlop viewed the

patient. Jones, recalling that Cato, the younger, after eviscerating himself, pushed his physician away because he feared the physician would replace the bowels and save his life, states that he was encouraged to do something. They proceeded to "replace the cold intestines through the hole where they had crawled out." The patient "made a good recovery and lived many years to finally die of cancer of the uterus."

Anatomy:

The anatomy, particularly the embryology, of the ovary and adjacent structures is the basis for most classifications of tumors of these structures.

The derivatives from the various fetal structures in the male and female are as follows (Cunningham).

	Female	Male
Wolffian Duct	1. Duct of epoophoron (Gaertner's duct). 2. Appendix vesiculosa (hydatid of Morgagni).	1. Ductus deferens (vas). 2. Ejaculatory ducts. 3. Seminal vesicles.
Mesonephros	1. Ductuli transversi of epoophoron. 2. Paroophoron	1. Efferent ducts of testis. 2. Aberrant ducts of epididymus. 3. Paradidymus (another aberrant body)
Müllerian Duct	1. Uterus 2. Tubes 3. Vagina	1. Appendix of testis. 2. Utriculus masculinus.
Genital ridge	1. Ova follicles 2. Rete of ovary (?)	1. Seminiferous tubules. 2. Tubuli recti. 3. Rete testis.

The organogenesis of the ovary is equally important as a basis for classification. The surface epithelium of the genital ridge proliferates into the mesenchyme in vertical cords (egg-tubes). The cells in these cords are pinched off in groups. One cell of each group develops into an ovum and the remainder into the encircling nutrient cells, the theca, follicular or granulosal cells. In the adult ovary, the remaining surface epithelium is scanty and it is still a question whether any new ova and follicles can develop.

These questions arise - are there any aberrant or residual egg-cords in the adult ovary from which tumors can develop? Are these rests (tubular or glandular) from which one could expect secreting cysts to arise? McCarty studied 50 normal ovaries and found epithelial cystic or tubular structures in 64%. Stevens states that he has observed such structures. Goodall in 1912 by painstaking serial sections had previously demonstrated the presence of these rests. The opinion of McCarty and others is that these tubules are not related to follicles but are remnants of egg-cords.

Classification:

All accepted classifications are on an embryological or histogenetic basis. However, due to lack of absolute knowledge regarding the site of origin of many of the tumors, these classifications are entirely tentative. Particularly unsatisfactory are the classifications based on clinical course (malignancy). Gardner's classification is of this type. The following taken from W. Blair Bell is modified to some extent (chiefly by omission of the divisions into malignant and benign).

Neoplasms of the Ovary

I. Intrinsic Origin.
  A. From normal functional tissues.
    (1) Lipidomata*
      (a) Capsular mesothelium, surface adenoma (Papilloma).

*Adam's term taken from the Greek meaning covering or lining.

(b) Granulosal-cell (See below for synonyms).
(c) Lutein-cell (?).
(d) Interstitial cell (?)
(e) Endothelioma and perithelioma (surface carcinoma).

(2) From connective tissues
(a) Fibroma
(b) Myoma
(c) Myofibroma
(d) Chondroma
(e) Osteoma
(f) Lipoma
(g) Sarcoma
(h) Rhabdomyosarcoma

B. From developmental relics.
(1) Adenomata
(a) Solid
(b) Pseudomucinous cystadenoma
(c) Serous cystadenoma
(d) Thyroma (?)
(2) Papillary adenoma
(3) Testicular adenoma (see below for synonyms)

C. From sex-cells: Teratoma
(1) Cystic
(2) Solid
(3) Neuroma (?)
(4) Thyroma (?)

II. Extrinsic Origin
A. Developmental inclusions
(1) Suprarenal (?)
(2) Endometrioma

B. Invasion from without
(1) Chorioepithelioma
(2) Endometrioma
(3) Carcinoma
(4) Sarcoma

C. Metastatic tumors

This classification does not conform to all the ideas of other writers. It disregards the follicular or retention cysts entirely. Apparently, this author regards them as inflammatory and not neoplastic and this seems to conform to the general opinion. Lutein-cell cysts are questionably or tentatively included with the tumors from normal tissue because there is no proof that they arise from the theca cells. Such origin, however, is generally accepted. Interstitial cell tumors are questionably placed in the outline. Such tumors may not exist and nothing of significance was found in the literature to explain of what such tumors would consist.

