Chapter 11

DISEASES OF THE OVARY AND PAROVARIUM

Tumors constitute the principal lesions occurring in the ovary, and of these about 95 per cent are cystic. There occur also infections, mostly secondary inflammation, and endocrine disturbances with important functional and structural results.

Satisfactory classification of ovarian pathologic changes has long been one of the problems of systematic gynecologic teaching. The reason for this lies in the complexity of the organ's structure and physiology and the resulting complexity of its pathologic activities. The principal difficulty is with the great variety of benign growths and near-growths, some of which are real neoplasms and others only retention cysts.

In our previous edition we presented a classification of ovarian pathological conditions based upon causes as far as they were known at that time. In the intervening years there has been a great deal of work done on the classification of ovarian tumors. The material for such classifications has been gathered from Fischel's fundamental work on embryology of the ovary and also from the work of Robert Meyer, Schiller, Novak, and others. In 1947 Spencer and Reel presented an excellent classification based on the histogenetic origin of the tumors, and we have included it here because of its value in clarifying the origin of the tumors. We feel, however, that there is a need for a clinical classification of ovarian conditions for it is seldom possible to be sure of the type of tumor or cyst one is dealing with prior to operation, and even with the abdomen open microscopic examination is frequently necessary before the particular histogenetic derivation of the tumor can be determined. Hence we are offering the classification below and hope that it will be of help in clarifying the situation.

Clinical Classification of Diseases of the Ovary and Parovarium

CONGENITAL ANOMALIES
- Absence of Ovary
- Agenesis of Ovary
- Accessory Ovary

PROLAPSE OF OVARY AND CIRCULATORY CHANGES

INFECTIONS
- Inflammation (gonococcus and ordinary bacteria)
- Tuberculosis, Syphilis, and Rarer Infections

DISTURBANCES OF FOLLICULAR FUNCTION
- Follicular Atresia
- Follicular Cysts. Stein-Leventhal Syndrome
- Corpus Luteum Cysts
- Theca-Lutein Cysts. Follicular Atrophy

- BENIGN GROWTHS
  - Proliferating Cysts
    - Pseudomucinous Cysts
    - Serous or Papillary Cysts
  - Dermoid Cysts
  - Solid Growths
    - Fibroma, Myoma, Adenomyoma
    - Brenner Tumor
- OVARIAN CANCERS
  - Carcinoma
    - Primary
    - Secondary
  - Sarcoma
    - Primary
    - Secondary
- MALIGNANT TUMORS FROM OVARIAN MESENCHYMA
  - Endocrine Influence
    - Granulosa-Cell Tumors, Thecoma, Luteoma
    - Arrhenoblastoma
    - Gynandroblastoma
  - No Endocrine Influence
    - Dysgerminoma
- MISCELLANEOUS RARE TUMORS
- TUMORS OF UTERINE LIGAMENTS
  - Parovarian Cysts
  - Gartner Duct Cysts
  - Round Ligament Myomas
- TRANSPLANTATION OR HETEROPLASIA OR EMBRYOLOGIC RESTS
  - Endometrial Cysts
  - Pelvic Endometriosis

Histogenic Classification of Ovarian Tumors by Spencer and Reel

I. Ovariogenetic: (tumors developing from tissues of true ovarian structure)
   A. From the *mesenchymal core* of the ovary.
      1. From fetal cell remnants *without error in sex chromosomes*
         a. Granulosa cell tumors
         b. Theca cell tumors
      2. From fetal cell remnants *with error in sex chromosomes*
         a. Arrhenoblastoma—male
         b. Disgerminoma—neuter
      3. From interstitial tissues *without sex potential*
         a. Fibroma
         b. Angioma
         c. Myoma and fibromyoma
   B. From the *surface epithelium* of the ovary (prosoplasia toward the Müllerian duct)
      1. Serous cystoma (tube)
      2. Endometrioma (endometrium)
      3. Pseudomucinous cystoma (cervix)

II. Nonovariogenetic: (tumors developing from tissues not normally present in the ovary)
   A. By displacement into the ovary in fetal life
      A. Early—teratoma
         a. Mature—dermoid
         b. Immature—embryoma

2. Late—tissue from structures contiguous to the ovary during embryological development
   a. Hypernephroma—adrenal
   b. Mesonephroma—kidney
   c. Brenner tumor—urogenital epithelium
   d. Ganglioneuroma—sympathetic ganglia

B. By displacement into the ovary in adult life
   1. Metastases of malignant tumors—Krukenberg, etc.

III. Carcinoma of Undeterminable Histogenesis
   A. Carcinoma simplex, scirrhous carcinoma, plexiform carcinoma, etc.

CONGENITAL ANOMALIES

Absence of one or both ovaries may occur in association with other congenital malformations of the genital tract but only a few cases have been reported. Nichols and Postoloff reported an interesting case in which the ovary on one side was in its normal location and the other ovary was found under the edge of the liver. In this case the kidney and ureter on the same side were also missing.

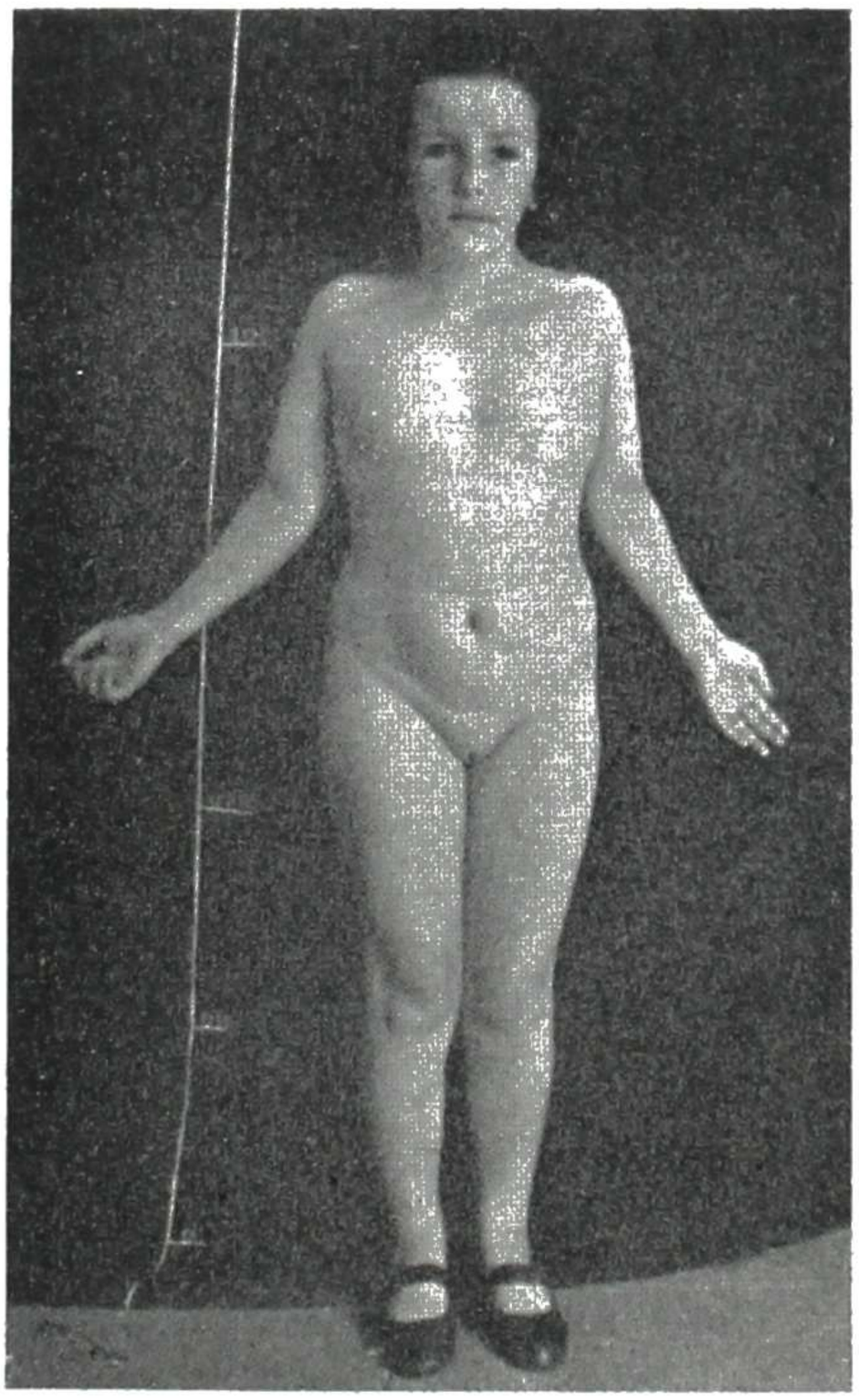


Fig. 841.—Characteristics of a patient having rudimentary ovaries. Note accentuated cubitus valgus described by Turner. (From del Castillo, de la Balze, and Argonz: J. Clin. Endocrinol., June, 1947.)

In 1938 Turner described a condition in which the patient showed signs of infantilism associated with webbing of the neck and a deformity of the elbow (cubitus valgus). He reported seven cases, and in those patients in whom a pelvic examination was done the uterus was small and no ovaries

could be felt. Later, a syndrome in which one finds rudimentary ovaries associated with ovarian insufficiency and an increase in the gonadotrophic hormones was described almost simultaneously by Varney and his co-workers and by Albright et al. in 1942. In 1944 Wilkins and Fleischman applied the name of ovarian agenesis to its clinical entity because the fundamental lesion is one of primary ovarian insufficiency due to rudimentary ovaries. Microscopic sections from such ovaries show none of the differentiated elements which characterize the normal ovary. Clinically these patients are of short stature, and retarded sexual development, with an absence or markedly diminished growth of axillary and pubic hair. The breasts are not developed, the external genitalia have an infantile appearance, and the uterus is very small

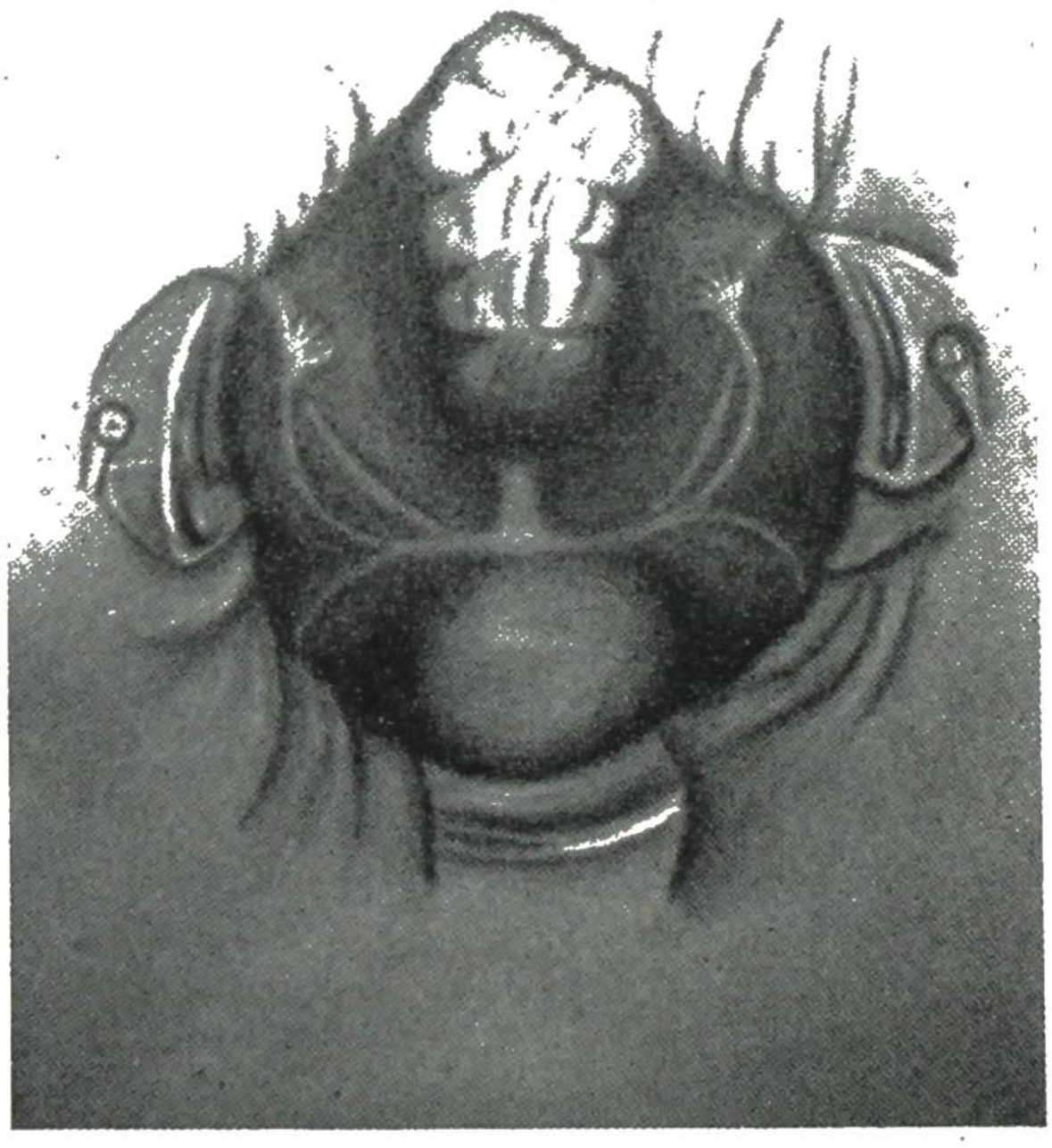


Fig. 842.—Drawing made during the surgical intervention in a case of rudimentary ovaries. The small size of the uterus and the hypotrophy of the round ligaments, tubes, and broad ligaments are observed. Underneath the tubes two whitish cords are seen corresponding to the rudimentary ovaries. (From del Castillo, de la Balze, and Argonz: J. Clin. Endocrinol., June, 1947.)

and hypoplastic. The skeletal system shows a delay in bone aging, diffuse osteoporosis, and vertebral chondrodystrophia. Associated with this condition are frequently found congenital anomalies such as webbing of the neck, cubitus valgus, syndactylism, and coarctation of the aorta. The diagnosis of primary ovarian failure in these cases is made from the clinical picture plus tests for hormonal secretion. There is an increase in the follicle-stimulating hormone in the urine and a marked decrease in estrogen. Albright explains that this is due to the fact that since there is no estrogen in the blood to inhibit the hypophysis, it oversecretes, giving a spill-over of gonadotrophic hor-

mone in the urine. Del Castillo, de la Balze, and Argonz reviewed this entire subject in 1947, discussing in detail the differential diagnosis and reporting eight cases of their own. Fig. 841, taken from their article, shows a seventeen-year-old girl who had never menstruated; note the webbing of the neck and the bilateral cubitus valgus and absence of pubic hair and short stature. The operative findings in another of their cases is shown in Fig. 842. Later in 1947 Lisser et al. presented an additional 25 previously unpublished cases.

Another abnormality occasionally seen is supernumerary ovaries beneath the pelvic peritoneum; there may be two or more sections separated by deep folds. The practical importance of this condition is that when both ovaries are removed these accessory ovaries may function and produce estrogen or they may form ovarian tumors.

PROLAPSE OF OVARY

A large heavy ovary is likely to sink low in the pelvis, especially if its supporting attachments are weakened through subinvolution after labor or through congenital deficiency. The enlargement is often due to the formation of numerous follicular cysts, giving the enlarged "cystic ovary" described later.

Prolapse of the ovary does not ordinarily become of clinical importance unless it drops into the peritoneal cul-de-sac back of the uterus. In this situation it may give rise to pressure symptoms, especially during the menstrual congestion or at the time of ovulation. The principal disturbance comes in those cases in which the ovary becomes adherent in this location, and cannot move on pressure as it normally does.

In most cases giving trouble, the principal complaint is dyspareunia, with the discomfort located high inside rather than at the vaginal entrance. Occasionally there is pain on bowel movement or pressure discomfort when the rectum is filled. In some retrodisplacement cases, the ovary is found low in the cul-de-sac under the corpus uteri, and the disturbance from its fixation there may furnish the principal symptoms.

As to treatment, there may be prolapse and fixation of one or both ovaries without any symptoms. Consequently, when the condition is found in the course of an examination, question the patient carefully to determine if there are symptoms due to it before disturbing her with knowledge of its presence.

When there are troublesome symptoms, the knee-chest posture may aid by gravitating the tender ovary out of the cul-de-sac or by lessening circulatory disturbance in it. If movable and pushed out of the cul-de-sac during examination, it may stay in the improved position. Occasionally correction of the retrodisplacement with a pessary will keep it up out of the way comfortably.

If the ovary is adherent, it may be possible to stretch light adhesions by digital pressure or by use of the mercury pressure bag. If there is persistent discomfort despite conservative measures, operation is advisable to correct the painful condition. Very often there are more important associated lesions requiring operation, and the prolapsed ovary is taken care of incidentally, by removal or fixation, as conditions indicate.

Interference with the circulation to the ovary causes it to become edematous and occasionally cystic. Retrodisplacement of the uterus, with a consequent prolapse of the ovaries, is a common etiologic factor in this condition. Other causes are pressure on the vessels by tumors of other organs, varicose veins, a chronic twist in the pedicle not sufficient to cause a gangrenous ovary, and trauma (operative or otherwise). These ovaries are usually a little larger than normal, and the chief microscopic finding is edema and chronic passive congestion.

INFECTION OF OVARY

Infections include inflammation which may be due to contagious disease or to ordinary pyogenic bacteria (gonococcus, streptococcus, staphylococcus, colon bacilli), and tuberculosis and syphilis.

Inflammation of the ovary is usually secondary to salpingitis or other adjacent inflammation. There may be one or more points of infection with the usual infiltration and swelling—the inflammation involving both the follicles and the interfollicular connective tissue. It may or may not progress to the stage of abscess formation. When an ovarian abscess forms, it is usually in connection with tubal suppuration, hence it was considered along with salpingitis.

The ovary, instead of becoming infected, may simply become surrounded by exudate, which compresses it, damaging it and causing cellular infiltration of the connective tissue (both the capsule and stroma). In time this round-celled infiltration forms scar tissue, and as it contracts it further interferes with the graafian follicles, so that they atrophy or form small cysts. From this process the functionating part of the ovary becomes reduced in size, and the organ may come to consist simply of a mass of fibrous tissue with small cysts scattered through it. This condition is called cirrhosis, and ovaries thus affected are designated as "cirrhotic ovaries," not to be confused with the Stein-Leventhal syndrome.

The other type of inflammation of the ovary is that in which the infection comes by way of the blood stream. This is seen at times in various general infectious diseases, particularly mumps and scarlet fever. The fact should be kept in mind that pelvic symptoms during the course of acute infectious diseases may be due to oophoritis, which may require additional rest and care during convalescence. Ohlmacher gives an excellent review of oophoritis parotidea.

The pathologic findings are the same as those seen in acute inflammation elsewhere in the body. There is edema with dilated capillaries and leukocytic infiltration.

The acute inflammation may resolve, leaving no permanent damage, or it may result in a chronic inflammation with adhesions and permanent damage to the tissue. The common finding in these cases is a mass composed of ovary, tube, and exudate, with or without abscess. In tuboovarian abscess either a tubal abscess ruptures into the ovary or an ovarian abscess ruptures into the tube and the two become fused. Microscopically there is a marked round-cell infiltration. Later there may be destruction of the follicular apparatus and sclerosis of the remaining stroma.

Tuberculosis of Ovary

Tuberculosis of the ovary is almost always secondary to tuberculosis elsewhere. Direct extension is the usual method of infection, and it is commonly secondary to tubal tuberculosis. According to the statistics of Orthmann, in 307 cases of genital tuberculosis the ovary was involved in 33.9 per cent. In the gross the ovary is usually embedded in adhesions and studded with tubercles. In the late cases there are areas of caseation surrounded by thick, ragged walls. Cases of tuberculosis of the ovary associated with ovarian cysts have been reported.

Microscopically discrete tubercles are found in the superficial layers of the ovary. When a follicle or corpus luteum is involved, tubercles are found in the wall of the structure.

The symptoms and treatment are the same as for the more frequent tubal tuberculosis, the details of which are given in the preceding chapter.

Syphilis of Ovary

The protean manifestations of syphilis no doubt affect the ovary in structure and function, and this is to be kept in mind when pelvic symptoms or disturbance appear in patients who have syphilis.

There are only a very few authentic cases of syphilis of the ovary in the literature. In the case reported by Gellhorn and Ehrenfest the gumma was centrally located, indicating its systemic origin. Microscopically it was a granulomatous mass containing a large number of plasma cells and eosinophiles.

DISTURBANCES OF FOLLICULAR FUNCTION

It is surprising how much structural change can be brought about in the ovary by mere disturbances of function. A slight misdirection of the endocrine influences which control normal ovulation may lead to follicular changes in the ovary of marked extent. The most common example of this marked structural change due to functional deficiency is "follicular atresia," in which the ovum dies and the follicle ceases growing and eventually shrivels. This occurs regularly on a large scale, for only a small percentage of the thousands of young follicles go on to maturity. Some of the follicles in which the ovum dies do not shrivel and disappear but fill with fluid which increases, resulting in the formation of small cysts (follicular cysts). Occasionally a corpus luteum instead of progressing normally will develop an increasing amount of fluid (corpus luteum cyst).

The above changes in the ovary occur without any causative lesion of other organs. Reference will be made to changes in the ovary brought about by lesions in other organs. Belonging to this class are the theca-lutein cysts, which may enlarge the ovaries till they fill the pelvis and lower abdomen, and follicular atrophy of the cortical functioning portion of the ovaries.

Follicular Cysts

Follicular cysts are simply unruptured graafian follicles which have become dilated. The increase in the fluid of the follicle and the consequent formation of a small cyst are due to failure of the follicle to rupture. This

failure to rupture may be caused by functional disturbance in the ovarian-pituitary endocrine cycle or it may be caused by mechanical difficulty due to deep situation or to thickening of the tunica albuginea or to peritoneal adhesions covering the surface of the ovary.