The term, endothelioma, is used here in the sense of mesodermal origin in distinction to the term carcinoma, denoting epidermal origin; i.e., like "endothelioma" of pleura. Other writers prefer the term carcinoma. It is the malignant form of surface adenoma or papilloma mentioned previously. The group designated as "perithelioma" likewise has no right to a special name. The term is descriptive and denotes a perivascular arrangement of cells. Therefore, in position of (e) above the term "surface carcinoma" could be inserted.

Group B is the most disputed group. Bell avoids many arguments by the heading "developmental relics." This does not commit one very closely and includes relics of egg-tubes, misplaced surface epithelium, reti ovarium, etc. The arguments over which of these elements actually is responsible do not appear to be significant however. The main point of controversy is whether or not such relics are the actual sources for the cystadenomata. The main argument for acceptance of this theory is that such remnants are common in the ovary (McCarty 65%) and that there are no other cells which could possibly give rise to the tumors. Against this theory is the argument that the ova, follicular cells or surface epithelium have never been demonstrated under any circumstance to secrete pseudomucinous material. A metamorphosis from egg-tube cells to secreting cells has no parallel in tumors anywhere in the body.

The inclusion of the cystadenomas in this group would be contested by many other writers. The alternate theories are (1) the cystadenomas arise from mesonephric inclusions in the ovary and (2) they are teratomata with a one-sided growth of glandular elements. The mesonephric inclusion theory has for its support the fact that epoophoron, uterus

and the tubes (glandular secreting organs) arise from mesonephric elements. The advocates of the teratoma theory have shown that in a certain percentage (14) of cyst-adenomata teratoid elements are present. Such a combination is very strong evidence for this theory especially since pseudomucinous secretion appears too foreign to germinal cells.

Like many others (including Ewing), Bell makes no distinction between smooth and papillary cystadenomata. Clinically, there is no question that such a distinction is valuable. Some men (i.e. Broders and others) regard the papillary tumors as all potentially or actually malignant. Genetically, no distinction can be made. Finally, like all other similar tumors, no transition between benign and malignant forms has been demonstrated.

The inclusion of thyroma with cystadenoma is not in agreement with most writers. Students of this tumor definitely classify it as a dermoid tumor showing an overgrowth of thyroid tissue. (Also known as Strum Ovarii, etc.)

Testicular adenomas are extremely rare tumors. Meyer and also Popoff have studied this tumor extensively. The tumors occur most frequently in hermaphrodites either true or false, and seem to be better classified as a foreign inclusion in the ovary.

Group C in Bell's classification is generally accepted. However, there does not appear to be a need to place neuroma and thyroma into a special class. They are teratomata showing one-sided development.

On the basis of these composite discussions, taken from the various writers, a classification is made trying to incorporate the most generally accepted theories.

<u>Ovarian Cysts</u> (combined classification)

A. Inflammatory Types.
   I. Follicular and simple serous cysts.
      (a) Single
      (b) multiple
      (c) Fused (multilocular) multiple cysts.

B. Neoplastic cysts.
   I. From normal functioning tissue.
      (a) Epithelial
         (1) Surface epithelium
            adenoma
            Papilloma
            Carcinoma
         (2) Granulosal-cell tumors
         (3) Lutein-cell tumors
      (b) Connective tissue
         (1) Fibroma
         (2) Myoma, etc.

   II. From development relics
      (a) Adenomata (?)
         (1) Solid
         (2) Cystic
            Pseudomucinous, smooth and papillary
            Serous, smooth and papillary.

   III. From sex cells (teratomata)
      (a) Solid teratomata
      (b) Cystic teratomata
         Dermoid, thyroma, neuroma, cystadenomata (?), etc.