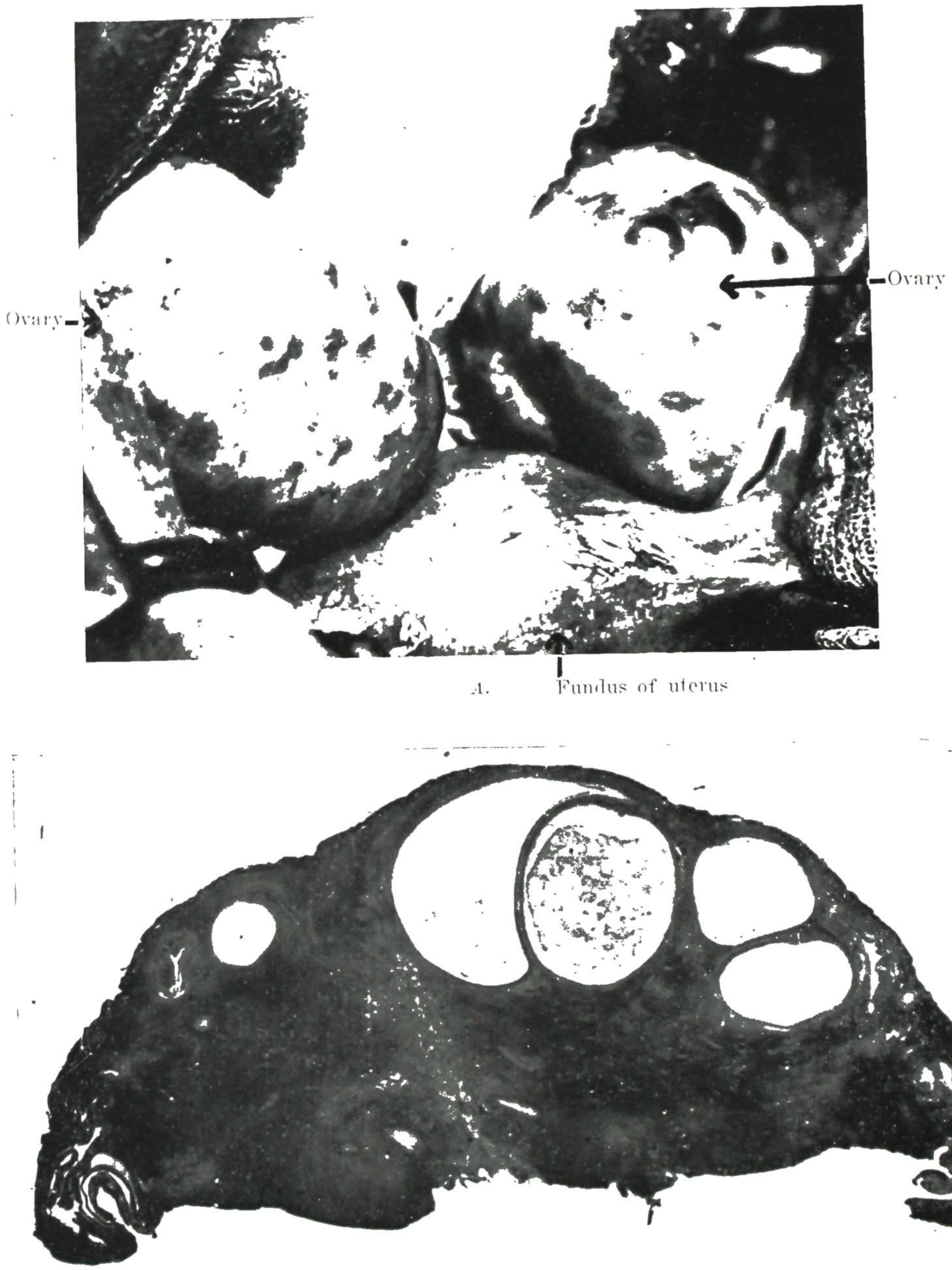
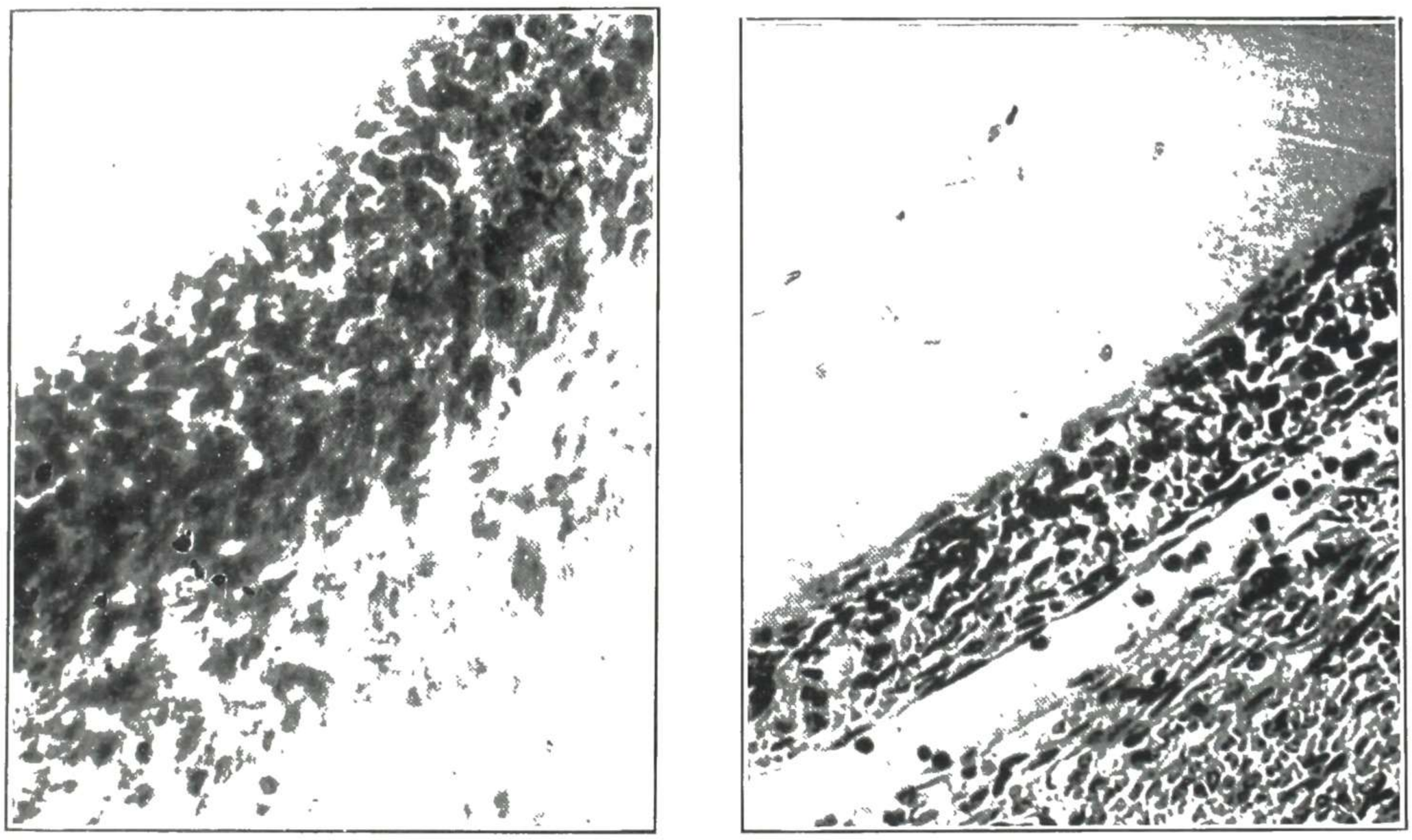


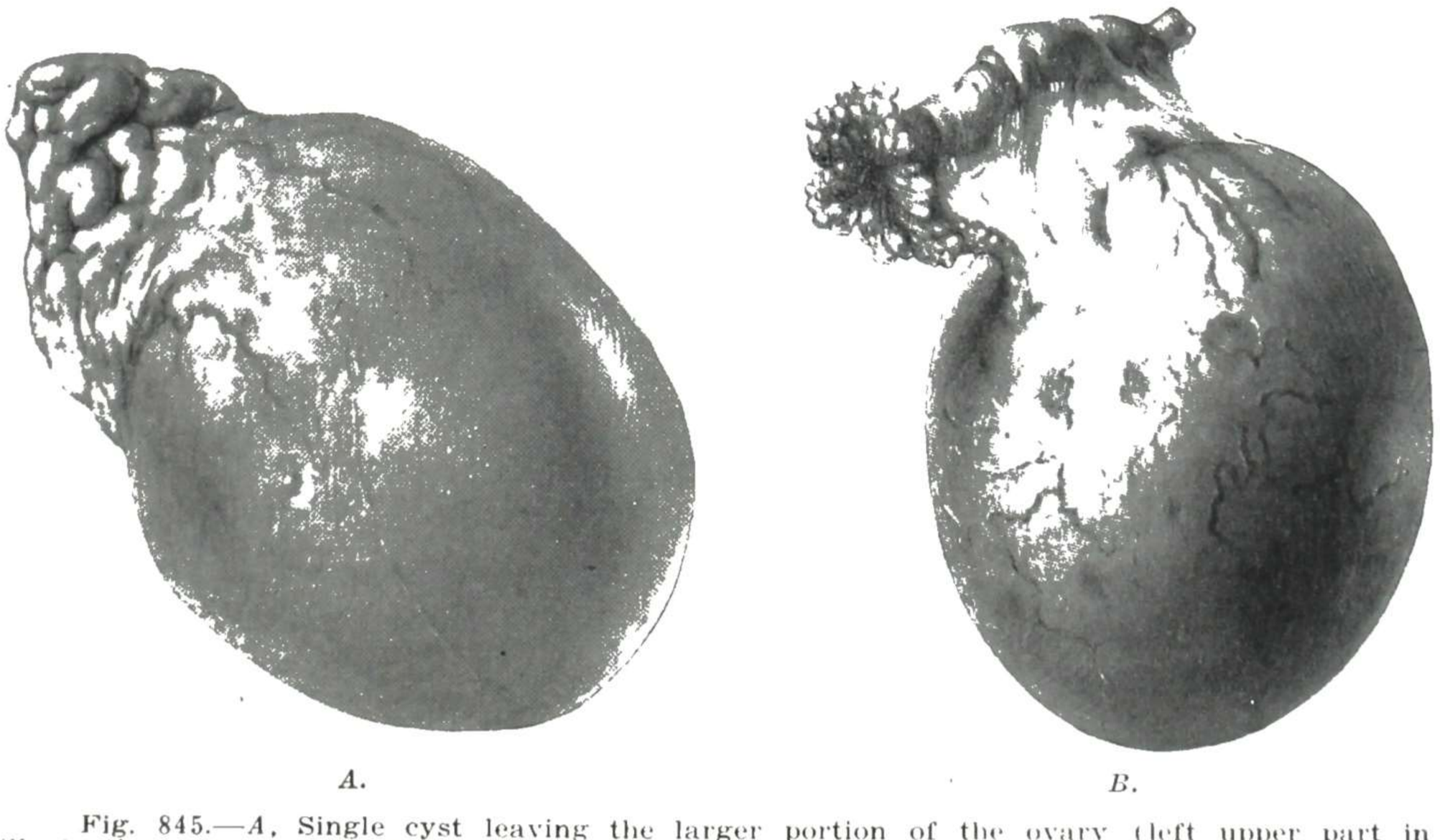
Fig. 843.—Polycystic ovaries. *B*, Cross section of ovary. (From Ingersoll and McDermott: Am. J. Obst. Gynec., July, 1954.)

These cysts vary in size, the average size being that of a pea. When superficially placed, the little cyst protrudes above the surface of the ovary as a translucent vesicle. In marked cases the ovary may be studded with these



A. *B.*

Fig. 844.—*A*, Lining of follicular cyst. The membrana granulosa may still be recognized though it is markedly compressed by the increased intracystic pressure. *B*, Lining of a larger follicular cyst. The membrana granulosa is thinned out due to pressure, and there is evidence of beginning disintegration. Gyn. Lab.



A. *B.*

Fig. 845.—*A*, Single cyst leaving the larger portion of the ovary (left upper part in illustration) intact. *B*, In contrast to specimen shown in *A*, this cyst formation involves the entire ovary, which had to be removed together with the tube. Gyn. Lab.

cysts. On cut surface they are usually seen in the cortex but occasionally are situated deeper. Sometimes there is a single large cyst.

The cyst wall consists of an outer fibrous layer containing blood vessels running parallel to the lining. In the younger cysts the lining may still show the granulosa-cell characteristics. In the larger older cysts the lining is usually missing; if present, it generally consists of a single layer of low cylindrical or cuboidal epithelial cells with central dark-staining nuclei. Figs. 843 to 845 show the characteristics of follicular cysts.

Symptoms and Treatment.—These follicular cysts are small and rarely produce serious symptoms. While a single cyst often involves only a part of the ovarian substance (Fig. 845, *A*), in other instances it may be found to affect the entire organ (Fig. 845, *B*). They are frequently found in chronic oophoritis, and an ovary may contain fifteen or twenty of them and still not be more than twice its normal size (Fig. 843, *B*).

Such a condition is designated by the term "hydrops folliculi" and also by the term "cystic ovary." This condition is not an indication for operation, unless there are serious complications or unusually severe symptoms. A marked cyst discovered in the course of an operation for some other pelvic lesion is ordinarily resected, with the minimum sacrifice of normal tissue.

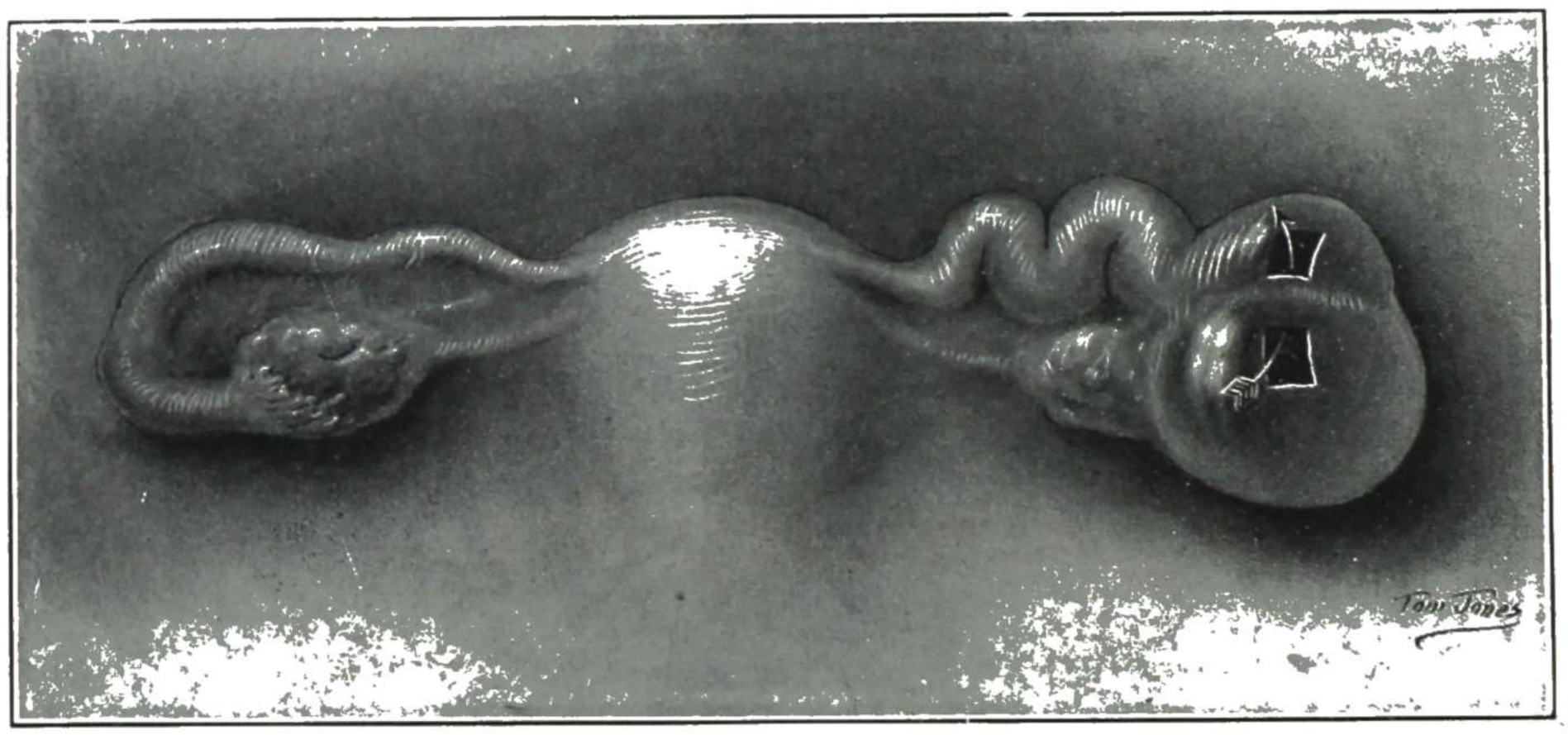


Fig. 846.—A tuboovarian cyst. The arrow, passing in one window and out of the other, indicates the communication between the ovarian and the tubal portion of the cystic mass.

The important point in treatment is to overcome the endocrine disturbance which interferes with ovulation and starts cyst formation.

In certain cases the failure to ovulate and the resulting cyst formation is due to old exudate or adhesions about the ovary or to thickening of the capsule.

Tuboovarian Cyst.—A simple cyst of the ovary may break into an adherent tube, or a dilated tube containing fluid (hydrosalpinx) may become adherent to an ovary and break into it. In either case the wall of the resulting cavity is formed by both the tube and ovary, and the resulting cyst is designated "tuboovarian" (Fig. 846). These cysts are usually small.

Stein-Leventhal Syndrome

Stein described a syndrome in which there were menstrual irregularities, featuring especially amenorrhea, a history of sterility, in some cases a masculine type of hirsutism, and in some a retarded breast development and obesity.

The ovaries in these cases were usually enlarged bilaterally by numerous cysts. In 1949 Stein reported 75 patients seen in private practice for over a period of twenty years on whom he had done the wedge resection operation which he originated, and in 1950 Ingersoll and McDermott reported 21 cases observed at the Massachusetts General Hospital over a twelve-year period. The older explanation for the thickened epithelial covering was that it was due to hormonal disturbances or to inflammation. In some cases, where one ovary is cystic and surrounded by adhesions, inflammation undoubtedly plays a part; however, in the typical Stein syndrome we probably have a combination of endocrine disturbances and a newer explanation which was first offered by Reynolds and more recently by Delson. A detailed description of the work of Reynolds and Delson in the blood supply of the ovary and its importance in normal endocrine and ovarian function has been given in Chapter 1 under Physiology and Anatomy. Reynolds, in some experimental work in rabbits, induced corpus luteum cysts by injection of gonadotrophin. He found

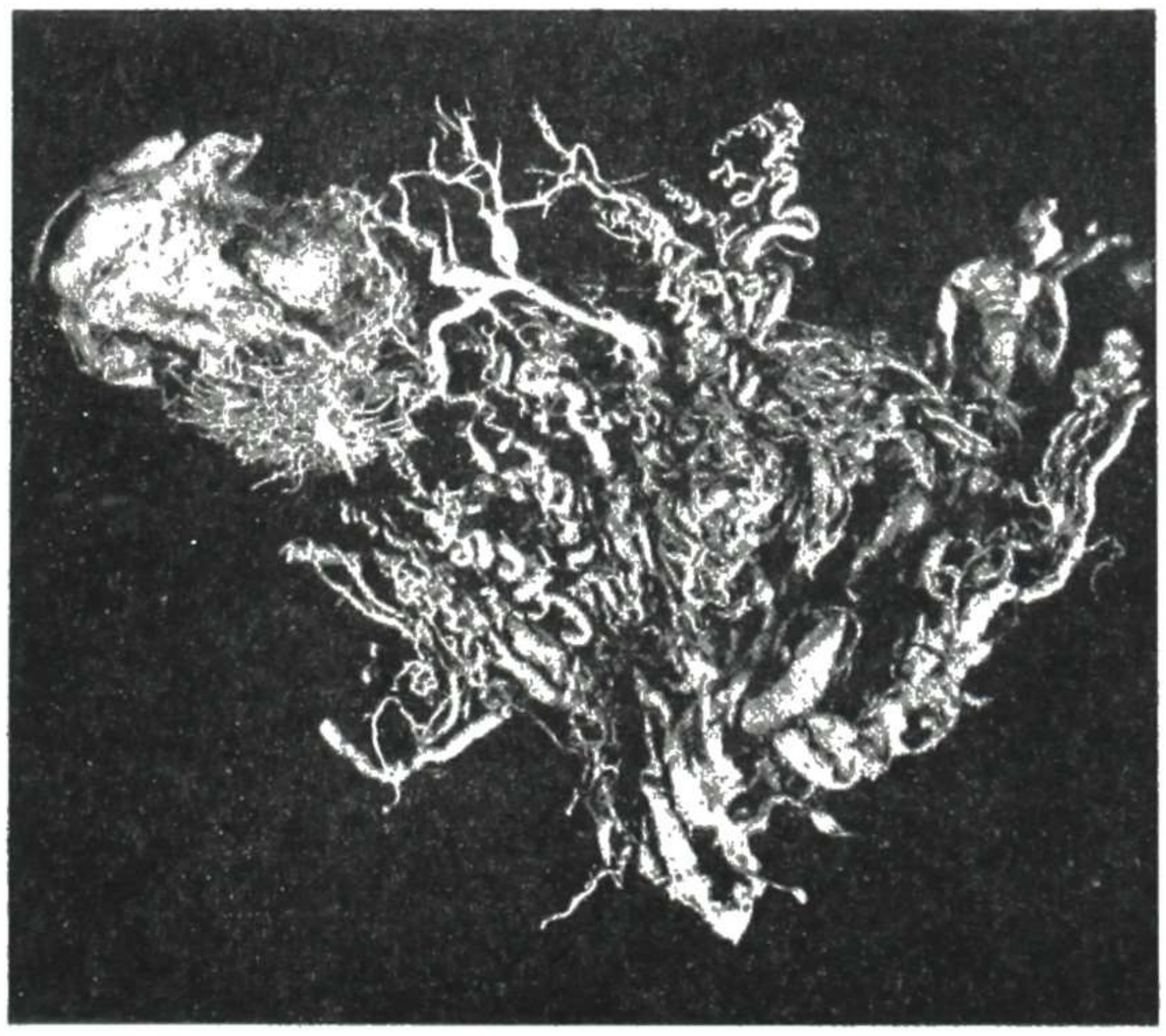


Fig. 847.—Cast of ovarian arterial and venous pattern, from a forty-six-year-old woman, para i, gravida i, with history of fibroid uterus and metrorrhagia. Note: Follicle cyst appearing as a solid cast with a fine vascular fringe around it. The arterial and venous configurations are quite different. There is "paying-out" or uncoiling of arterial spirals in the vicinity of the cyst. Arteries leading to the cyst are few and stand out in "sentinel" fashion. The fine vascular fringe around the solid cyst is venous in configuration. Observe how, with the intermingling of the arteries and veins, venous engorgement might affect uncoiling of the arteries. (× 1½) (From Delson: Am. J. Obst. & Gynec., June, 1949.)

that the arteries in these cases, instead of having the usual spiral arrangement of orderly coils, had coils that were what he called "paid out" or straightened out in the area of the corpus luteum cysts. Normally there is a gradual lowering of the blood pressure along the ovarian vessel as it goes through the various spirals to its end, but with the straightened vessel the hydraulic principle of streamlined flow eliminates the pressure-reducing mechanism so that there is an excess passage of fluid and congestion in the area of the cyst, causing a transudate into the cyst itself. Delson, as is shown in Fig. 847, found this same type of arterial abnormality in relation to cysts in the human.

In the early development of the cyst there is estrogen present in the cyst, but as the transudate increases the granulosa cells are compressed and grad-

ually atrophy, hence in large cysts there is very little estrogen in the follicle. Occasionally cystic ovaries are found in infants and it is most common after the third week of extrauterine life. In late fetal life there is a rapid development of the arterial spiraling, which is thought to be due to the maternal estrogen. After birth this spiraling gradually disappears and is usually completely gone about the third or fourth month of life. Delson feels that the same process causing this condition in adults is present also in children, namely, a straightening out and distortion of the ovarian spiral arteries.

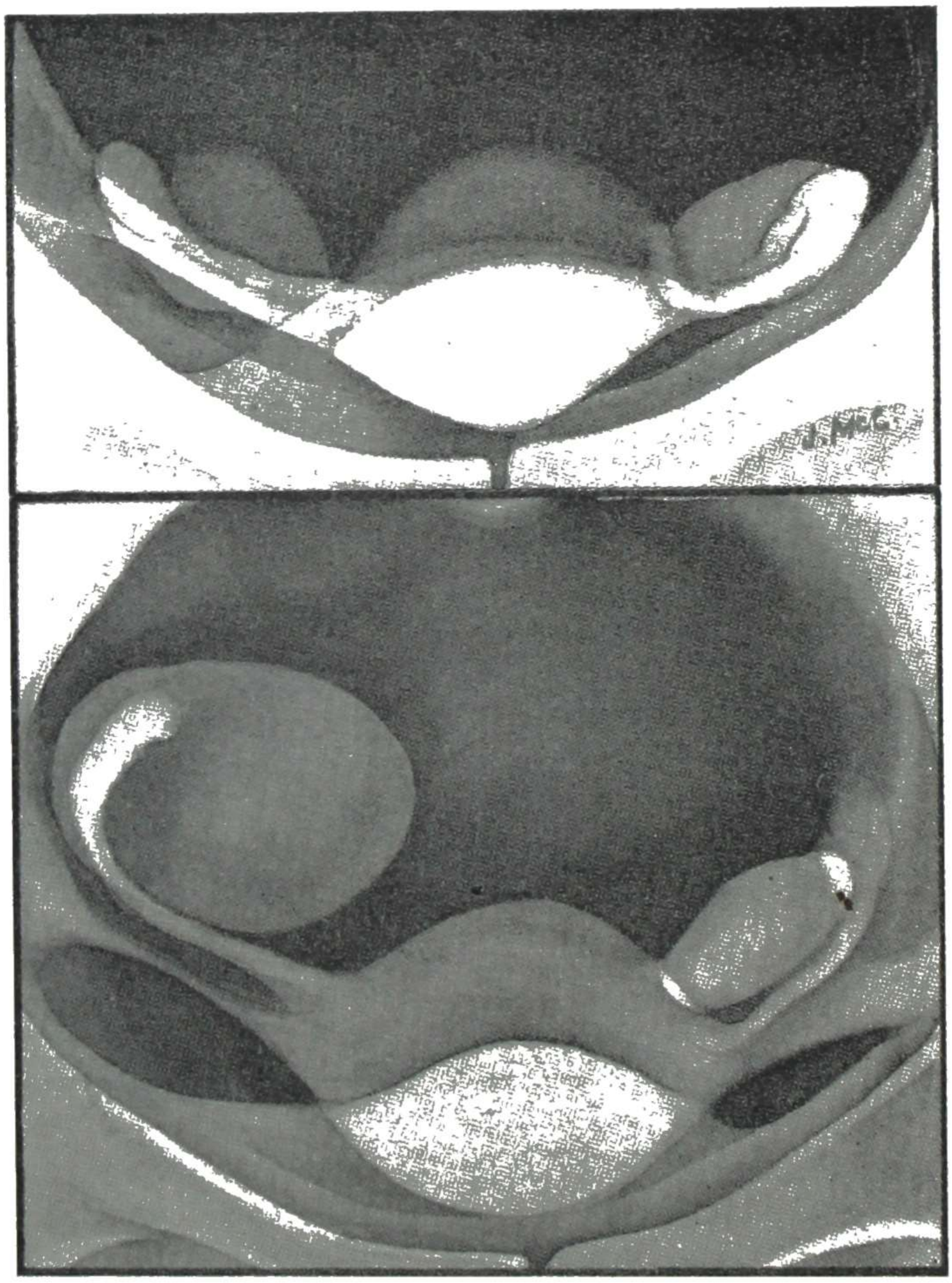


Fig. 848.—*A*, Normal uterus, ovaries, and patent tubes. *B*, Same patient, six months later; lutein cyst of right ovary. Gynecography in sterility survey; transuterine inflation with carbon dioxide. (From Stein: Progress in Clinical Endocrinology, January, 1950.)

Diagnosis.—As already mentioned, the chief symptoms of these patients are amenorrhea and sterility. It may also be associated with irregular periods with diminished bleeding. Prior to the onset of the condition the patient may have normal periods gradually becoming irregular and scanty and followed

by a period of amenorrhea. There is usually no other evidence of gross endocrine abnormality, though about 50 per cent of the cases do have some hirsutism.

On pelvic examination the chief findings are enlargement of the ovaries symmetrically and sometimes a small cyst on the surface. Stein has emphasized the advantage of gynecography in the diagnosis of this condition, and Fig. 848 is taken from his article showing the findings in the case of bilateral polycystic ovaries. Culdoscopy or exploration through the cul-de-sac is also beneficial where there is doubt as to the diagnosis. Colpotomy is also helpful in making an accurate diagnosis in questionable cases.

Treatment.—It has been shown time and again that these patients do not respond to any known hormone therapy, but excellent results are obtained by the bilateral wedge operation suggested by Stein. In a case of ours which occurred long before this condition was described, Dr. H. S. Crossen resected the cortex over a good portion of both ovaries. This patient, who had been a sterility problem prior to the operative work, had four living children delivered subsequent to it, and came back to see if we could replace the cortex as she felt that her family was large enough. In a report in 1951, Leventhal and Cohen added an additional ten cases taken from reports at the Michael Reese Hospital.

Corpus Luteum Cysts

Corpus luteum cysts are, as their name indicates, derived from corpora lutea, which, instead of undergoing the regular process of absorption and cicatrization, undergo a cystic change. Microscopic examination of the wall of such a cyst will show the lutein cells, characteristic of the corpus luteum. Corpus luteum cysts are usually not larger than an egg, but cases have been reported in which the cyst was the size of a child's head. In cut section the striking thing is the lining membrane, which is brownish yellow or orange yellow, depending upon the amount of lutein and blood pigment present. The lining separates easily from the connective tissue wall. In the older cysts there is sometimes only a single layer remaining. The cells are usually covered over on the cavity side by a thin layer of connective tissue, but this may be absent. Occasionally the lutein cells have disappeared, and in these cysts there is usually marked hyaline degeneration of the wall. The central cavity is sometimes filled with an old blood clot.

Corpus luteum cysts, like follicular cysts, require removal only when giving trouble. It is possible that the luteum cells may multiply instead of degenerating, thus forming a neoplasm with exaggerated progesterone effect. Wheelon and Wilson reported a case of corpus luteum cystoma to which they attributed the patient's amenorrhea. But Novak questions the likelihood of the evanescent lutein cells alone forming a tumor. In discussing "luteoma" in connection with granulosa-cell tumors, he says that in most cases the so-called "luteoma" is really an adrenal adenoma of the ovary, the tendency of which is masculinizing rather than feminizing when it shows any definite endocrine effect.

Occasionally marked changes in the structure of the ovary are brought about by altered endocrine activity in a distant organ or by a growth in the

distant organ causing an upset in the normal endocrine balance. There are two main types of such changes found in the ovary: the theca-lutein cysts and follicular atrophy.

Theca-Lutein Cysts

Etiology.—It is now well known that hydatidiform mole, chorionepithelioma, or adenoma of the pituitary can cause marked enlargement of the ovaries, due to the formation of multiple theca-lutein cysts. Excess of anterior pituitary hormone is the fundamental cause.

Pathology.—These cysts are almost always found in association with hydatidiform mole or a chorionepithelioma. The abnormal pregnancy causes a marked increase in the amount of the gonadotrophic hormone in the body.

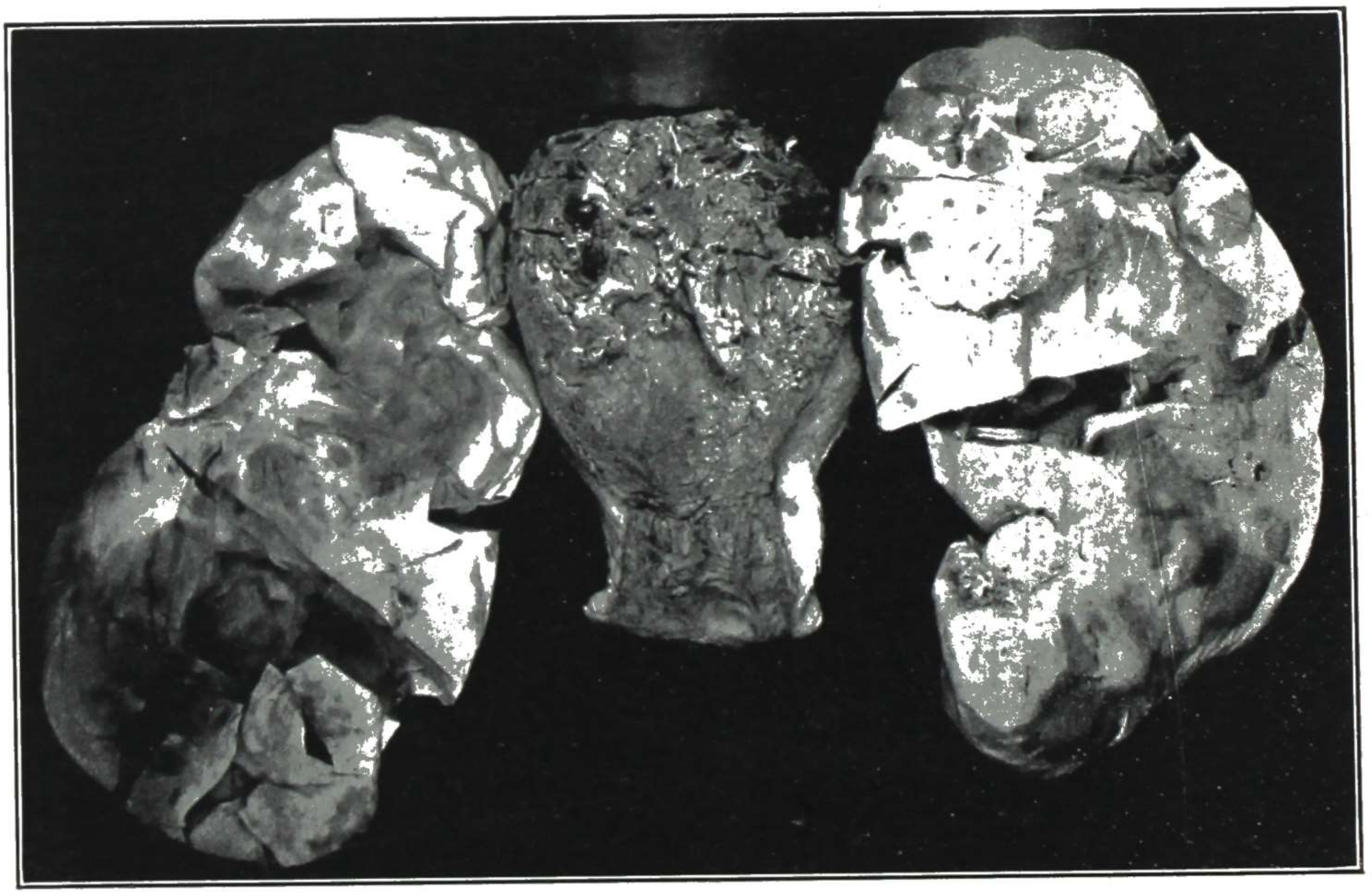


Fig. 849.—Bilateral theca-lutein cysts of the ovaries associated with a chorionepithelioma. Gyn. Lab.

(This specimen reached the laboratory through the kindness of Dr. George Ives, who has added to our teaching collection a number of instructive specimens contacted in his work in pathology.)

This in turn causes a marked increase in the number and size of the follicles in the ovary so that the ovary may become very large. In one of our cases the ovaries filled the pelvis and lower abdomen. Most of these follicles become luteinized but fail to rupture. Fig. 849 shows theca-lutein cysts of the ovary resulting from a chorionepithelioma of the uterus. The ovaries are studded with thin-walled cysts of different sizes. These enlarged ovaries resemble the ovaries of experimental animals that have been given large amounts of the pituitary-like hormones from the urine of pregnancy.

Microscopic.—The cysts are found to be lined with lutein cells. These may be derived from the granulosa layer or from the theca interna or from both.

Diagnosis and Treatment.—The diagnosis is made on the history and progress of the case, together with various laboratory tests as outlined below.

An abnormally rapid increase in the size of the uterus during pregnancy together with rapid enlargement of the ovaries should lead one to suspect this condition. Bleeding usually occurs as an early sign. If minute cysts are passed and microscopic examination shows them to be dropsical villi, the diagnosis is confirmed. An Aschheim-Zondek test which is positive in high dilutions is suggestive, but it must be remembered that multiple pregnancy will give the same findings, due to the extra amount of placental tissue present. An x-ray is of no value under three months and a negative result even at four months is not conclusive as to the presence or absence of a fetus.

The immediate treatment, when the diagnosis is positive, is interruption of the abnormal pregnancy by emptying the uterus. The elimination of the pathologic process in the uterus may cause the ovarian cysts to subside and the ovaries to return to normal. If a chorionepithelioma is found, a complete hysterectomy and bilateral salpingo-oophorectomy followed by deep x-ray therapy is indicated, as explained in Chapter 8.

Follicular Atrophy

This condition may be secondary to hyperplasia or adenoma of the adrenal cortex, basophilic adenoma of the hypophysis, or pineal tumor. The exact mechanism causing the serious ovarian changes is still under discussion. Cushing felt that they are caused by the primary altered function of the pituitary due to the tumor composed of functioning basophile cells. Goldzieher and Koster, in discussing adrenal conditions, feel that in many of the cases the primary condition is one of adrenal hyperplasia or tumor. It is well known that basophilic adenomas are associated with marked hyperplasia of the adrenal as well as with hyperplasia of other endocrine organs, but whether the pituitary is the primary cause of the changes found has been questioned by many. An interesting discussion of various points is given under "Dyspituitarism" by Cushing, in the Harvey Lectures of 1932-1933, and under "Adrenals" by Goldzieher and Koster.

Novak reports extreme atrophy of the ovary with disappearance of the follicular apparatus in a case of adrenal cortex hypernephroma. In one of our cases of amenorrhea and developing masculinity, there was adrenal cortex hyperplasia. The ovaries were somewhat enlarged with atretic-follicular cysts, but the microscopic picture (Fig. 850) indicated serious disturbance of the follicular apparatus tending toward destruction. Compare this dense ovarian cortex, showing only a few remnants of the follicular apparatus, with the normal ovarian cortex of childhood in Fig. 9, showing the usual abundance of functionating elements. The clinical symptoms corresponded with the follicular atrophy. The menstrual flow had gradually diminished and had been entirely absent for the last six months. There were definite developments toward masculinity, consisting of appearance of hair generally, pubic hair extending upward toward umbilicus, hair on the face (Fig. 851), and hypertrophy of the clitoris toward the male type of glans.

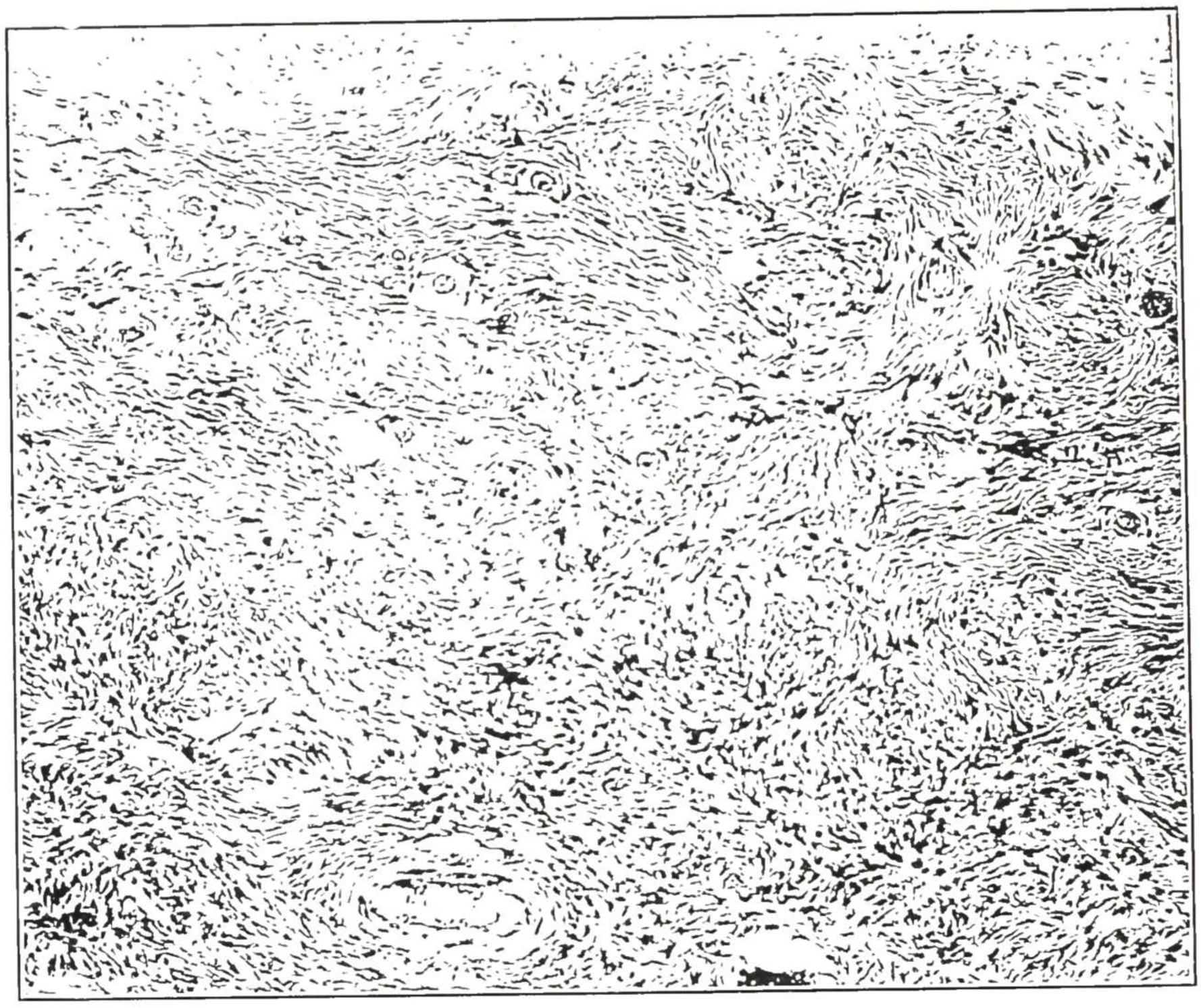


Fig. 850.—Atrophy of the follicular apparatus of the ovary due to hyperplasia of the adrenal cortex. Patient, aged nineteen years, had had amenorrhea for six months and was developing masculinity. Compare this atrophic follicular zone with the same area in a normal ovary (Fig. 9). The facial hirsutism in this case is shown in Fig. 851. Gyn. Lab.

Fig. 851.—Hypertrichosis on the face in a patient of ours who had a hyperplasia of the adrenal cortex.

OVARIAN TUMORS

No discussion of ovarian tumors would be complete without some mention of Ephraim McDowell, who performed the first ovariotomy in the world. He was born in 1771 of an old Virginia family and later moved with his family to Kentucky. Young McDowell, after serving an apprenticeship under a preceptor who was a graduate of the University of Edinburgh, journeyed to that greatest of European medical schools, where he remained during the years 1793 and 1794. In addition to his regular studies he attended the lectures of the brilliant and inspiring John Bell, who was a lecturer in anatomy and surgery.