   IV. Developmental inclusions
      (a) Testicular adenomata
      (b) Suprarenal, etc. (?)
      (c) Endometrioma (?)

   V. Metastatic and Extension tumors.

This classification disregards fimbrial and broad ligament cysts. Fimbrial cysts according to most but not all writers are ovarian cysts developing on the fimbrial side of the ovary and including in their growth the end of the tube by extension. The term "fimbrial" therefore signifies position rather than etiological difference. Broad ligament cysts are of two types. One group arises from the epoophoron. These are usually small and covered by the peritoneum of the broad ligament on both sides. The other groups are various types of cysts similar in nature to ovarian cysts. They have been accepted by some as arising in aberrant ovaries in

the broad ligament. Others, chiefly those who believe cystadenomas arise from mesonephric elements, state that all these broad ligament cysts arise from the epoophoron and argue that this is an indication that all cystadenomas are of mesonephric origin.

Clinical-Pathological Considerations:

Retention cysts or follicular cysts.

Nothing of particular significance was found regarding these cysts. Weinstein states that in 167 female patients operated upon for mild or chronic appendicitis, 14% had rightsided follicular cysts and only 2.4% leftsided cysts. He believes this is an indication that chronic appendicitis produces an ovaritis and subsequent retention cysts. (It is possible that in these cases of rightsided cysts the symptoms of "chronic" appendicitis were due to the cysts themselves.)

Lutein-cell cysts.

There are several reports of sudden severe abdominal hemorrhages from these cysts. The only other point of interest found is that some rare forms of ovarian carcinoma and adenomata can arise from these cells. Ewing states that in cases of uterine "moles" the cysts are multilocular and bilateral in 70 to 90% of cases. After delivery of the mole, the cysts regress. They are not present in chorioepithelioma.

Cystadenomata and Dermoids.

The general pathology of these tumors is well-known. The cystadenomata manifest three lines of growth: epithelial hyperplasia, epithelial secretion and growth of the wall. The epithelial hyperplasia is of variable growth. When it grows more quickly than the fibrous wall, it becomes thrown up into papillae. When secretion within the cyst increases, the papillae become flattened out. Genetically, therefore, a papillary cyst is considered to be no different than a smooth cyst. Papillae are said to denote rapidity of growth of the epithelium. When secretion is more rapid than the growth of the fibrous wall rupture occurs. When rupture is from one loculation into another, no damage is done; when a surface loculation breaks, the contents escape into the peritoneal cavity.

The general pathology of teratomata likewise needs little comment. Solid forms are the types with little secretion; otherwise they do not differ from the cystic types. Entodermal elements are the least common. Unusual curiosities can be developed, for instance, the dermoid may contain a carcinoma of breast or skin which metastasizes within the dermoid.

Several types of statistical studies on these groups of tumors have been made in the past few years. It is extremely difficult to correlate these reports because of differences in terminology and methods of study. They can be abstracted only in somewhat disconnected paragraphs.

Relative Incidence

B. Bell and Daknow (2603 collected cases)

Cystadenomata	48%
Carcinoma, primary and secondary	20%
Cystic teratoma	14%
Papilloma (papillary cystadenomata?)	9%
Fibromata	6%
Sarcomata	2%
Other varieties	1%

B. Bell and Daknow - malignant tumors (224 cases).

Carcinoma	88%
Sarcoma	8%
Teratoma	3%

Green-Armytage (India)

13,422 patients.

437 ovarian tumors	3.25%
110 ligamentous and fimbrial cysts	.8 %

Simple cystadenomata	257	56%
Malignant tumors	59	12%
Papilliferous cystadenomata	45	10%
Dermoids	38	8%
Chocolate cysts	38	8%
Twisted cysts	37	8%

Cysts in childhood are not rare.

Wells - 1000 ovariotomies, 3 in children.
Gardner - 607 tumors, 5.6% under 20.