For many years ovarian tumors had been recognized as invariably being fatal, and such great men as William Hunter had pronounced any operative removal as incompatible with life. However, in 1785, John Hunter surmised that in certain cases operation was practical, though he had never attempted it himself. John Bell, however, had shown by careful postmortem work the feasibility of removing ovarian tumors. In 1795 McDowell began his practice in Danville, Kentucky, and soon became one of the foremost surgeons west of the Alleghenies, performing all operations then known to surgery from amputation to tracheotomy; also he was regarded as a skilled lithotomist and frequently operated on strangulated hernia. In the latter part of 1809 McDowell was called to a village sixty miles away on consultation to see a Mrs. Crawford who, the two attending physicians assured him, carried twins. On examination, however, he found that she was not pregnant but had a large tumor. Well aware of the hopelessness of her condition without operation and also of the danger of fatal peritonitis from operation, he explained to her the facts of the situation and offered to operate if she so desired. The brave woman chose to take this chance for life. The operation was performed and she recovered and lived for thirty years after surgery. McDowell was a prudent and conscientious man, and hence he waited until he had operated on two other patients successfully before he was willing to recommend the operation to the medical profession. He made a report of his experiences in the *Philadelphia Medical Journal* and was severely criticized by many of the leaders of that day. Gradually, however, recognition of the advisability of the operation became universal, and in 1897 the Kentucky State Medical Society erected a monument to McDowell's memory. Through the efforts of the Kentucky physicians and others interested, the home of Dr. McDowell has been preserved and filled with momentoes of those early days and tributes paid him by leaders of the profession in America and Europe. They recognized also that great credit was due to courageous, patient Mrs. Crawford, and in May of 1935, in the McDowell Park in Danville, the Kentucky State Medical Society dedicated a monument to Jane Todd Crawford, heroine of the first operation for ovarian tumor. Later there was built and dedicated to her a modern motor road following the lonely wooded trail along which this brave woman made her way in that historic ride from her pioneer home, now Greensburg, to the home of Dr. McDowell in Danville, called the Jane Todd Crawford trail.

Clyde L. Randall, in a series of 1,112 cases of ovarian tumors, found the distribution shown in the accompanying table.

OVARIAN TUMORS (EXCLUDING INFLAMMATION), BUFFALO GENERAL HOSPITAL, 1936-1947

			PER CENT	CASES
Malignant			16.2	180
Potentially malignant			4.4	49
Endometriosis with "chocolate cyst"			26.4	294
Benign cystomas			47.3	
Simple	20.3%	226		
Cystadenomas	14.9%	166		
Dermoids	12.0%	134		526
Fibroadenomyomas			0.7	8
Brenner			0.5	5
Fibromas			4.5	50
Totals			100.0	1,112

BENIGN GROWTHS

Under this heading are grouped the proliferating cystadenomas (pseudomucinous and serous), dermoid cysts, and solid growths such as fibromas, myomas, and Brenner tumors.

PROLIFERATING CYSTS

These tumors, which develop from the surface epithelium of the ovary, include the serous cysts and pseudomucinous cysts. Since both of these date back to a common ancestor, the primitive epithelium of the coelomic müllerian duct system, the lining cells possess the same potentialities as those of the müllerian duct epithelium, hence they may imitate any section of this epithelium, such as the tubal, endometrial, or cervical. This explanation helps to clarify the many different types of epithelium found in these tumors.

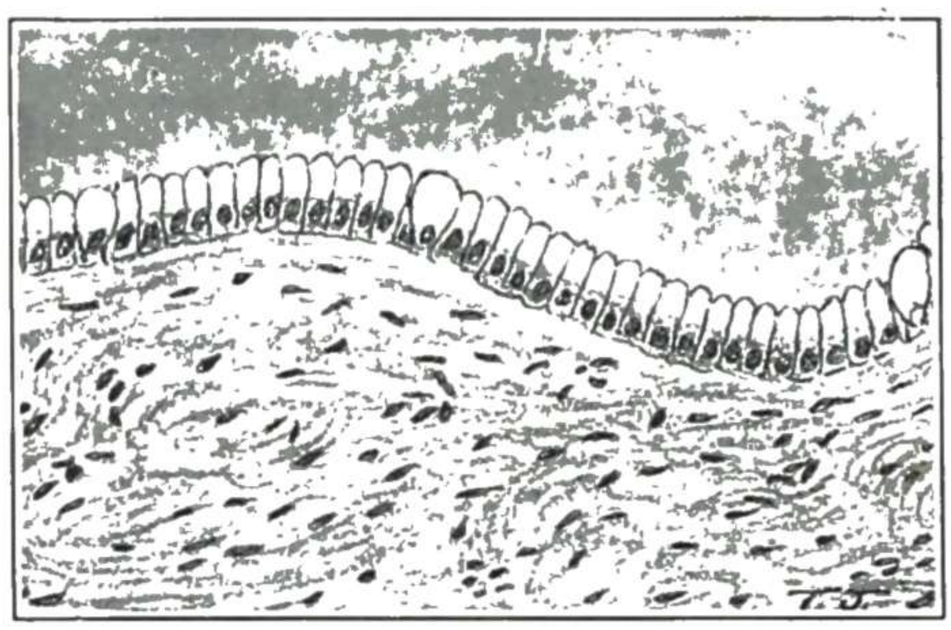


Fig. 852.

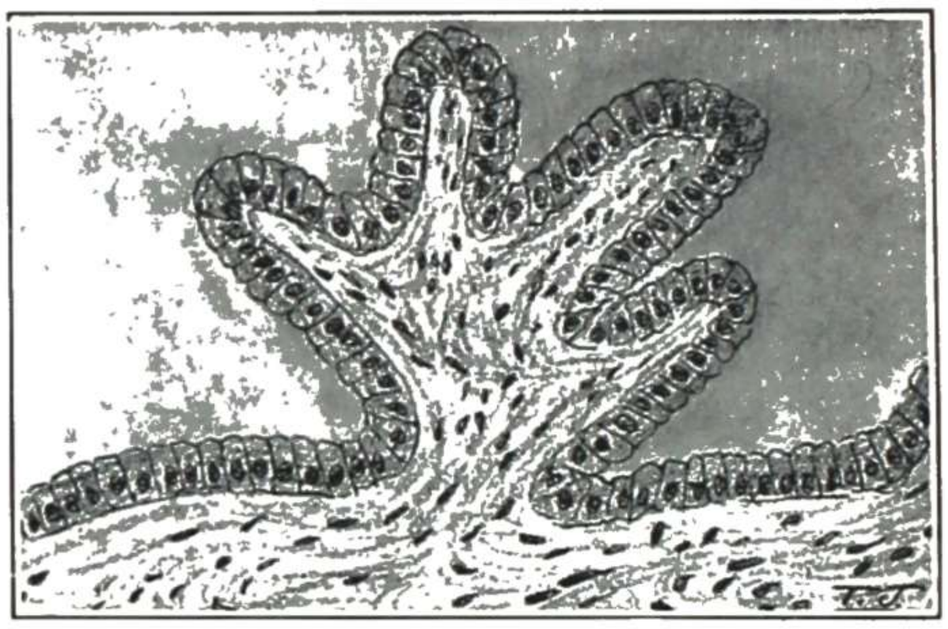
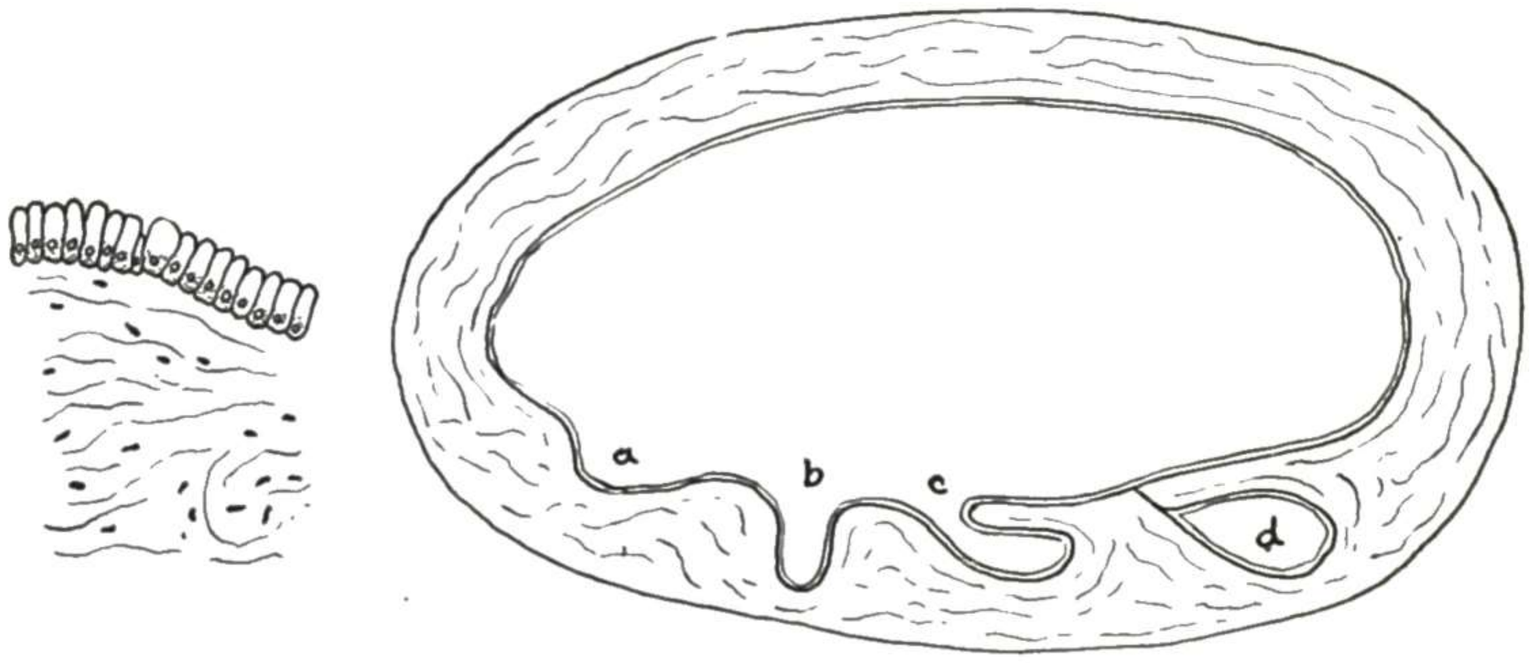


Fig. 853.

Figs 852 and 853.—Indicating the difference between the cells lining a pseudomucinous cyst (Fig. 852) and those lining a serous cyst (Fig. 853), as explained in the text. Columnar cells, nonciliated, containing pseudomucin. Goblet cell present.



A. *B.*

Fig. 854.—*A*, High power microscopic field showing the type of cells lining a pseudomucinous cyst. *B*, Illustrating the process by which secondary cysts are formed.

Proliferating cysts are the ovarian tumors which attain such a large size. This is the form of growth ordinarily referred to when an "ovarian cyst" or "ovarian tumor" is spoken of.

The term "proliferating" is given to these growths because they have the faculty of generating new cysts within the original cyst or on the outside of it. They increase in size persistently, and there is no means of stopping their growth, except removal. The two types of lining cells are shown in Figs. 852 and 853.

Pseudomucinous Cystadenomas

This form of tumor is known also as "paramucinous cystadenoma" and as "cystadenoma evertens." In these cysts the contents consist of a jellylike

material which is secreted by the epithelial cells lining the cyst. This gelatinous material is the distinguishing characteristic of the pseudomucinous cystadenoma. On chemical examination it shows the reaction for paramucin or pseudomucin (not precipitated by acetic acid, but precipitated by alcohol as delicate threads, which are insoluble in water; mucin is precipitated by acetic acid, and albumin is precipitated by heat). The color of this gelatinous material depends on the amount of blood coloring which has diffused through it from hemorrhage into the cyst, as explained later.

Histogenesis.—As explained in Chapter 1, the surface epithelium of the ovary is derived from the same epithelium as that forming the müllerian duct system, and hence, according to Schiller, remnants of the embryonic coelomic cells in this surface epithelium under the influence of certain unknown stimuli may develop into neoplasms having the characteristics of various portions of the genital tract. Those found in pseudomucinous cysts resemble the clear mucus-secreting cells of the cervical canal. Some of these cysts arise from Walthard rests from which the Brenner tumors are formed, and Barzilai states that the Brenner tumors form the origin of pseudomucinous cysts. This idea is supported by the findings of Dockerty, who found Brenner tumors in the wall of 30 per cent of the pseudomucinous cysts which he studied. Ribbert suggested that the origin of these tumors was from intestinal epithelium, and undoubtedly this is one source, as they are frequently found in association with dermoid and teratomatous cysts.

Pathology.—As the contents are formed by the secretion of the cells lining the cyst, there is a constant increase in the amount, and this causes constant internal pressure, which keeps the wall of the cyst tense. In this way the epithelial layer is kept spread out and does not usually pile up along the wall in the form of papillary projections. Rather the pressure tends to depress portions of the wall, and as the epithelial cells multiply they are pushed farther out in the wall in the form of glandlike depressions, hence the name "evertens." The depressions may become occluded at the neck and are thus cut off from the main cavity forming secondary cysts (Fig. 854). These secondary cysts are found in great numbers about the primary cyst, and occasionally one or more of the secondary cysts may become as large as the primary one.

The rule that pseudomucinous cysts are evertent is not absolute. In nearly all such cysts there are a few insignificant epithelial ingrowths, and in rare cases these growths may predominate, giving a distinct character to the growth (pseudomucinous cystadenoma invertens). Such atypical pseudomucinous cysts are nearly always small, indicating that there was not much internal pressure.

The tumor is usually multilocular, appearing as a collection of cysts, with a smooth, firm, glistening surface (Fig. 855). If the wall is thick, the surface is white. If the wall is thin and translucent, the color of the fluid within can be seen shining through. The cut surface of the cyst wall shows numerous intramural cysts of varying sizes. Spurs and septa are frequently seen and represent the remains of adjacent cysts (Fig. 856).

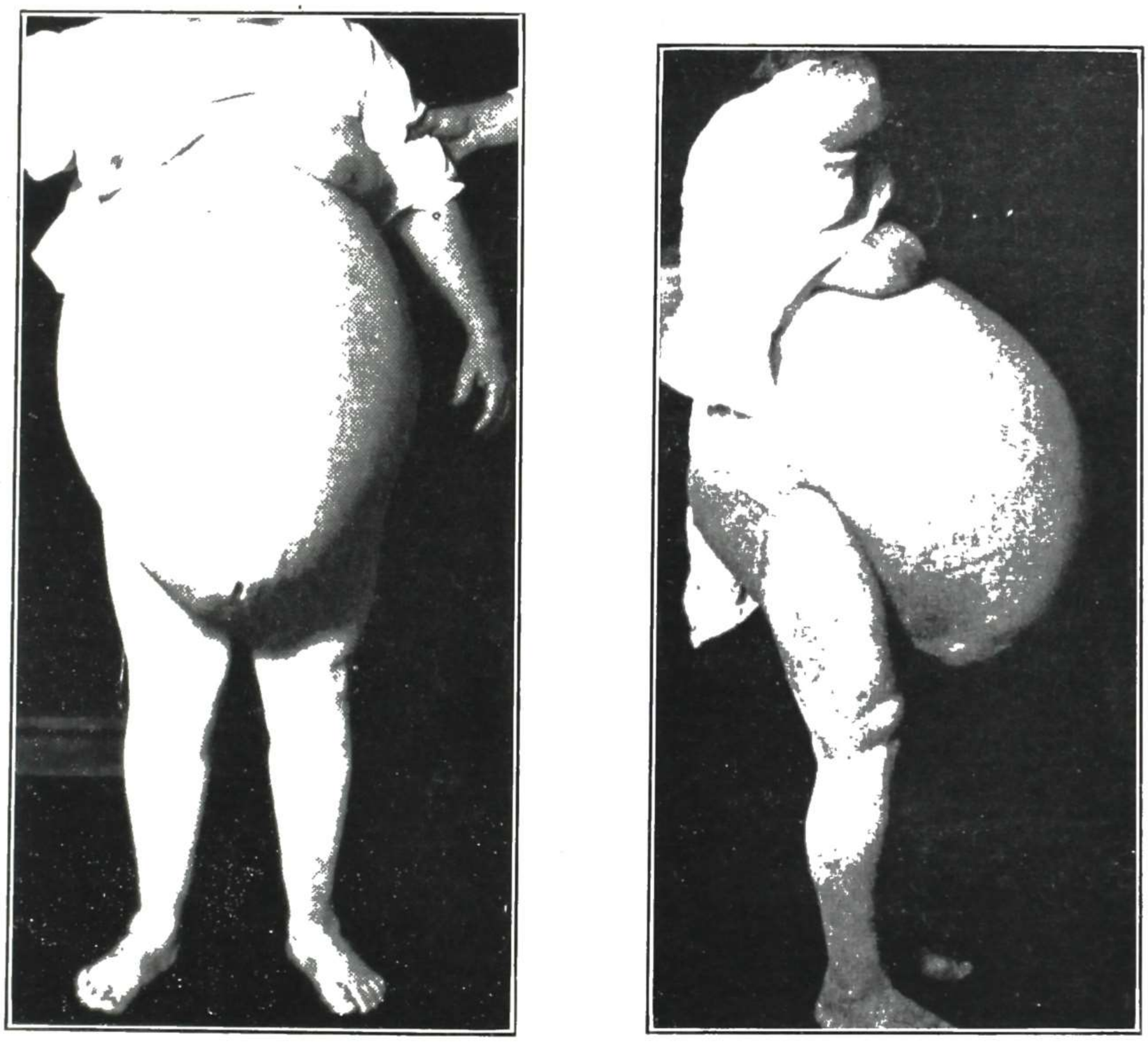
Allan and Hertig, in an analysis of 1,740 ovarian tumors covering a forty-three-year period, found that 21 per cent were pseudomucinous cysts. C. L. Randall reviewing 1,112 ovarian tumors found that 14 per cent were benign

cystomas and these were fairly evenly divided between serous and pseudomucinous cysts. C. T. Beecham, in a review of 332 primary ovarian tumors, found an incidence of 9 per cent of pseudomucinous cysts and 21.3 per cent of dermoid cysts.

Fig. 855.—Pseudomucinous cyst. This tumor weighed 20 pounds and contained 4,000 c.c. of fluid. The size is shown by the ruler in the foreground.

Fig. 856.—A pseudomucinous cystadenoma of the ovary. Notice the development of secondary cysts in the wall of the large cyst. (From Kelly: Operative Gynecology.)

These pseudomucinous cysts may grow to a very large size. Lynch gives an interesting compilation of "Mammoth Ovarian Tumors" in his monograph on *Pelvic Neoplasms*. In his review of the literature, he found 103 tumors weighing between 100 and 200 pounds, 9 between 200 and 300, and one, reported by Spohn of Texas, weighing 328 pounds. No standard method of



A. *B.*

Fig. 857.—Seventy-five-pound ovarian cyst. *A*, Front view of the patient. *B*, Side view of the patient. (From Crossen and Soule: Am. J. Obst. & Gynec.)

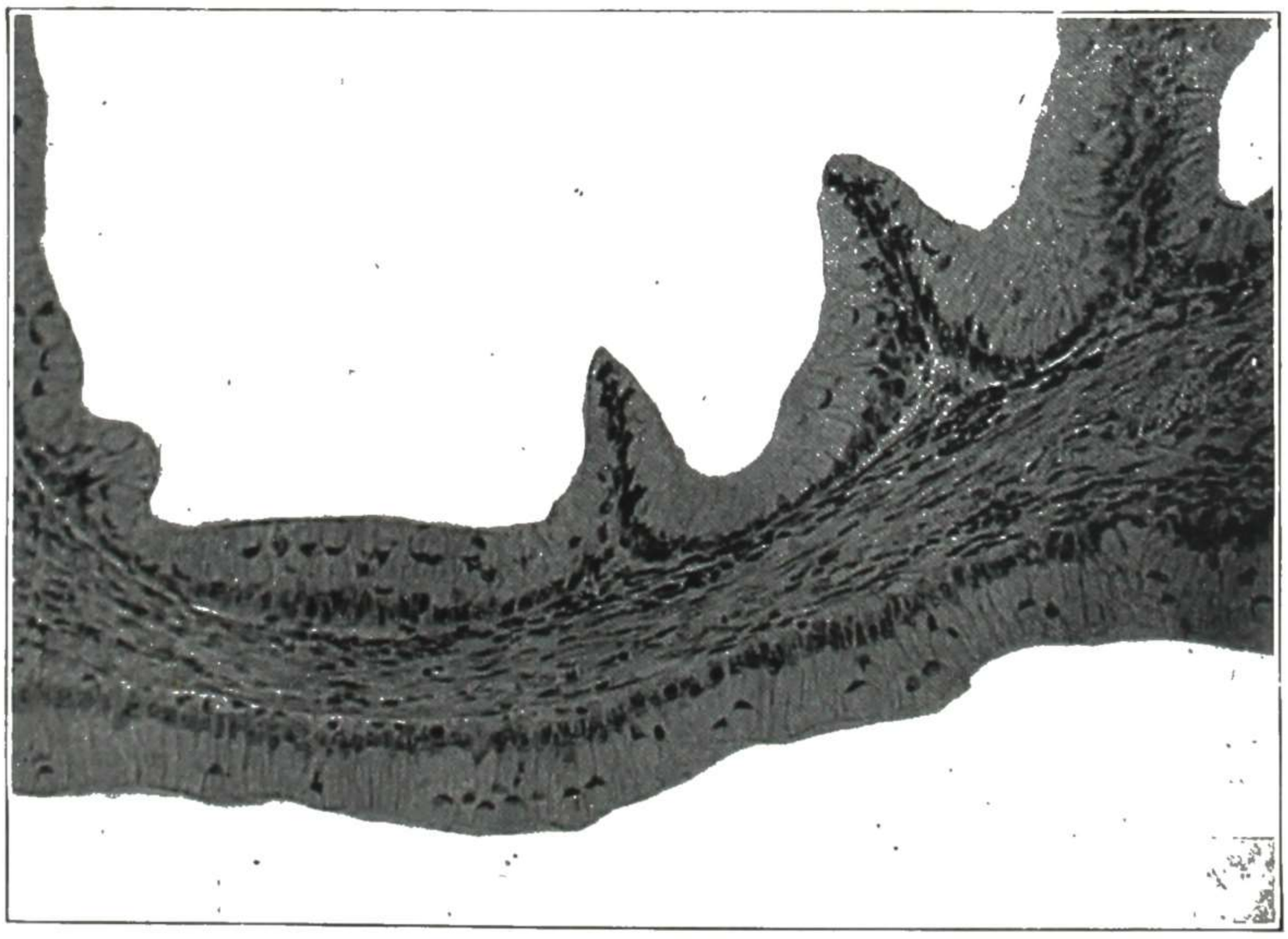


Fig. 858.—Pseudomucinous cyst of ovary, high power, showing the typical cells lining a pseudomucinous cyst. Notice that the cells are very long, stain only lightly on account of the pseudomucin, and the nucleus is placed at the base. Gyn. Lab.

estimating the weight of these tumors has been followed. In the case reported by R. J. Crossen (Fig. 857) the patient was weighed immediately before and after operation, which seems to be the most accurate of the reported methods of arriving at the weight of the tumor.

Microscopic.—The walls of the cysts usually contain three layers—an outer fibrous layer, a middle layer of more cellular fibrous tissue, and an epithelial lining. The lining consists of high cylindrical cells containing a basal nucleus (Fig. 858) similar to those lining the cervical canal but devoid of cilia. If there is marked intracystic pressure, these cells are flattened. The cells are in a single layer. Goblet cells are commonly found. Numerous small cysts are seen microscopically.

Implantation Recurrences.—These cysts are nonmalignant. Of course a complicating malignancy may develop in the cyst, but fortunately this is not common. Cures after complete removal of these cysts are close to 98 per cent. Care should be taken, however, in removing these cysts not to allow the contents to spill into the peritoneal cavity, as implantation metastasis is apt to occur. If this does happen and the condition becomes progressive, the jelly-like substance is so thick that it clogs the peritoneal lymphatics. A foreign body peritonitis results, producing granulation tissue, giant cells, and connective tissue. This condition as designated "pseudomyxoma peritonei." Pseudomyxoma peritonei may start also from a pseudomucinous growth in some other structure; e.g., the appendix.

These cases must be operated on frequently, because this is the only way in which the material can be removed. Biggs reported removing 350 pounds of this material in twelve operations over a period of nine years before death claimed the patient at seventy-five years of age. Death is usually due to mechanical interference in the abdominal cavity and adjacent tissues.

Serous Cystadenomas

This form of tumor is known also as "papillary cyst" and as "cystadenoma invertens." The contents of the serous cyst partake of the nature of serum and do not present the gelatinous character of that of the pseudomucinous variety. On chemical examination, the contents show a large amount of albumin and no pseudomucin. The contents of the serous cysts, like those of the other variety, may vary much in color and consistency—this variation being due to the amount of hemorrhage into the cyst.

Histogenesis.—As with the pseudomucinous cyst the serous cysts also develop from the surface epithelium of the ovary, and, as Brazilai points out, the lining of these cysts resemble tubal epithelium.

Pathology.—The cells apparently have no secretion, and consequently there is no marked intracystic pressure as there is in the pseudomucinous cyst. On account of this absence of internal pressure, the cells, as they proliferate, pile up, forming papillary projections into the interior of the cyst (Figs. 859 and 860); hence the name "invertens." These papillary masses (consisting of a layer of epithelial cells and some stroma), when they come in contact with the opposite wall of the cyst, penetrate the wall and appear outside as papillary growths on the external surface of the cyst (Fig. 861).

Usually a few glandlike eversions may be found in the wall, but they are insignificant. Occasionally, however, a serous cystadenoma will present nearly altogether evertent growths (glandlike projections into the wall of the cyst)—serous cystadenoma evertens.

McCarty made a careful study of cases of serous cystadenoma in which both ovaries were removed. In many of these cases one ovary contained the cyst and the other appeared grossly normal. He found that 100 per cent of these grossly normal ovaries (removed prophylactically because of a serous cyst of the other ovary) contained small cortical cystic structures, while only

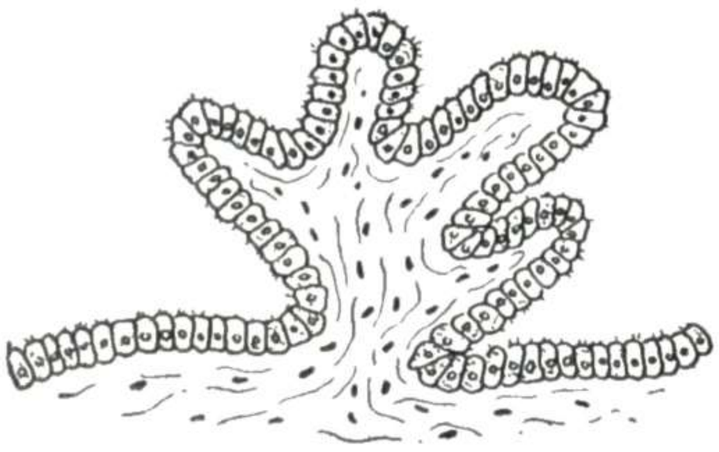


Fig. 859.

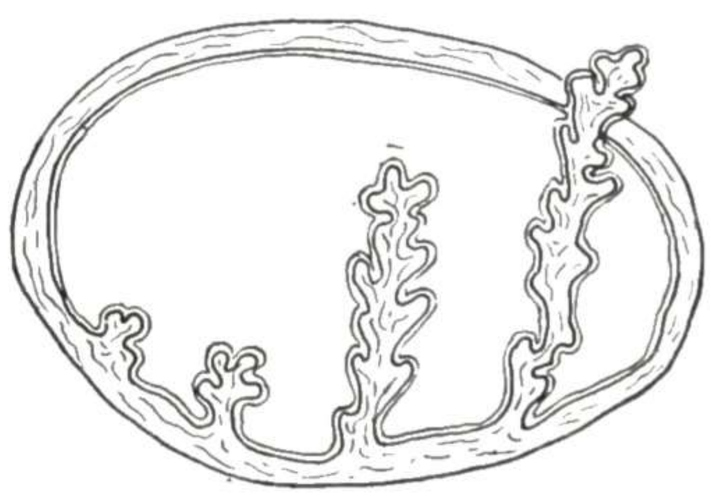


Fig. 960.

Fig. 859.—High power field of papillary projection showing ciliated, cuboidal cells.
Fig. 860.—On right, papillary projections in cyst.

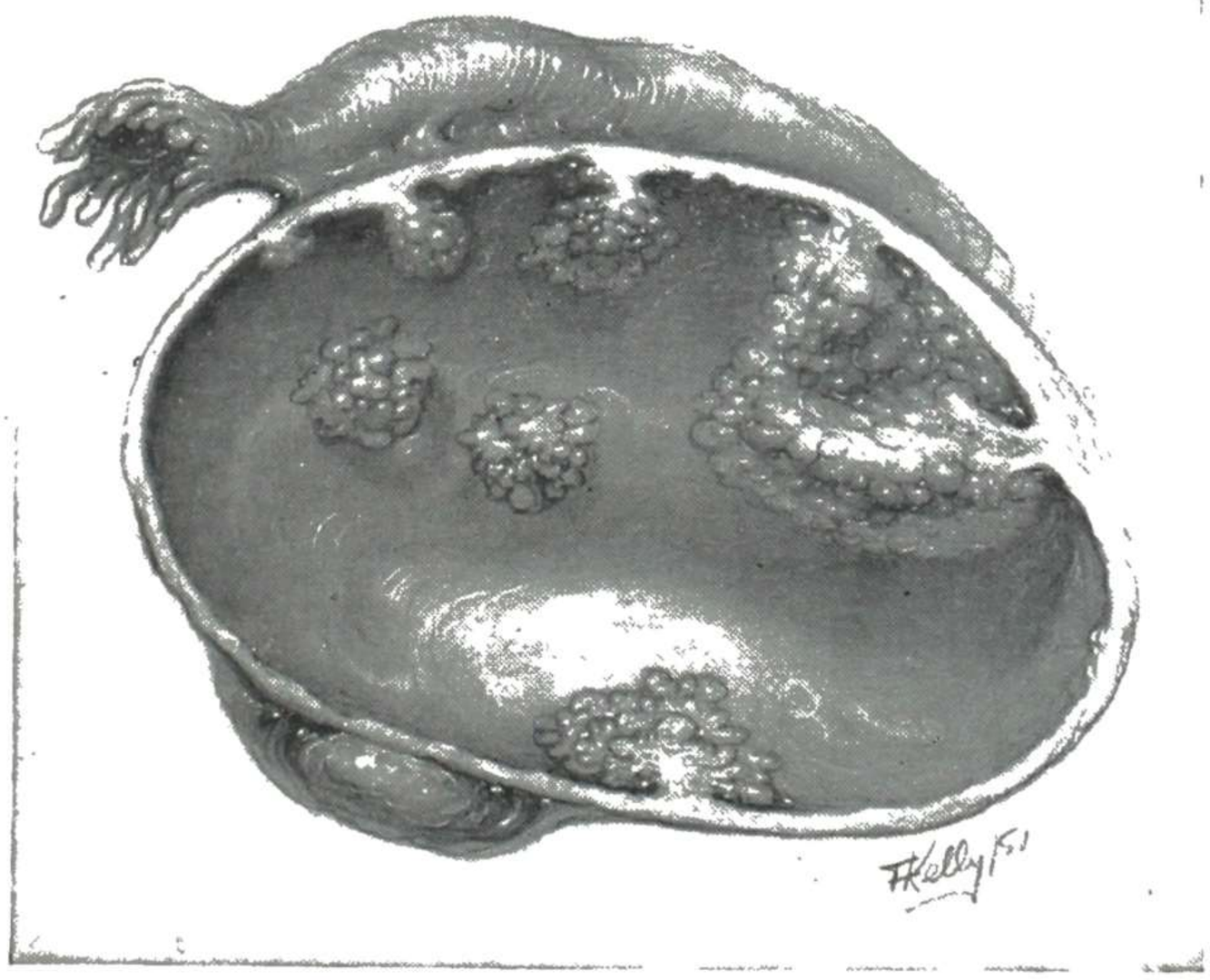


Fig. 861.—A papillary cystadenoma sectioned and showing the papillary projections into the cyst cavity. When these papillae penetrate the opposite wall, papillary carcinoma is the usual result.

60 per cent of a normal control group contained them. Two of the prophylactically removed ovaries showed beginning tumors arising from small epithelial cystic structures in the cortex, one an early carcinoma and the other a beginning papillary cyst. He concludes from his study (a) that most papillary ovarian cysts develop from the small germinal epithelial cystic structures found in the cortex of the normal ovary, and (b) that the grossly normal ovary associated with a papillary cyst of the other ovary is a potential danger and should be removed if the age of the patient permits.

Microscopic.—The cells lining the serous cyst are uniform in size and one layer thick. They are low cylindrical, with a centrally placed nucleus and a granular cytoplasm (Fig. 853), and the papillary masses present the pictures shown in Figs. 862 and 863.

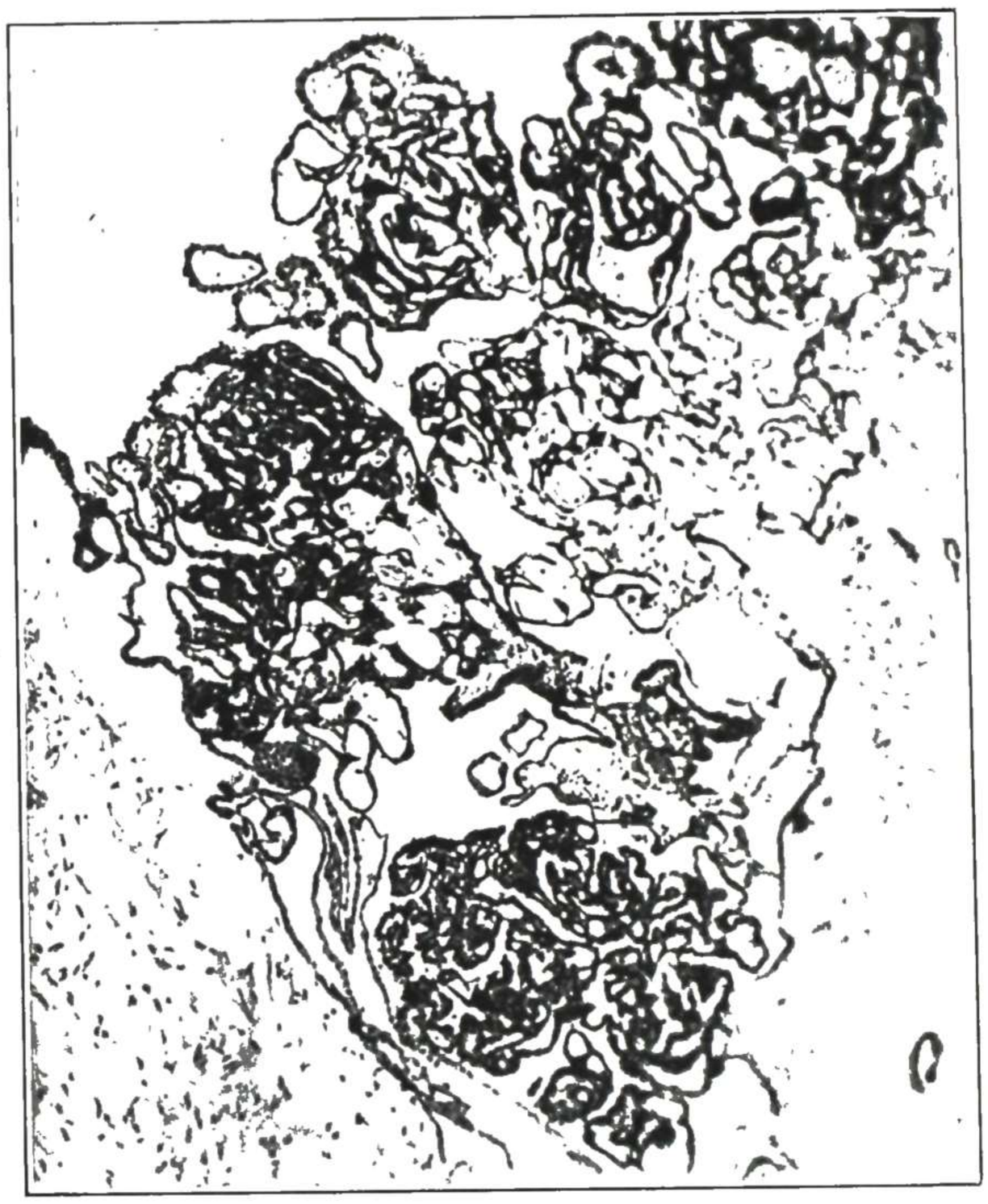


Fig. 862.—Papillary cyst. Low power of lining, showing its papillary character. Gyn. Lab.

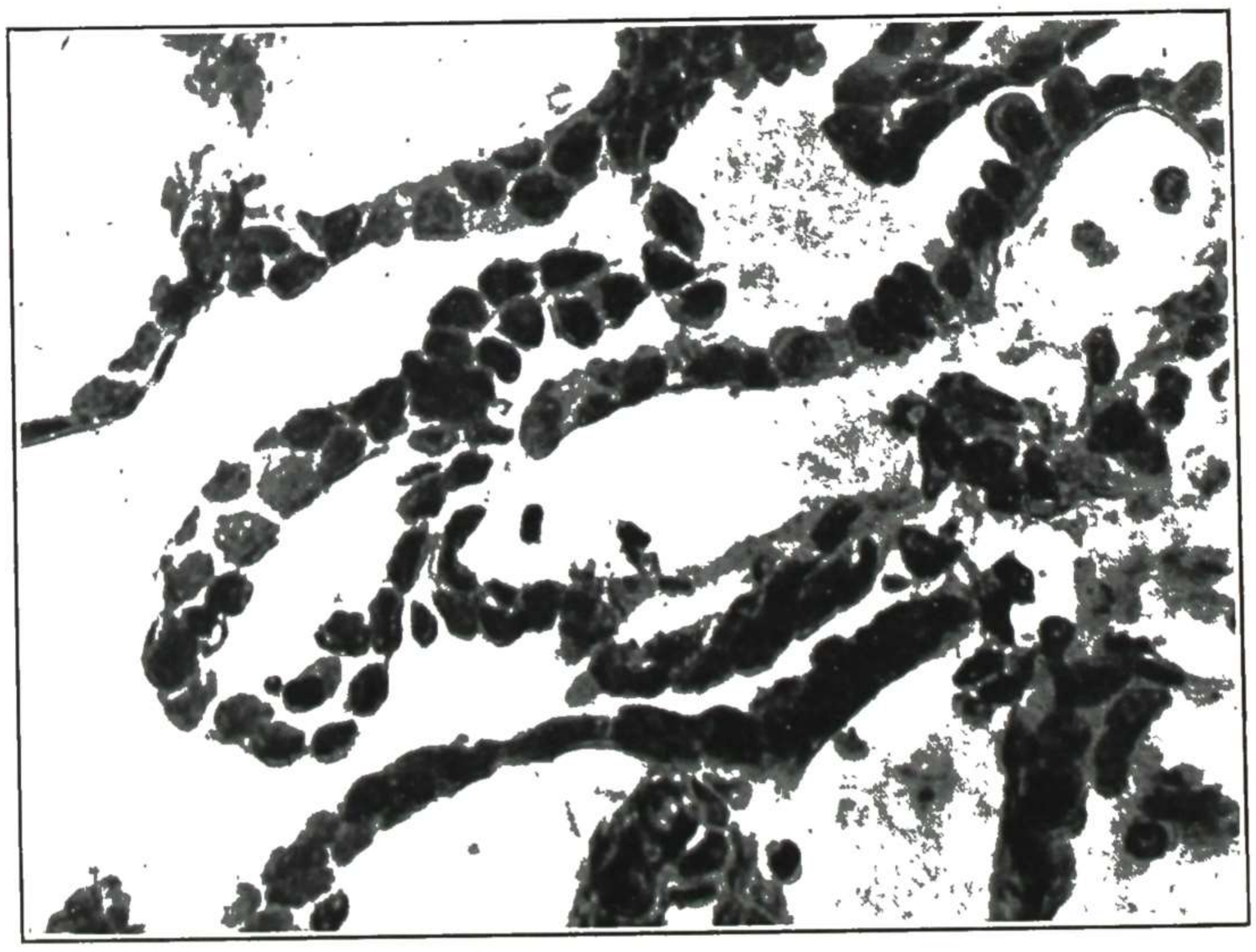


Fig. 863.—Papillary cyst. High power, showing the character of the cells covering the papillary projections. Gyn. Lab.

Malignancy.—These serous cysts have a greater tendency to develop malignant complications than do the pseudomucinous variety, and because of their tendency to be bilateral both ovaries should be removed except in young patients. The percentage of cures is distinctly lower than with pseudomucinous cysts.

The characteristics of the pseudomucinous and serous cysts may be presented and contrasted concisely as follows:

Pseudomucinous Cyst	Serous Cyst
1. Contents gelatinous and secreted by the cells lining the cyst—may be any color.	1. Contents serumlike and not secreted by the cells lining the cyst—may be any color.
2. Secondary growths consist of glandlike projections outward (evertent) from the cavity into the wall, forming small cystic cavities in the wall.	2. Secondary growths consist of papillary projections inward (invertent) from the wall into the cavity, forming papillary masses which extend across the cavity and penetrate the opposite wall.
3. Lining cells contain pseudomucin, are columnar, with some goblet cells, and are not ciliated.	3. Lining cells contain no pseudomucin, are plain columnar, without goblet cells, and are ciliated.
4. Usually unilateral.	4. Usually bilateral.
5. Rarely ruptures spontaneously.	5. Usually ruptures at an early stage, because of perforation of the wall by the papillary ingrowths.
6. Rarely causes peritoneal metastases.	6. Usually causes peritoneal metastases, consisting of widespread papillary growths.
7. Rarely undergoes malignant change.	7. Frequently undergoes malignant change.
8. Very common.	8. Not so common.

Clinical Manifestations

Taking up the clinical manifestations of the proliferating cysts (both pseudomucinous and serous), it is found that they may **occur** at any age but are most frequent during the period of greatest ovarian activity, i.e., between the twentieth and fiftieth years.

In **shape,** a proliferating cyst may be spherical and regular in outline, indicating a single large cyst, or it may be irregular, presenting nodules indicating a multilocular cyst. In **size** these cysts vary from a small tumor the size of an egg to a large tumor filling the whole abdomen.

As to **appearance** when exposed by abdominal incisions, the wall of the cyst presents a white, glistening appearance. The thinner portions are straw-colored or green or black, according to their fluid contents. The surface of the cyst may be perfectly smooth, or may be covered by a papillary growth, or may be bound to adjacent structures by adhesions. The tumor usually has a distinct pedicle.

The **cyst wall** consists of three layers—an outer and inner firm fibrous layer, with a middle layer of looser tissue between them. In the middle layer of loose connective tissue the vascular supply is distributed.

The **contents** of cysts present marked contrast in consistency and in color. The contents may be thin like water (serous cysts), or thick and viscid and of gelatinous consistency (pseudomucinous cyst). The contents may be almost colorless or straw-colored or a dirty yellow, or green or black. The color de-

pends on hemorrhage into the cyst. The coloring matter of the blood becomes the coloring matter of the cyst contents.

As these cysts enlarge they bear various **relations** to adjacent structures. If they rise out of the pelvis and enlarge in the abdomen, they may attain a very large size before producing serious symptoms. There they have plenty of room and expand freely, pushing aside the surrounding organs. If they become caught under the pelvic brim and develop in the pelvis, they soon begin to cause pain and other disturbances from pressure and distortion of the organs.