Summary of Wiel's, Downe's, Loeb's and Loeb-Levy's series:

Cyst, single or multiple	50	32%
Dermoids or teratoma	49	32%
Sarcoma	20	13%
Sarcoma or carcinoma	19	13%
Carcinoma	14	8%
	152	

Parity:

	Cystadenomata	Papillary	Dermoid	Fibroma	Carcinoma
Total cases	212	95	122	58	161
Percentage					
Single	27	17	22	19	19
Married	73	83	78	81	81
Nulliparous	34	20	21	13	33
Parous	66	80	79	87	67

The percentage of nullipara in the cystadenoma and carcinoma group is higher. Nulliparity increased to about 40% in cases of bilateral cysts.

Abortions: 200 cases (Whitehouse) only 3.2% had repeated abortions; indicating little influence.

Menstruation: Whitehouse, in a collected series, 70% of total and 45% of those before the menopause had no disturbance. "The influence upon menstrual function is very slight."

Fleming: (152 cases).

Simple serous cysts: 15% with irregular bleeding -- "Disturbance slight."

Serous Cystadenomata:

Bleeding	23%
Dysmenorrhea	15
Metrorrhagia	31
Menorrhagia	23

"Disturbances fairly frequent"

Pseudomucinous cysts:

Irregular menses	21%
Menorrhagia	18
Metrorrhagia	18
Dysmenorrhea	26

Papillary Serous Cystadenomata:

Dysmenorrhea	32%
Menorrhagia	32
Metrorrhagia	21

Carcinoma:

Irregular bleeding	44%
Menorrhagia	12

Teratoma:

Dysmenorrhea	30%
Metrorrhagia	20
Menorrhagia	25
Irregular menses	25

From Fleming's data, it appears that menstrual disturbances are quite common. She adds that 70% of the cases have no history of miscarriages and this is approximately equal to the percentage present in other pelvic conditions.

Side Involved: From Popoff's review of bi-sexuality, sex reversal, etc., it appears quite definite that the right ovary is less stable than the left. A review of statistics on cysts dealing with the side involved yielded only the following (McIntyre).

	Malignant	Doubtful	Benign	Total
Left	17	6	37	60
Right	24	4	30	58
Not stated	5	1	3	9

Apparently, in case of cysts, there is no difference in frequency of the side involved.

Bilateralism:

E. T. Bell:

Serous papillary cystadenoma	75%
Pseudomucinous	25

Ewing:

Serous	60%
Pseudomucinous	18
Carcinoma	66

Fleming:

Simple cysts	33%
Serous (smooth)	68
Pseudomucinous	33
Serous (papillary)	12
Carcinoma	40

Lochane:

Pseudomucinous	17%
Serous	33
Carcinoma	44
Dermoid	6

McIntyre:

Malignant	27%
Benign	14

Masson and Hamrick:

Pseudomucinous, benign	22%
Pseudomucinous, malignant	28

It is not possible to make an average of these statistics. Ewing's figures appear to be about the estimated average.

McCarty's study of the opposite normal-appearing ovary in cases of unilateral papillary cysts is of interest. He found in the normal ovary microscopic epithelial cystic structures in 100% in contrast to 64% in cases of bilaterally normal ovaries. In 2 of these cases, the structures had gone on to the formation of tumors. His impression is that the opposite ovary contained the elements for the formation of the cyst and that it is not transferred from the affected ovary.

Malignancy in Cysts:

It is questionable if one can speak of malignant degeneration of a cyst. No one has ever observed such a change. Some writers claim that benign tumors are always bening and malignant ones had this characteristic from their beginning. The theory of malignant transformation of benign growths however is supported by the behavior of other types of tumors, i.e., bowel, skin, liver. At present, therefore, it is permissible to speak of malignant changes, precancerous and potentially cancerous lesions.

Relative incidence of carcinoma (all types) is listed as follows:

B. Bell and Datow	20%	(includes metastatic)
B. Bell and Datow (232 cases)	12%	(primary)
Green-Armytage	22%	
Doderlin	10%	
Liffert	16%	
Whitehouse	21%	
Bride	21%	
Fleming	20%	

No average of the entire group can be made.

The percentage of malignant change according to type of cyst is given as follows:

Pseudomucinous (both papillary and smooth)

Pfannenstill	2%
Masson and Hamrick	7%
Mayfield	6%
Fleming	8%
Masson & Hamrick	26%

Serous (both papillary and smooth)

E. T. Bell	25%
Pfannenstill	50%
Fleming	38%

Papillary serous:

Fleming	12%
Lochrane	61%

Teratomatous cysts:

Frankl	1 - 2%
Grawzdell	7%
Ssokolow	10%
Rohdenburg	10%

Lochrane studied the papillary cysts and gives the following incidence of malignancy:

Papillary serous	61%
Papillary pseudomucinous	50%
Internally papillary cysts	38%
Externally papillary cysts	97%

He concludes that external papillae almost always show evidences of

malignancy.

Peritoneal implants in papillary cysts:

The implantation of fragments of the papillae and their growth at these points does not truly constitute the malignant state. Histologically, the implants may be entirely benign. They nevertheless continue to grow and secrete. Ascites may be the only evidence of their presence. If the fluid is absorbed, this sign is absent. Later secretion may overtake absorption and symptoms of "recurrence" begin. Intervals of 15 to 20 years before the recurrence are recorded. In some cases, laparotomies have been done one or more times during the interval and the implants have been observed over a period of many years in an unchanged condition. Finally, in a few cases, the implants have been killed. The process apparently is one of overgrowth and "strangulation" by fibrous tissue coming from around the site of the implant. In some unusual cases, biopsies during this course have been taken and have demonstrated a terminal malignant change.

Students of this unusual phenomena of benign peritoneal implants emphasize the benign characteristics: small size, delicate structure, non-invasive nature, fibrous and avascular attachment. The cases with definitely invasive characters always have a rapidly fatal course. The distinction between the two types of implants is worthwhile because of the difference in prognosis. Opening of the abdomen has a beneficial effect on the regression? It is suggested that the irritation to the serosa stimulates the fibrous tissue overgrowth of the implants. When benign implants are found, excision of the primary cyst is recommended. Removal of as many of the implants as possible can be done. Taylor thoroughly reviews this subject. He collected 46 such cases and added 5 more.

Pseudomyxoma Peritonei presents very much the same situation as discussed above. The interval before the "recurrence" may be as much as 22 years. In addition to the process already described in this case, another factor is present. The myxomatous material becomes caught in the lymphatic channels. The plugging and the fibrosis closes off these channels and increases the severity of the condition. A thick, heavy peritoneum impregnated with the secretion is the usual finding.

Biological activity of ovarian cysts and tumors:

The phases of endocrinopathy are so confused at present that very little in the way of explanation or conclusions can be drawn. This is particularly true in regard to sex characteristics. Some extraordinary things are reported. An example is the case reported by Crew in which "a hen, mother of many chickens, began to assume the appearance and behavior of a rooster, and became the father of a number of chickens."

It can be safely said that the cysts described so far have no significant biological activity except possibly the effect on menstruation and parity. Possibly an exception may have to be made in case of children. Frank in 3 cases observed precocious sexual development in all three. One of these was a malignant teratoma, another a "medullary" carcinoma and the third an "embryonal alveolar" carcinoma. In the last tumor, a high hormone content was found and the child's urine showed a similar unusual hormone content. This suggests that the tumors probably belonged to the granulosal-cell tumors to be described below. Another possible exception is in case of the dermoids with a preponderance of thyroid tissue. It has been suggested that hyperthyroidism may occur.

There are 3 tumors of the ovary characteristically associated with sex changes: testicular adenoma, the granulosal-cell tumor, and the disgerminoma. All of these are popular tumors at the present time and quite extensively discussed. They are only moderately rare and the reported numbers is rapidly increasing. The characteristics of each are briefly reviewed by Robert Meyers (most active writer on the subject). His theories of origin are not entirely accepted.

Disgerminoma. Synonym: "seminoma."

This tumor is most frequently found in pseudo-hermaphrodites (Meyer: 48 cases, 27 pseudo-hermaphrodites). It occurs in young individuals. Its characteristic cell is the same cell as that in the common teratoma of the testis. Considerable argument is found as to whether this is a sperm-cell tumor. Ewing very emphatically classifies it with the teratomata. The tumor (in the female) has no hormone activity but is included in this group because of its frequent presence in pseudohermaphrodites.