When the papillomatous growths within a cyst pierce the cyst wall (which happens most frequently in the serous cyst), peritoneal implantations may occur. In some cases these peritoneal implantations grow rapidly and fill the pelvis with papillary masses. In such a case the first impression, when the abdomen is opened, is that the pelvis is filled with a cancerous mass, which cannot be removed and which will soon cause death. Accordingly, in not a few cases, the operator, after scraping out some of the papillary bleeding growth, has closed the abdomen and told the patient or her friends that there was an inoperable cancer and that she could not long survive. Some such patients get entirely well after the operation. In other cases malignant change has already begun or begins later and the patient dies of carcinoma. In still other cases the growth itself becomes so extensive as to interfere with the functions of adjacent organs and thus causes death.

DERMOID CYSTS

Dermoid cysts, according to Ewing, constitute 10 per cent of all ovarian tumors, though some series give a much higher percentage. They are present at birth but are not discovered usually until later in life, between thirty and forty, when their growth begins to cause symptoms. Early in life they grow rapidly, but remain stationary after reaching a certain limit of development. About 12 per cent of dermoids are bilateral.

Histogenesis.—The exact origin of these interesting tumors is not known. One theory is that they arise from the undifferentiated somatic cells of segregated blastomeres in the early embryonic life. The other theory is that they develop from ova either by parthenogenesis or in an undeveloped or abnormal fertilized egg. In favor of this latter theory is the fact these tumors are found in the ovary and not elsewhere in the body. The cystic dermoid tumor represents an adult type of growth and the solid teratoma an embryonal type; these latter are discussed under Malignancies of the Ovary.

Dermoid cysts are usually globular in shape and dull white in color. They contain structures associated with epidermal tissues, such as hair, teeth, bone, sebaceous material resembling fat. Specimens are shown in Figs. 864 and 865 from a tumor removed by Dr. Benjamin Fox, West Frankfort, Illinois. Extensive hemorrhage was present.

Occasionally on close inspection hair can be seen through the wall. They have a doughy consistency, with very hard areas where bony structures are present. When opened, a fatty, semisolid sebaceous material flows out. Hair and skin are nearly always present. The tumors contain elements of all three

layers of the blastoderm as has been shown by Bonnet. The solid tissue is usually on one side of the tumor and is called the "dermoid plug."

Blackwell, Dockerty, Masson, and Mussey in a study of 100 consecutive tumors found ectodermal derivatives in 100 per cent of the tumors, mesodermal structures in 93 per cent, and entodermal derivatives in 71 per cent of these cysts. Malignant lesions occurred in 3 per cent of cystic teratomas.

The following is a partial list of tissues which have been found in dermoids: Skin and its derivatives, sebaceous glands, hair, sweat glands, and bone, especially the maxillae containing teeth. Up to 300 teeth have been found in one cyst. Rokitansky observed the eruption of permanent teeth after the discharge of the milk teeth. Milk teeth are more common in teratoma, while the permanent teeth are usually found in dermoids. Long bones, digits, fingernails, and skull have been found. Brain tissue with its derivatives, intestinal loops, thyroid tissue, (struma ovarii), eyes, salivary glands, may occasionally be found. Even rudimentary fetuses have been described, such as a pelvis with hairy pubes and a vulva and clitoris. Brains with ventricles, spinal cord, and a few complete extremities, have been observed. Fig. 866 shows opened dermoids in the gross, and Fig. 867 a microscopic picture of the wall structures.

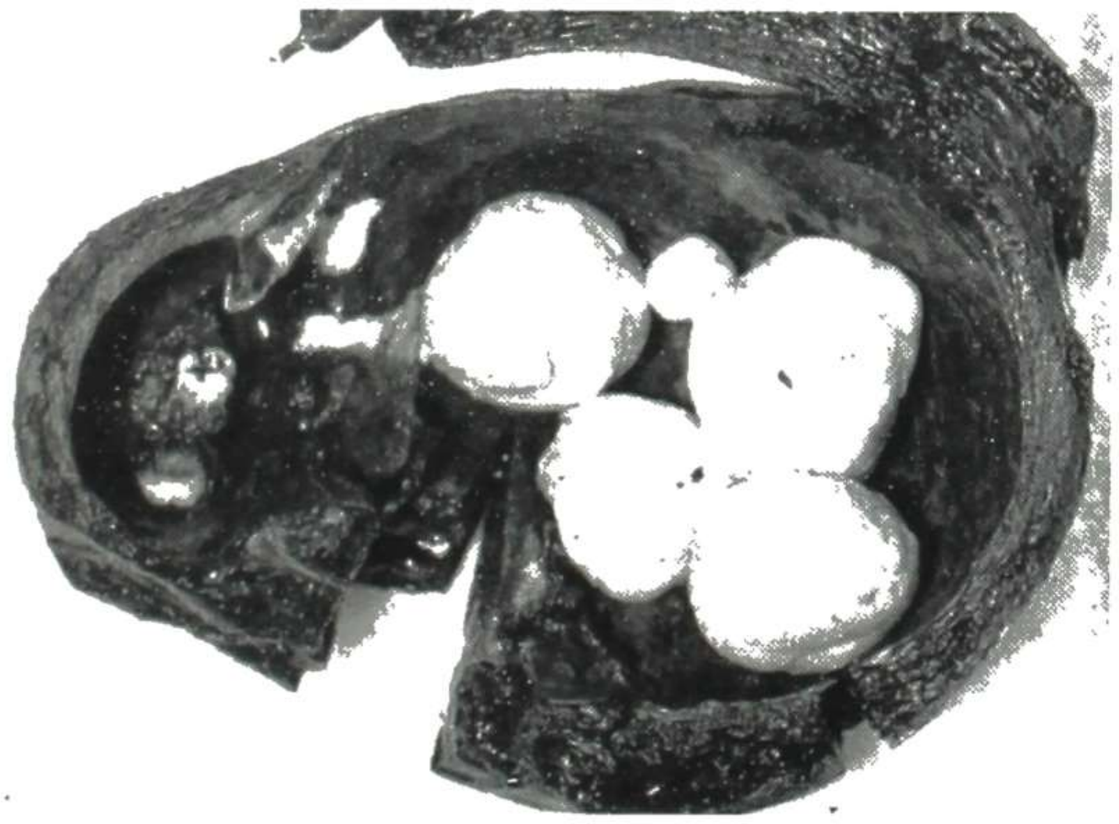


Fig. 864.

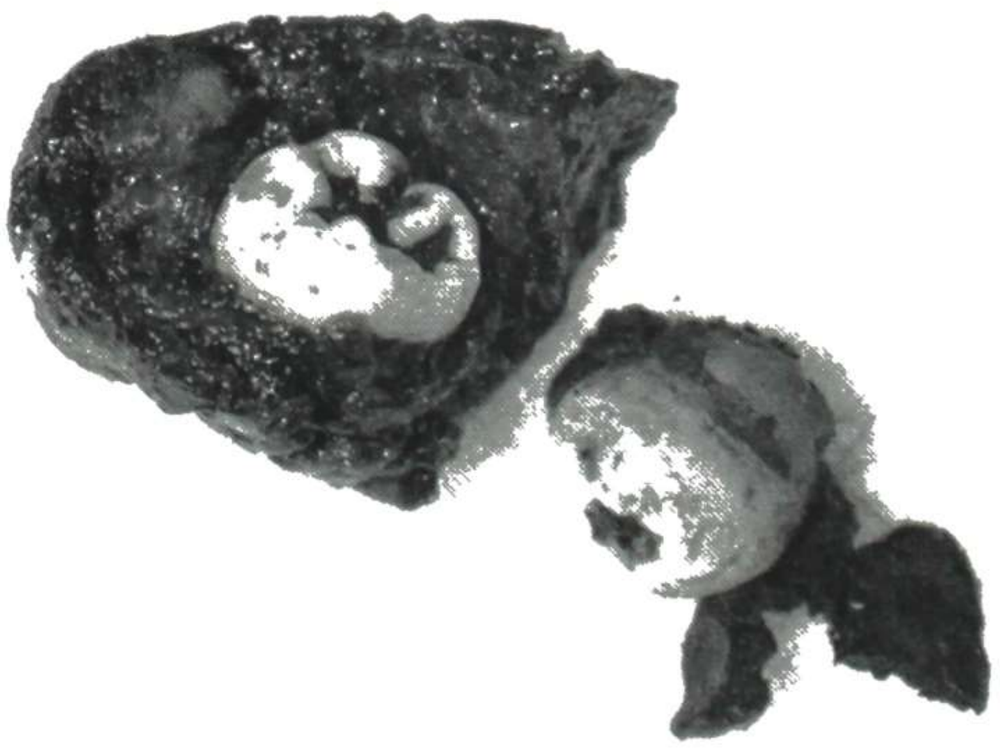


Fig. 865.

Fig. 864.—Dermoid with a twisted pedicle. Marked hemorrhage into the wall of the cyst. The teeth stand out clearly. (This specimen was removed by Dr. Benjamin Fox and sent to Dr. L. S. N. Walsh and is used with their permission.)

Fig. 865.—A close-up of the teeth present in the cyst shown in Fig. 864.

Ewing states that dermoids become malignant in about 3 per cent of the cases and the type of malignancy is usually squamous-cell carcinoma of the contained epidermis.

Rupture of dermoid cysts is a common occurrence, and the discharge of the irritating sebaceous material causes a marked peritoneal reaction and dense adhesions.

Symptoms and Diagnosis.—Dermoid tumors may appear at any age. They have been found in children at birth and in women at ninety years. Dermoid tumors of the ovary are comparatively small, rarely getting larger than a child's head. But they are more dangerous than the ordinary large cysts, for the dermoid cysts usually present more and firmer adhesions, and their con-

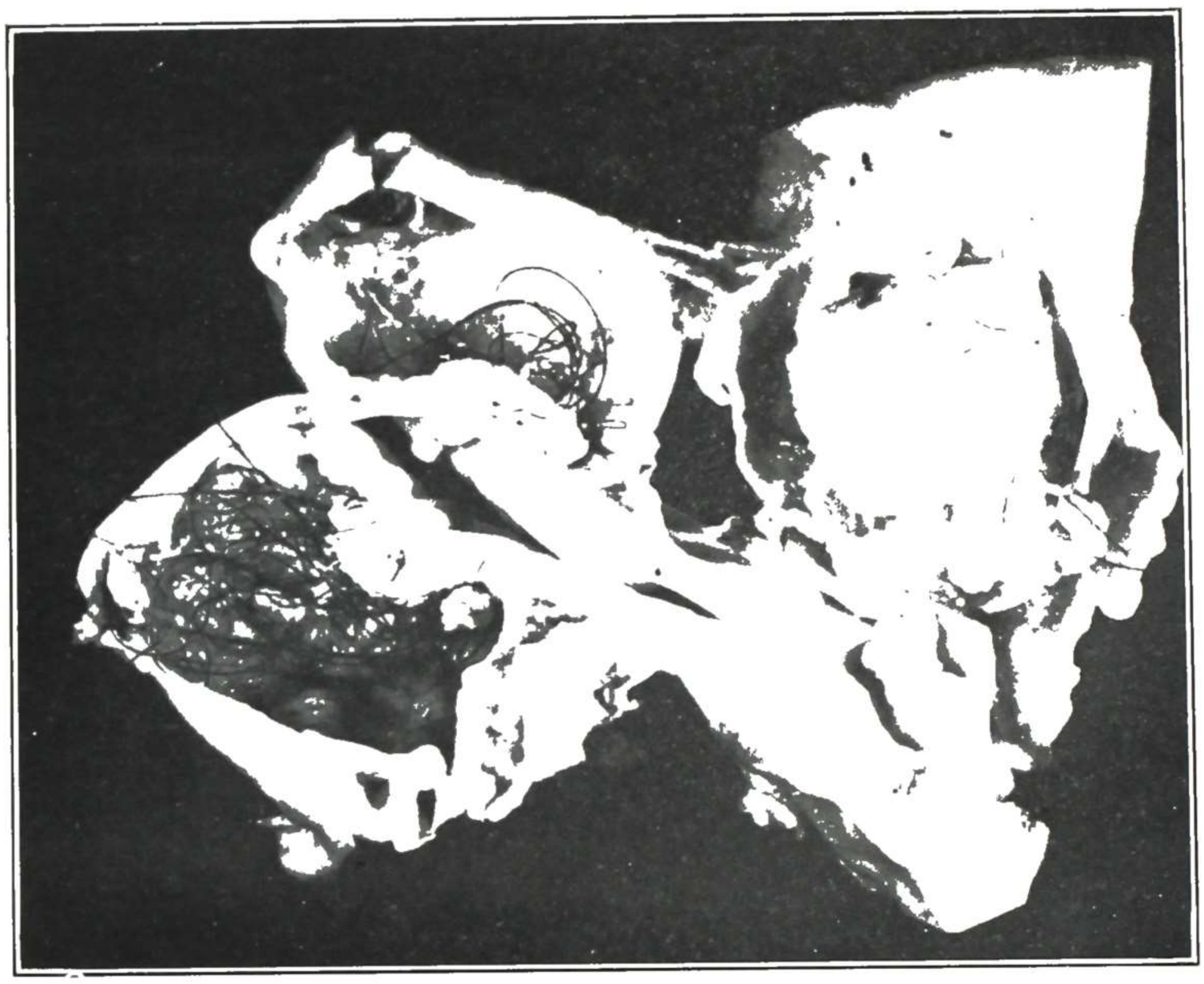


Fig. 866.—Dermoid cyst of the ovary. Gross specimen, showing several teeth in the lower right portion of the specimen and hair in the cystic portion on the left. Gyn. Lab.

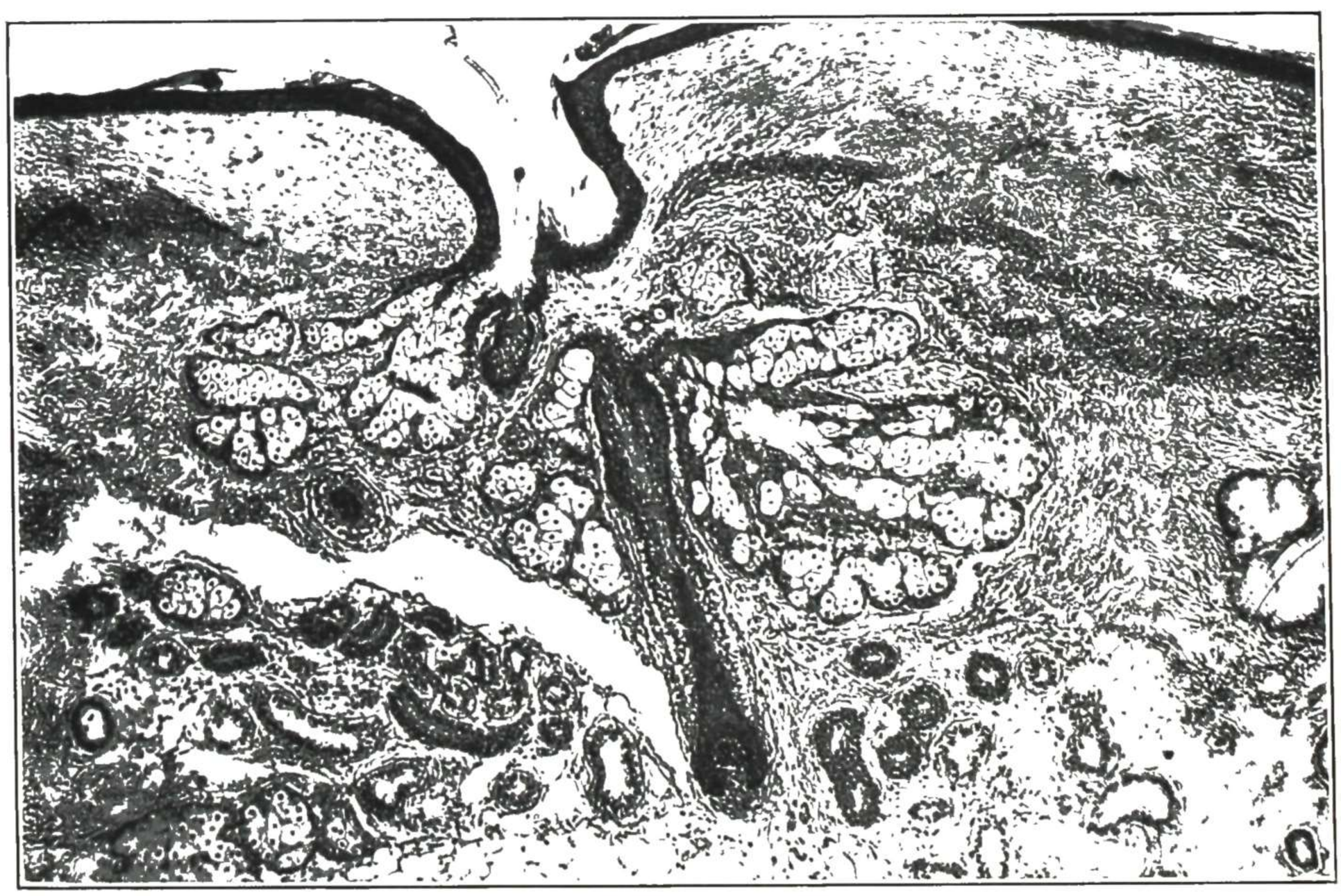


Fig. 867.—Dermoid cyst. Microscopic picture showing a hair follicle, sebaceous glands, sweat glands, and squamous epithelium. Gyn. Lab.

tents are more irritating, so much so that the escape of any of the contents into the peritoneal cavity is likely to cause a peritonitis.

The symptoms of dermoids are about the same as for ovarian cysts in general, which are given in detail later in this chapter. In dermoid cysts there may be present a firmer surface on palpation. As they often contain bone or teeth, x-ray examination may assist in determining the character of the pelvic mass felt in pelvic palpation.

Morris and Rosenthal in studying a series of 79 cases, found teeth or bone alone or in combination, in 39 cases or nearly 50 per cent. They remark, "Had x-ray been more frequently employed a high percentage of these tumors could have been diagnosed before operation."

Dermoids are more liable to suppuration and abscess formation than the ordinary cyst. Such abscess may rupture into the lower bowel, with discharge of bony material from the rectum. In such case differential diagnosis must be made between dermoid cyst and extrauterine pregnancy as the original trouble.

Quinby reports a dermoid which ruptured into the bladder. Carter, Thomas, and Pearse reported a dermoid cyst which ruptured into the bladder and into the sigmoid, producing a very complicated condition. By means of pelvic, cystoscopic and gastrointestinal x-ray examinations the details were finally worked out.

Treatment.—The treatment of dermoid tumors which have become large enough to be appreciated and give trouble, is removal by operation, the same as for proliferating cysts. The fact that they may develop malignancy is an additional reason for prompt removal.

SYMPTOMS AND DIAGNOSIS OF OVARIAN CYSTS IN GENERAL

An ovarian cyst usually develops slowly and may attain considerable size before it is discovered. Often it is noticed then only by accident.

The earliest symptoms are a feeling of weight and pressure in the pelvis, bladder irritability, slight menstrual disturbance, constipation, and perhaps some pain with bowel movement. The symptoms are not distinctive, but simply indicate some disturbing factor in the pelvis. As the tumor increases in size, distinct pressure symptoms appear and the general nutrition becomes affected. There is enlargement of the abdomen, swelling of the feet from pressure on veins, pain from pressure on nerves, and dyspnea from pressure on the diaphragm. There appear, also, stomach disturbances, emaciation, and progressive weakness. In some cases there are attacks of local peritonitis, with severe abdominal pain and some fever, but these inflammatory symptoms are due to complications and do not belong to the natural history of the tumor.

Ovarian cysts grow slowly, usually taking several years to reach a large size. But they seldom stop growing. They persistently enlarge until the patient finally dies from exhaustion brought about by pressure effects on vital organs.

The diagnosis in typical cases is easy, but in complicated cases it may be very difficult, and in exceptional cases a positive exact diagnosis is impossible before operation. Tapping the cyst through the abdominal wall as an ex-

ploratory measure is not advisable. An adherent coil of intestine may be punctured, or cyst contents may leak into the peritoneal cavity and cause fatal peritonitis. In a doubtful case, an exploratory abdominal section is safer and far more satisfactory in diagnostic results.

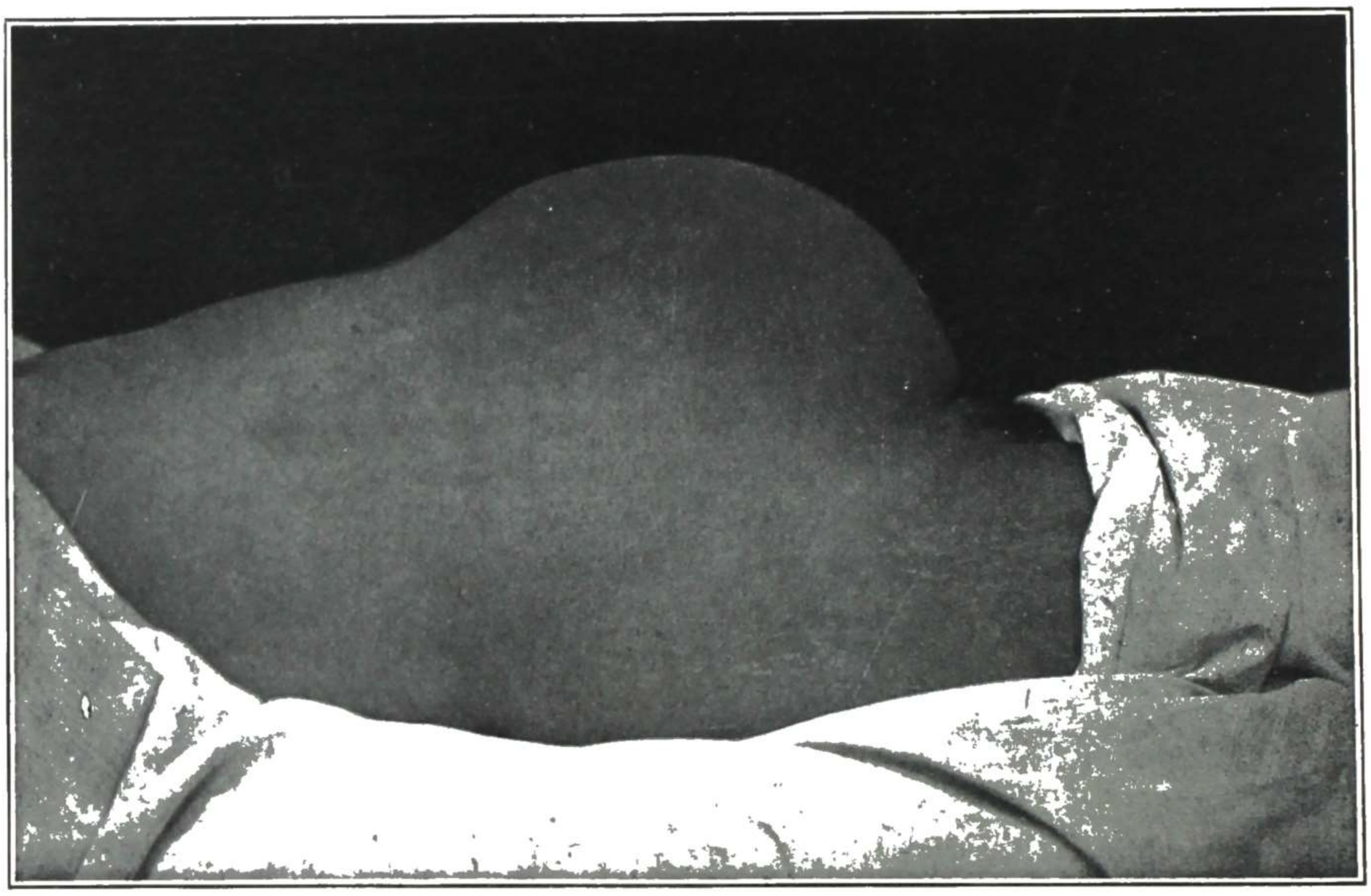


Fig. 868.—Patient with a large ovarian tumor.