Granulosal-cell tumors: Synonyms: carcinoma cylindratosum; carcinoma folliculoius; oophoroma folliculare; folliculoma. Also known by the names of various writers: Van Kahlden, Isbruch, Newmann, Meyer, Brenner, Te Linde, Gottschalk, Picard, Tietze. Of these, "Brenner's tumor" is one frequently used. About 50 of these tumors are now on record. They occur at any age, the majority between 20 and 50. They are characterized by the cellular appearance of granulosal or follicular cells, high content of female hormone and hyperplasia of the uterus and endometrium. Enlargement of breasts and galactorrhea may occur. Bleeding is a common symptom and precocious sexual development in children is probably always present.

In a typical case small round clear (microscopic) areas in the tumor may be seen which appear exactly like a young developing follicle. A single cell in the space appears like an ova. Proof that the cells are actually granulosal is not yet established. Most writers feel that the central cell is not an ova but a desquamated lining cell. The fluid is thought to be follicular fluid. Great variability in arrangement of the cells is present. There may be a follicular, cord or strand-like or irregular arrangement. The tumors are malignant but metastasize slowly. Excision results in cure in about 80% (Meyer). They may be bilateral.

Arrhenoblastoma (arrhenos meaning male). Synonym: adenoma tubulare testiculare, testicular adenoma, Pick's tumor.

This tumor is extremely odd. Defemi-nization results: atrophy of breasts, falling out of head hair, atrophy of uterus, amenorrhea, enlargement of clitoris, development of male type of hair, beard, voice, etc. All of these changes disappear after removal of the tumor. The cytology of some of the tumors is identical with that of an atrophic testis, i.e. testicular tubules and interstitial cells without spermatogenesis.

As in the previous tumor, the variation is marked. The tubules may be markedly irregular in form and some of Meyer's microphotographs show a cytology so anaplastic as to suggest teratoma or sarcoma. Apparently the tumors do not metastasize. Popoff gives an excellent discussion of the embryology and physiology of this tumor.

Mortality (operative)

The following percentages are listed by Whitehouse.

Author	Cases	Benign%	Malignant%	Total%
Kerr	250	---	---	4
Donald	252	---	---	2
Bride	100	4	10	5
Whitehouse	200	4	8	5
Green-Armytage	547	4	25	7
Total	1349			5

The mortality of hysterectomy is about 2% (Kerr). The higher mortality of ovariotomy is due to the poor condition of the patients and the more complicated pathology (size, adhesions, etc.)

End Results: are difficult to summarize. Some series are small; others fail to state clearly the term of follow-up and often differences in classification make it impossible to correlate the groups.

Type of tumor	Author	Cases	Time of follow-up	Well	Dead
Non-papillary serous cystadenoma	Fleming	13	?	57%	29%
Papillary serous cystadenoma	Fleming	19	?	79	0
	Moench	254	3 yr.	--	27
Pseudomucinous cystadenoma	Fleming	38	?	76	20
Cystic carcinoma	Moench	72	3 yr.	--	56
Carcinoma: solid or indefinite	Moench	77	3 yr.	--	62
	Fleming	25	?	--	61
	McIntyre	63	?	--	67
Dermoid	Fleming	20	?	88	22

Some other data is of interest. Moench: deaths in patients with ascites, 57%; with ruptured pseudomucinous cysts, 54% at end of 3 yr. Deaths in those with apparent metastasis at operation, 75%; without metastasis, 42%. Those with metastasis limited to the pelvis had a better chance to live 3 years than those with pelvic and abdominal metastasis: 39% against 23%. In the entire group (carcinoma and papillary cysts), it is interesting to note that the proportion of deaths after removal of one ovary (22%) is identical with that after removal of both (21%). An analysis of this last point is not given. The deaths in bilateral tumors was 44% and 18% in those with unilateral tumors. The statement regarding the mortality after unilateral or bilateral ovariotomy is difficult to understand.