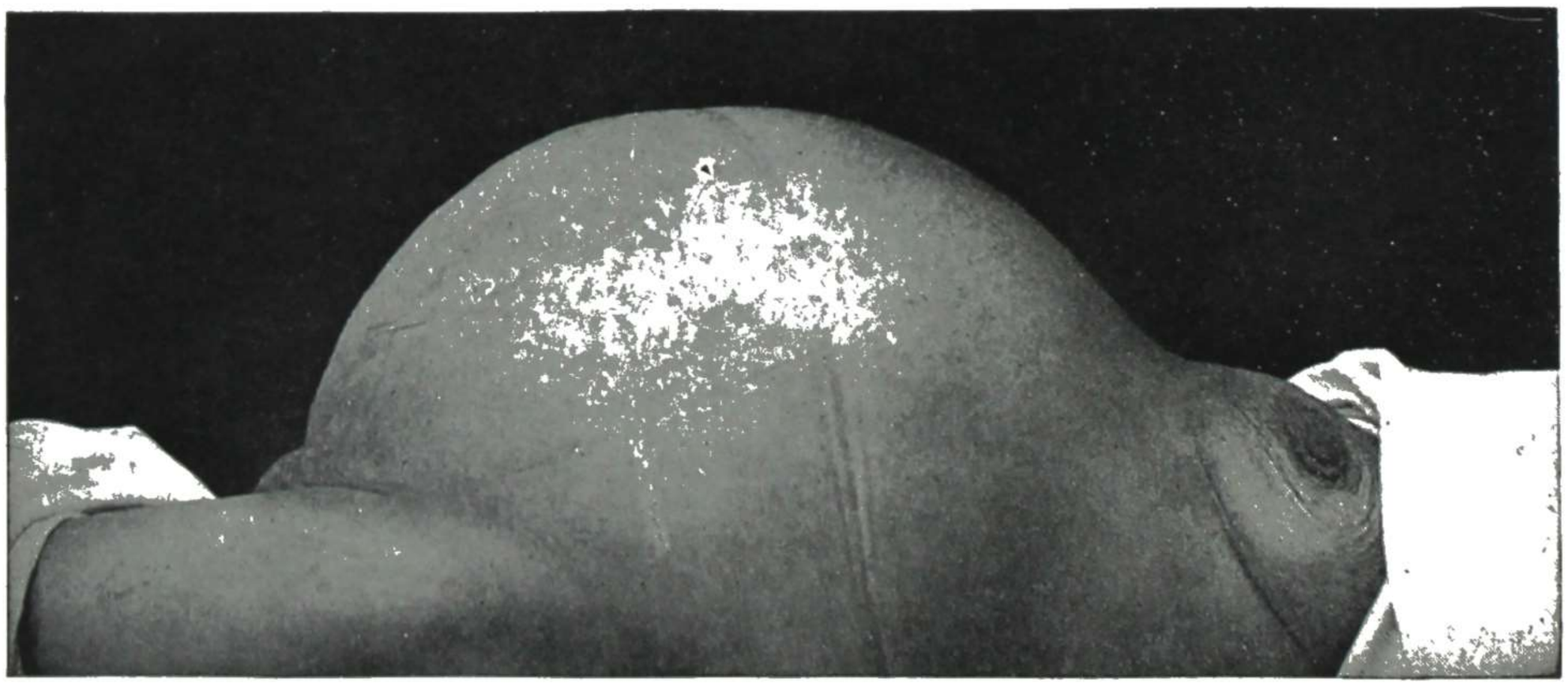


Fig. 869.—Extreme ascites. In the patient of whom this photograph was taken, the abdomen was so distended with fluid that the wall was raised higher than the mesentery would permit the intestine to float, giving dullness about the umbilicus as well as elsewhere. The rise of the wall from below is rather abrupt. There is also edema of the wall, as shown by the persisting groove where the skirts were fastened about the waist.

In taking up the differential diagnosis of ovarian cysts in general, it is at once apparent that the symptoms and diagnostic points are different in the different sized tumors.

Small Ovarian Cyst.—Considering the small ovarian cyst according to the seven principal diagnostic points in the palpation of pelvic masses (position, size, shape, consistency,

tenderness, mobility, attachment—see Bimanual Examination of Corpus Uteri and Other Pelvic Masses, Chapter 2), it is found that an ovarian cyst of this size presents the following characteristics:

1. Is situated in the lateral part of the pelvis, though in exceptional cases it may drop down directly behind the uterus or in front of it.

2. The small ovarian cyst is the size now under consideration—about as large as the fist or a little larger.

3. Is approximately spherical, though may be made uneven by secondary cysts.

4. Contains fluid (fluctuates).

5. Is not tender, unless complicated by inflammation or by torsion of pedicle.

6. Is freely movable, unless complicated by adhesions or caught under the sacral promontory.

7. Is attached in the lateral part of the pelvis. Apparently arises from the tubo-ovarian region. Lies beside the uterus, but is not attached to it and does not ordinarily modify it in any way, except to cause some displacement toward the opposite side.

If the cyst is uncomplicated, there is no history of pelvic inflammatory attacks—that is, the mass has progressed to its present size independent of inflammation or hemorrhage, which identifies it at once as a new growth.

The following conditions may be confounded with a small ovarian cyst and must therefore be taken into consideration in the **differential diagnosis:**

a. Salpingitis with exudate.
b. Pyosalpinx.
c. Hydrosalpinx.
d. Tubal pregnancy.
e. Fibroid tumor of the uterus.
f. Retroverted pregnant uterus.
g. Broad ligament cyst.

Large Ovarian Cyst.—A growth large enough to cause the abdomen to be prominent (Fig. 868) must be differentiated from the following conditions:

a. Tympanites and "phantom tumor."
b. Obesity.
c. General ascites (Fig. 869).
d. Pregnancy (normal, with hydramnios, extrauterine).
e. Cystic fibroid of uterus.
f. Distended bladder.
g. Tumor of some abdominal organ.
h. Tuberculous peritonitis.

COMPLICATIONS

Having determined that an ovarian cyst is present, we must then consider certain complications that may be present or that may appear later. These complications are as follows:

1. Local peritonitis, forming adhesions.
2. Hemorrhage into the cyst.
3. Rotation of the cyst, producing torsion of the pedicle.
4. Inflammation and suppuration of the cyst.
5. Rupture of the cyst.
6. Ascites accompanying the tumor.
7. Intestinal obstruction.
8. Pregnancy accompanying the cyst.

1. **Local Peritonitis** is accompanied by some pain and tenderness over a part of the tumor. There may be some fever, but usually this symptom is not marked; the process con-

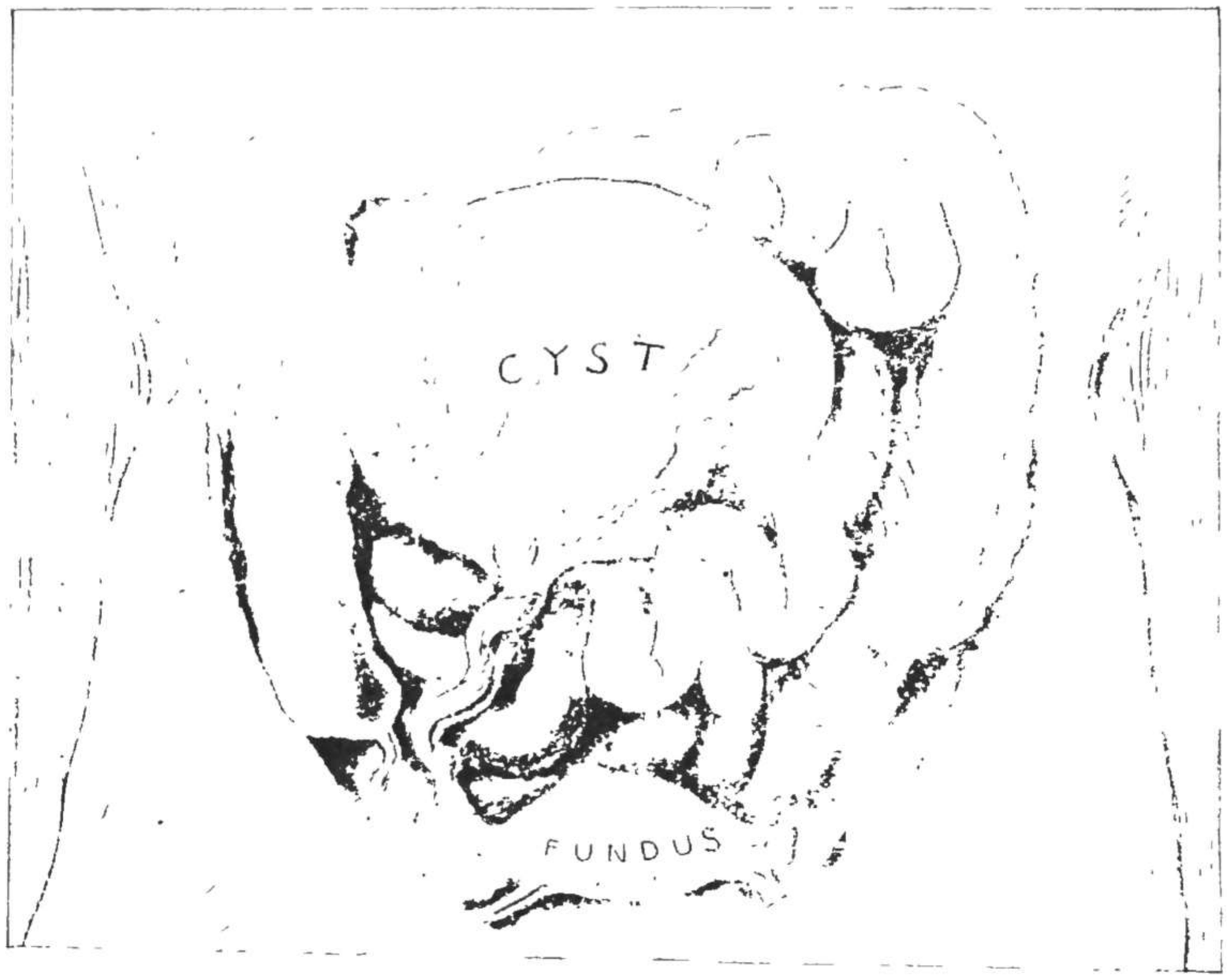


Fig. 870.—Ovarian cyst with a long slender pedicle. (From Montgomery: Practical Gynecology.)

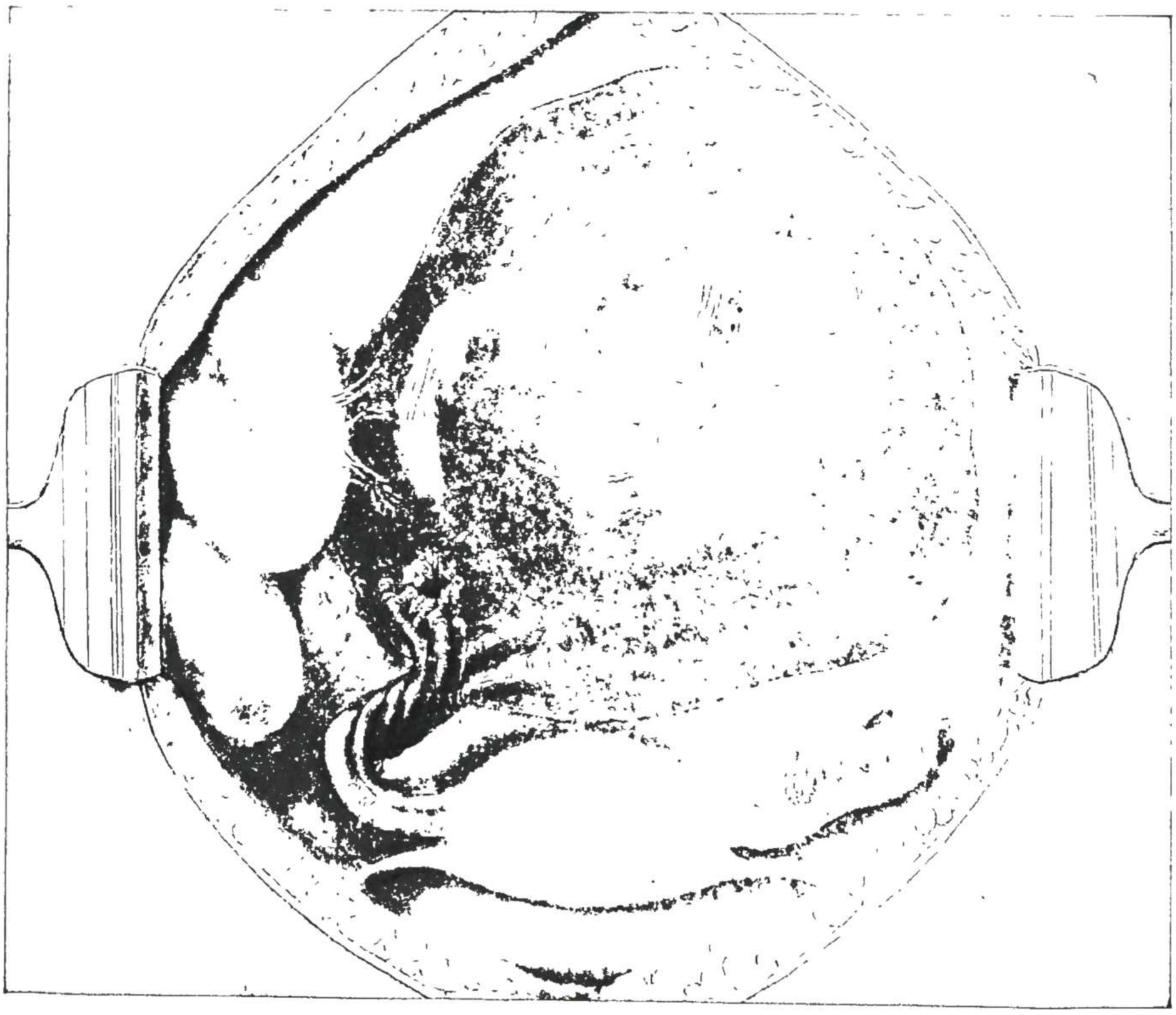


Fig. 871.—Indicating an ovarian cyst with twisted pedicle. The turning of the tumor twists the pedicle, blocking the circulation and causing thrombosis in the pedicle and throughout the tumor. The extravasation of blood causes the affected tissues to become black.

Fig. 872.—Dermoid cyst of ovary with torsion of pedicle causing thrombosis. At operation the tumor was so large and adherent that extension of the incision above the umbilicus was necessary for its removal. The twist in the pedicle, which included also the fallopian tube, showed two complete turns. It was necessary to remove the corpus uteri along with the tumor, and the uterus is shown opened. Color drawing from fresh specimen.

Fig. 873.—Double ovarian cyst with torsion of pedicle causing thrombosis. At operation the left tumor appeared as a black mass, due to extensive hemorrhage into it. The tumor of the other ovary showed no torsion and no circulatory disturbance. It was necessary to remove the corpus uteri along with the tumors. The twisted area has been untwisted. Notice at the edge of the uterus the clear-cut margin of the thrombosed area. The rounded swelling between the uterus and the tumor is due to a hemorrhage into the tissues just beyond the twist. Color drawing from fresh specimen.

sists simply of irritation at some portion of the outer surface of the cyst and the formation there of plastic exudate, binding the cyst to some adjacent organ or to the abdominal wall. In a few days the pains disappear, but the exudate remains, becomes organized, and forms an adhesion, which may interfere more or less with the subsequent operation.

2. Hemorrhage into the Cyst is what gives the various colors to the cyst contents. This hemorrhage usually takes place slowly in small quantities and without clinical symptoms. Occasionally, however, a copious hemorrhage takes place, usually from some interference with the venous return, such as twisting of the pedicle or pressure of an enlarged uterus, or it may follow tapping of the cyst. The hemorrhage may be so severe as to cause collapse of the patient.

3. Rotation of the Cyst may take place where the pedicle is long (Figs. 870 and 871). The amount of rotation varies from a half turn to several complete turns. Torsion of the pedicle is supposed to be favored by an injury, such as a fall or blow, and by active exercise, and also by the alternate filling and emptying of the bladder and the bowel, and during pregnancy by the enlargement of the uterus.

The effect of torsion of the pedicle on the circulation of the tumor depends, of course, on the amount of rotation. The veins are the first to suffer. The flow of blood in them is impeded, causing the tumor to become engorged, and there is hemorrhage into the interior of the cyst, either in the form of extravasation or the rupture of a vein with severe hemorrhage. If the twisting increases, there is thrombosis of the vessels (Figs. 872 and 873) and extravasation of bloody fluid into the peritoneal cavity, and later necrosis of the tumor, followed by fatal peritonitis. The symptoms of torsion of the pedicle are very marked. When a patient with an ovarian tumor complains of sudden pain in the abdomen and vomits, and there is a sudden increase in the size of the tumor, it is probable that torsion of the pedicle has taken place. In some cases there are repeated attacks of slight torsion. In cases where the circulation is diminished slowly, a new vascularization occurs and the cyst may become detached from its original site and become a parasitic cyst. Stevens states that when this occurs in children, it is most common on the right side and hence is frequently mistaken for appendicitis.

4. Inflammation and Suppuration of the Cyst are, of course, due to infection. The infection may come from the intestinal canal or from the bladder or from a fallopian tube or from tapping the cyst. The most common source of infection is the fallopian tube. The patient contracts salpingitis, adhesions form between the inflamed tube and the cyst wall, and infection spreads along these adhesions, and invades the cyst. Adhesions with some portions of the intestinal tract, especially with the appendix, may likewise lead to infection of the cyst. Tapping, which was formerly a common procedure, often led to infection of the cyst. Dermoid cysts are especially prone to suppuration. Infections of cysts are not uncommonly seen in the course of the acute infectious fevers, especially typhoid.

The symptoms of suppuration of the cyst are pain, fever, tenderness over the tumor, rapid pulse, exhaustion, and emaciation. If the suppurating cyst does not speedily cause death by peritonitis, it may later rupture into the intestine or bladder or vagina. The teeth, hair and pieces of bone discharged in rare cases from the urethra or rectum are usually due to suppuration of a dermoid cyst.

5. Rupture of the Cyst may be sudden, as from a fall or blow or other injury, or it may be the result of a gradual thinning of the cyst wall. The result of rupture of the cyst depends on the quantity and quality of the cyst contents. In unilocular cysts with non-irritating fluid, rupture may produce no severe symptoms. There are some weakness and abdominal pain and marked diuresis, the patient sometimes passing several gallons of urine in twenty-four hours. The abdomen, which was prominent from the tumor, becomes flattened and lax. The physical signs change from those of encysted fluid to those of free fluid. The cyst may not refill, and if no inflammation takes place, the patient recovers. But this favorable termination takes place only in rare cases. In the great majority of cases of cysts, rupture causes peritonitis, which may be very severe and rapidly fatal.

Rupture of a cyst is indicated by the sudden disappearance of the tumor or marked diminution in its size, accompanied by evidences of free fluid in the peritoneal cavity and collapse of the patient, and later peritonitis and death.

6. Ascites.—A small amount of ascitic fluid may be present with many cysts, but a large quantity is rare so long as the tumor retains its normal condition. Consequently, the presence of considerable ascitic fluid with an ovarian cyst becomes of diagnostic importance. The ascites may, of course, be due to some heart trouble or kidney trouble or liver trouble, or may be due to peritoneal tuberculosis. Aside from such complications, ascitic fluid is indicative of some serious complications; e.g., a papillary cyst, especially after malignant change, or rupture of an ordinary cyst.

7. Intestinal Obstruction.—This may be caused by direct pressure of the tumor or by adhesions which contract and narrow the intestine. It is, of course, a very serious complication and is indicated by the ordinary symptoms of intestinal obstruction appearing in the presence of an ovarian tumor.

8. Pregnancy may accompany an ovarian cyst, adding much to the difficulties of diagnosis.

TREATMENT OF PROLIFERATING AND DERMOID CYSTS

The treatment of these cysts is removal by operation as soon as found, if the condition of the patient will permit.

These ovarian tumors are not at all influenced by palliative measures, they do not stop growing spontaneously, and they tend to cause death within a few years. Consequently they should be removed as soon as found or as soon as the patient can be put in condition for the operation. Sometimes the patient is in such a weakened condition that she must be given a course of treatment before operation. Some general disease, such as kidney, heart or lung trouble, may make it necessary to delay the operation until the patient can be put in better condition.