Impressions:

1. There is an attempt at the present time to analyze ovarian cysts on a basis of cell origin.

2. The embryology and organogenis of the ovary is the basis for the various classifications.

3. Almost any classification is unsatisfactory to others because of the variability of opinion regarding the issue of origin.

4. One of the recently presented classifications is reviewed in light of the writings of other workers.

5. An attempt at a composite classification is given. (Turn to classifications).

6. Retention or follicular cysts appear to be inflammatory in origin?

7. Lutein-cell cysts are due to unusual hemorrhage into a corpus luteum. Sometimes excessive bleeding into the peritoneal cavity occurs. Multilocular bilateral luteal cysts are found in cases of uterine moles.

8. In the cystadenomata, the papillary or smooth structure is said to be due to the balance between growth of epithelium and amount of secretion. On this basis, papillary cysts are not genetically different from smooth cysts. Clinically, this is not borne out.

9. Ovarian cysts (neoplastic) are found in about 3% of gynecological patients. About 50% of these are cystadenomata, 20% carcinomata (primary and metastatic), 15% teratomata.

10. The average age of all types is about the same: 45 - 50. The teratomata occur at an earlier age and carcinomata at a slightly older age.

Childhood is not exempt. At this age the tumors are equally divided between cystadenomata, teratomata and malignancies.

11. The fertility of women with cysts is generally uneffected. In cystadenomata and carcinoma, the parity is somewhat lower and is definitely lower when the tumors are bilateral (histories of pregnancies).

12. Menstruation according to some authors is not affected; others show "fairly frequent" disturbances.

13. There is no greater frequency of involvement of one ovary over the other (except in follicular cysts?).

14. Bilateralism is a characteristic feature of certain tumors. The actual statistics vary so greatly that a summary is difficult: serous types, 33% to 75%; pseudomucinous, 17% to 33%. 60% for the former and 20% for the latter is the estimated average.

15. The incidence of carcinoma is estimated at 10 to 20% of all tumors of ovary. The incidence of carcinoma, according to the cyst type, is too variable to summarize: pseudomucinous 2 to 26%, serous (all types) 25 to 50%, papillary cysts 12 to 61%, teratoma 1 to 10%. Cysts with external papillae are nearly always malignant.

16. Implants on the peritoneum may be benign or malignant. When actually invasive, death occurs in a short time. In case of benign implants, as much as 25 years may intervene before a "recurrence" takes place. In such cases, symptoms are present only when secretion is faster than absorption. Malignant transformation may occur later or the implants may be killed by overgrowth of fibrous tissue. 58 cases of the latter course have been recorded.

17. Pseudomyxoma Peritonei is due to the same process except that the secretion is very heavy and soon plugs up the lymphatics. It may also be benign.

18. None of the usual types of cysts have any biological activity. Three rare tumors are associated with sex changes.

19. The disgerminoma is a tumor similar to the common teratoma of the testis but found in the ovary usually of pseudoheraphrodites. It otherwise has no sex activity.

20. Granulosal-cell tumors are not uncommon. They have a high content of female hormone and produce hyperplastic changes in uterus and breast and in children precocious sexual development. These changes regress after removal of the tumor.

21. The arrhenoblastoma (testicular adenoma) produces marked reversal of sex characteristics; the changes regress after removal of the tumor.

22. Estimation of end-results is difficult. The operative mortality in 1349 cases was 5% (double that of hysterectomy). About 25% of the cystadenoma of both types die within 3 years. The manner of death could not be determined from the data. About 56% of the carcinomatous cystadenomata and 65% of the other types of carcinoma die within 3 years.

23. The presence of ascites, pseudomyxomatous peritonei, and apparent presence of metastasis make the prognosis worse.

24. Long-time follow-up obviously would show greater differences in the outcome between the various cyst types.

25. The 25% of deaths within 3 years or sooner (3 different groups) in the benign cysts suggest that the character of this type is more malignant than generally appreciated.

\- - - -

N E X T W E E K

AMEBIC DYSENTERY