Then, again, the patient may be in such condition that a radical operation would be almost certainly fatal. In such a case it would, of course, be useless to operate. In some such inoperable cases the patient may be rendered temporarily more comfortable by tapping the cyst with a trocar and drawing off the fluid. In all cases of proliferating cysts, however, in which the patient is in suitable condition, the tumor should be removed by operation.

The importance of careful examination of the opposite ovary and of the ovaries in any pelvic operation was emphasized in an article by Cianfrani; in 1,500 apparently normal ovaries examined during a three-year period in the pathologic department of the Graduate Hospital, Philadelphia, he found three dermoids, one Brenner tumor, one fibroma, one granulosa-cell tumor, and one papillary cystadenocarcinoma. These ranged in size from a few millimeters to 1.5 centimeters. Five were discovered by careful examination at operation and two were discovered in routine pathologic examination in the laboratory.

OVARIAN TUMORS IN CHILDREN

Costin and Kennedy state that of the 200 cases of ovarian tumors in infants and children reported in the literature, approximately one-third were simple multilocular cysts, one-fourth were dermoid cysts, and in more than one-third the tumors were malignant. In their series the commonest ovarian tumor in children was teratoma.

Schaefer and Veprovsky point out that in children the diagnosis of ovarian tumors is rarely made except in tumors with endocrine activity. The most common complication is a twisted pedicle and this for some unknown reason occurs on the right side so that the case is usually diagnosed as an acute appendicitis. Stevens found that in children dermoid cyst with a twisted pedicle was four times as common as simple cyst with a twisted pedicle. The occurrence of other types of ovarian tumors in children will be discussed under Malignancies of the Ovary.

BENIGN SOLID TUMORS

This group of tumors arise from the musculofibrous framework of the mesenchyma, that is, the vessels, nerves, and lymphatics, and include the fibromas, angiomas, myomas, and fibromyomas. These are not truly of ovarian mesenchymal origin and hence in our outline are considered under Benign Growths. Another solid benign tumor included in this group is the Brenner tumor.

Fibroma of the Ovary

Ovarian fibromas are rare tumors comprising about 5 per cent of all ovarian tumors. Little is known about etiology of fibromas. They have been found at ages ranging from ten to eighty. They are bilateral in about 12 per cent of the cases, and ascites is almost always present if the tumor is at all large.

These may occur as small circumscribed tumors of white pearly appearance embedded in the stroma or on the surface of the ovary, or they may be diffuse, involving the entire ovary. Bomze and Kirshbaum reported a large one weighing 71 kg. On cutting into the tumor, it is usually found to be cartilaginous or of bony hardness, but it may be soft if edema or necrosis is present. Occasionally one finds areas of calcification and even ossification. A yellowish color is common (Fig. 874). Dockerty and Masson in a series of 312 fibromas removed from 283 patients found multiple ovarian fibromas in 10 per cent of the cases.

The association of ascites and hydrothorax with fibroma was reported in 1879 by Cullingworth. In 1937 Meigs and Cass called special attention to this syndrome and it has since become known as "Meigs' syndrome." Since this time numerous reports of this syndrome have appeared, and contrary to the original idea that it was associated only with fibromas, it has been found in association with thecomas, granulosa-cell tumors, Brenner tumors, and even ovarian carcinomas in which there were no pleural metastases.

Meigs emphasized that when associated with fibromas the ascites and hydrothorax disappear when the fibroma is removed. Formerly many of these cases were thought to be malignant and, because of the complications mentioned, inoperable.

The exact mechanism of the ascites and the hydrothorax which usually occurs on the right side is unknown. Geibel observed that when a fibroma was placed in a dry vessel it lost about one-third of its weight, from the oozing of serous fluid from its surface, in a period of twenty-four hours. Others feel that the firm fibrous tissue constricts the lymphatics at the hilum of the ovary,

causing an exudation of tissue fluids. In an experimental and clinical investigation as to the cause of the right-sided hydrothorax, Rubin et al. concluded that it was due to the "better development of the diaphragmatic lymph channels, the higher position of the diaphragmatic dome and the more intensive pumping action of the diaphragm on the right side."

As these tumors enlarge, their weight is apt to cause torsion of the pedicle with pain, and this is frequently the first symptom noted. Ascites rarely occurs in tumors smaller than 6 cm. in diameter, but Dockerty and Masson found it present in 36 per cent of the cases associated with fibromas larger than this, and the amount was usually proportionate to the size of the tumor. In only two of their 283 cases of fibroma was there a hydrothorax present.

Scotti-Douglas feels that all tumors benign or malignant accompanied by ascites and hydrothorax should be included in the Meigs syndrome if there is complete and permanent disappearance of the fluid after removal of the tumor. Rare tumors such as myoma or adenomyoma may develop in the ovary. Treatment of ovarian fibromas is removal.

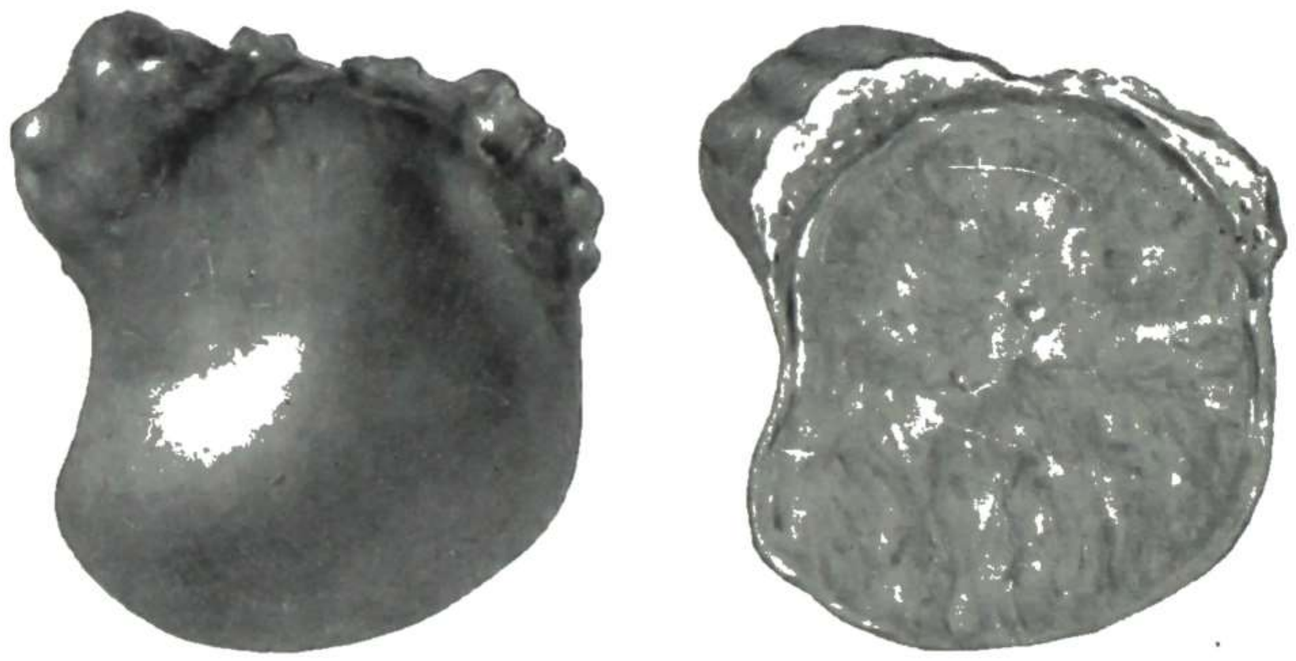


Fig. 874.—A small ovarian fibroma. Cross section, showing the typical fibromatous structure and a well-defined capsule. Gyn. Lab.

Brenner Tumors

There is a difference of opinion on the exact origin of the Brenner tumor. Meyer and later Danforth felt that they came from the Walthard cell islets, and the latter pointed out that there was a characteristic longitudinal grooving giving these tumors a coffee-bean appearance, the same type of marking as is seen in the Walthard cell islets. Schiller feels that the Brenner tumors as well as the other types of tumors such as the hypernephromas, mesonephromas, and ganglioneuromas result in inclusion of pinched-off elements of the coelomic epithelium and structures which are adjacent to the developing ovary in embryonic life and in the development of the ovarian pedicle. This pedicle develops comparatively late and hence remains in close approximation to regional tissue. If the two folds which enclose the ovarian ligament cut too deeply or are spaced wider apart than normal, Schiller feels that nonovarian tissue may be included, and he feels that the Brenner tumors with their transitional squamous epithelium are pinched off elements of the adjacent urinary system. Greene reviewed the literature on the various theories of the origin of Brenner tumors, and concludes that some develop from the surface epithelium of the ovary, others originate from the rete ovarii, and still others are derived from the ovarian stroma.

These tumors are usually unilateral and of moderate size. On cut surface, they are white in color and sharply defined and suggestive of a fibroma. The cystic type cysts usually contain pseudomucin.

Two types are described by Meyer: (1) solid tumors with or without small cysts, and (2) cystomas with or without pseudomucinous epithelium and containing nodules or Brenner cell tumors in the wall. A marked hyalinization of the stroma is characteristic, and there is a definite capsule present.

In the first type there are nests of epithelial cells embedded in the fibrous connective tissue. In the center of the nests there may be hollow spaces and cysts with indifferent cylindrical or mucous epithelium. Centrally, the cells are parallel to the long axis of the nodule, while peripherally they are at right angles.

If the differentiation of the cell foci tend primarily in the direction of cyst formation, the second type of Brenner tumor is the result. In this type actual cystomas appear and may or may not be lined by pseudomucinous epithelium. Maury and Schmeisser have reported a case of bilateral Brenner tumor in which the tumor in one ovary was of the first type and the one in the other ovary of the second type.

Various microscopic characteristics are shown in Figs. 875 to 878. Proescher and Rosasco, in reporting a case and discussing the subject, state:

> The epithelial part of the tumor does not develop from the ovarian parenchyma nor from the granulosa-cell islands, but from special cell elements which are not derived from the normal cells forming the ovary, but are abnormal cell inclusions which are found in Walthard's cell islands. According to R. Meyer, they originate from the celomic epithelium near the wolffian body, from which the epithelium of the müllerian duct is derived. The latter may form solid epithelial nodules, or larger formations of indifferent epithelium in abnormal locations, as in the tubes and ligaments. It may differentiate into mucous or columnar epithelium, like the surface epithelium of the ovary.
>
> Walthard's cell islands are capable of forming tumors which not only contain mixtures of Brenner epithelium and pseudomucinous and serous cysts, but pure areas of these types of cells may occur side by side. Also pseudomucinous cysts may form without Brenner epithelium. The Brenner tumors are linked genetically with the majority of the serous, partially fibrous, and adenomatous and papillomatous cystomata, including the adenofibromas and the mixed seromucinous tumors. Only a small percentage of the pseudomucinous cysts and cystomata originate from Walthard's cell islands. The majority constitute the endodermal part of a teratomatous anlage, which dates back to the early segmentation of the ovum.
>
> The Brenner tumors have no clinical peculiarities save their frequency of occurrence at an advanced age, 50 per cent occurring after fifty years of age. They are benign and no metastases or recurrences have been observed. Malignant tumors arising from Brenner's epithelium are, so far, not known.

In a recent article Reagan reviews the gross and microscopic pathology in a series of 23 specimens. In a clinicopathologic study of 31 cases of Brenner tumors Johndahl et al. found that the majority of the patients were in the postmenopausal age group.

Novak, in reporting a series of cases, gives the following summary:

> This paper is based upon the study of 17 cases of Brenner tumor of the ovary, including the 14 new cases herein reported. This brings the total of reported cases to 122, though new instances are being reported more and more frequently. The tumors are benign, and produce no characteristic symptoms. When small they are, therefore, likely to be found only accidentally in operations for other indications. They may, however, reach a very large

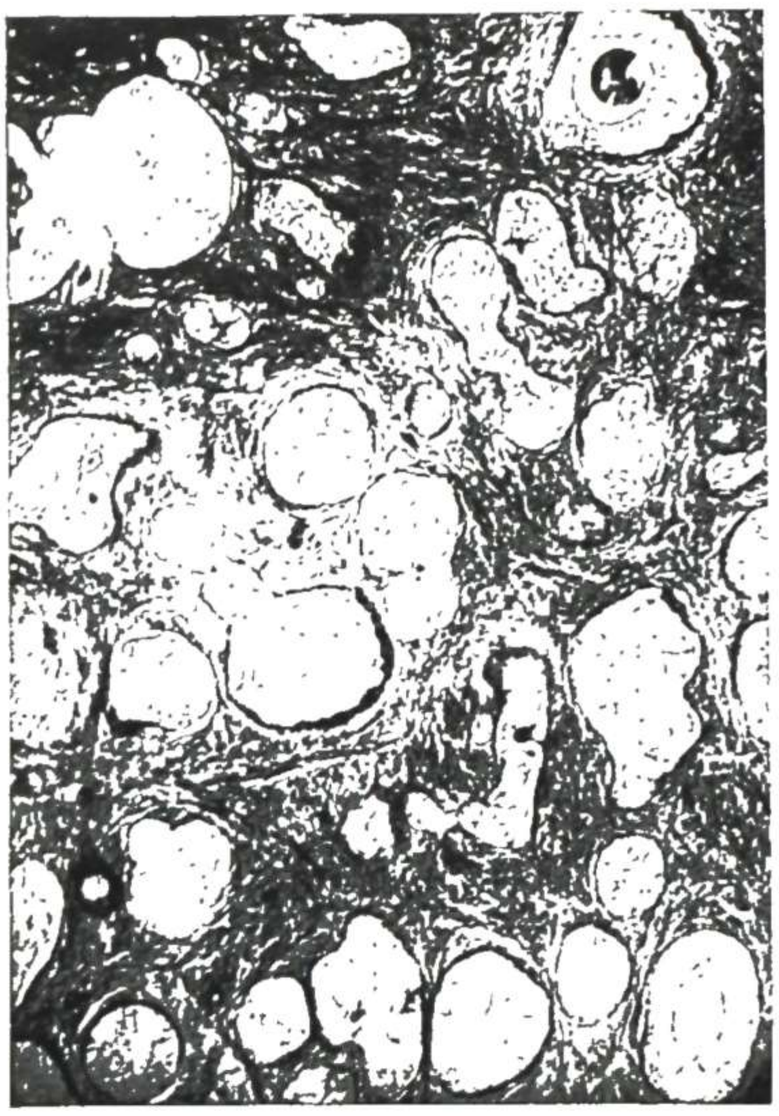


Fig. 875.

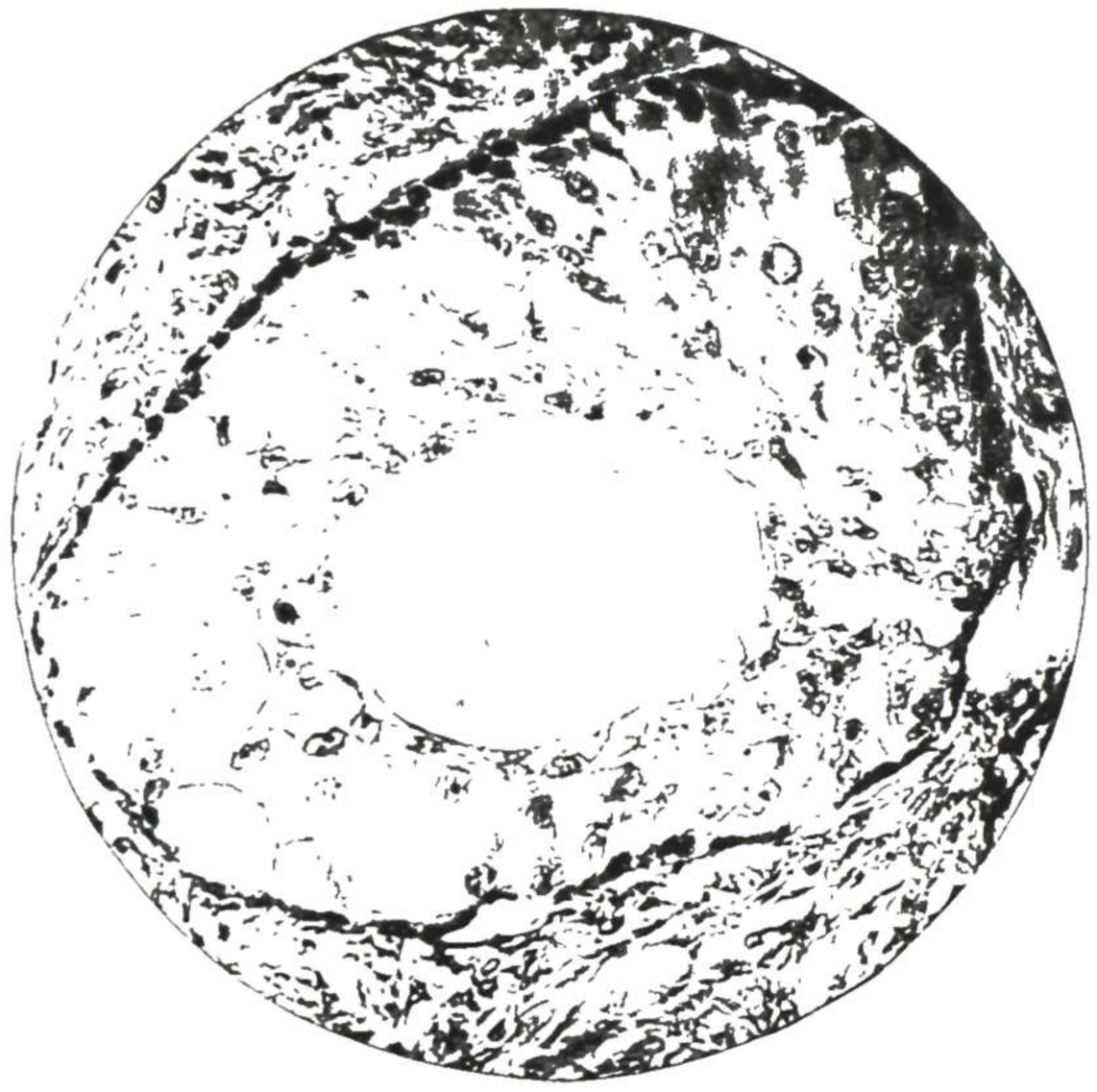


Fig. 876.

Figs. 875 and 876.—Brenner tumor. Fig. 875, Characteristic picture at low power. Irregular stroma, epithelial masses varying in shape. They are partly hollow. They contain mucin. Narrow hyaline bands surround the epithelium. They are small cysts. Fig. 876, Partly hollowed out, pseudomucin containing epithelial mass. The outermost cells are conspicuous by their small, dark nuclei. (From Plaut: Surg., Gynec. & Obst.)

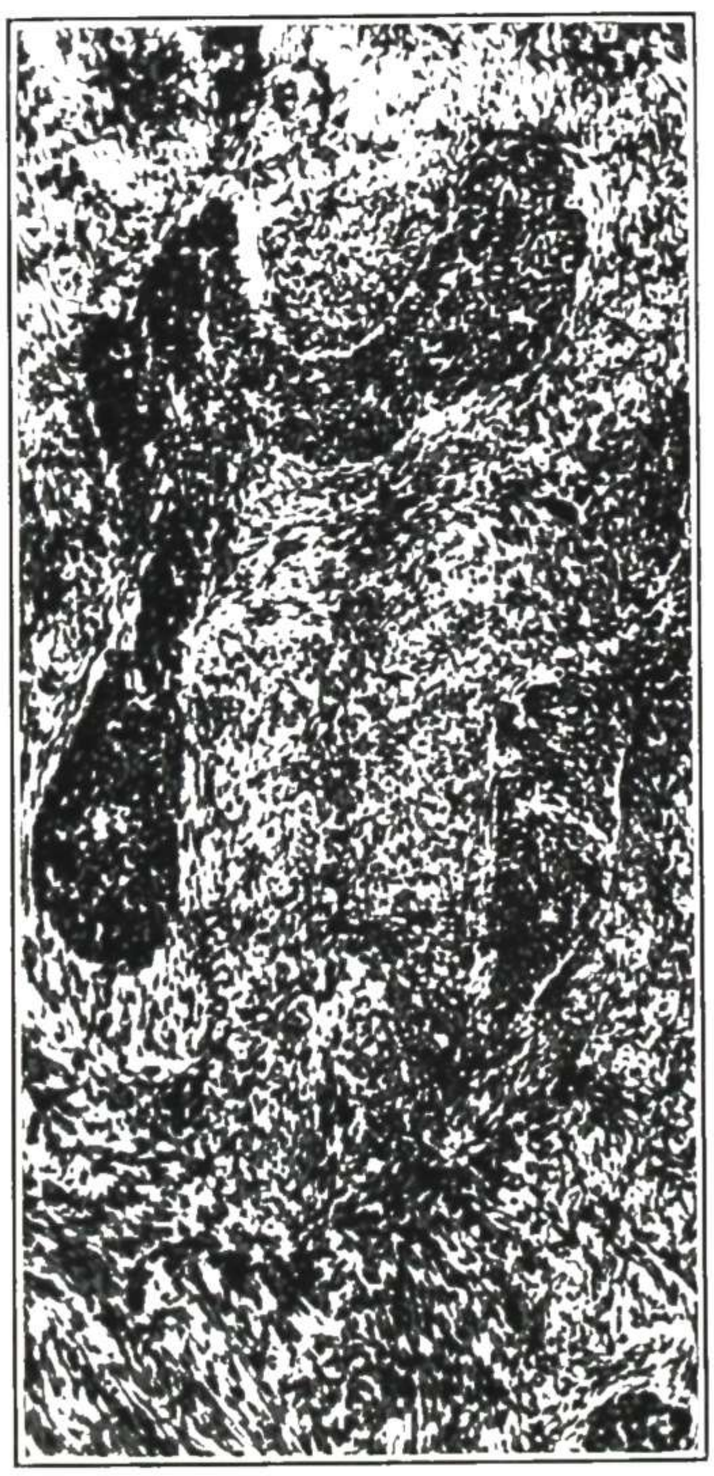


Fig. 877.

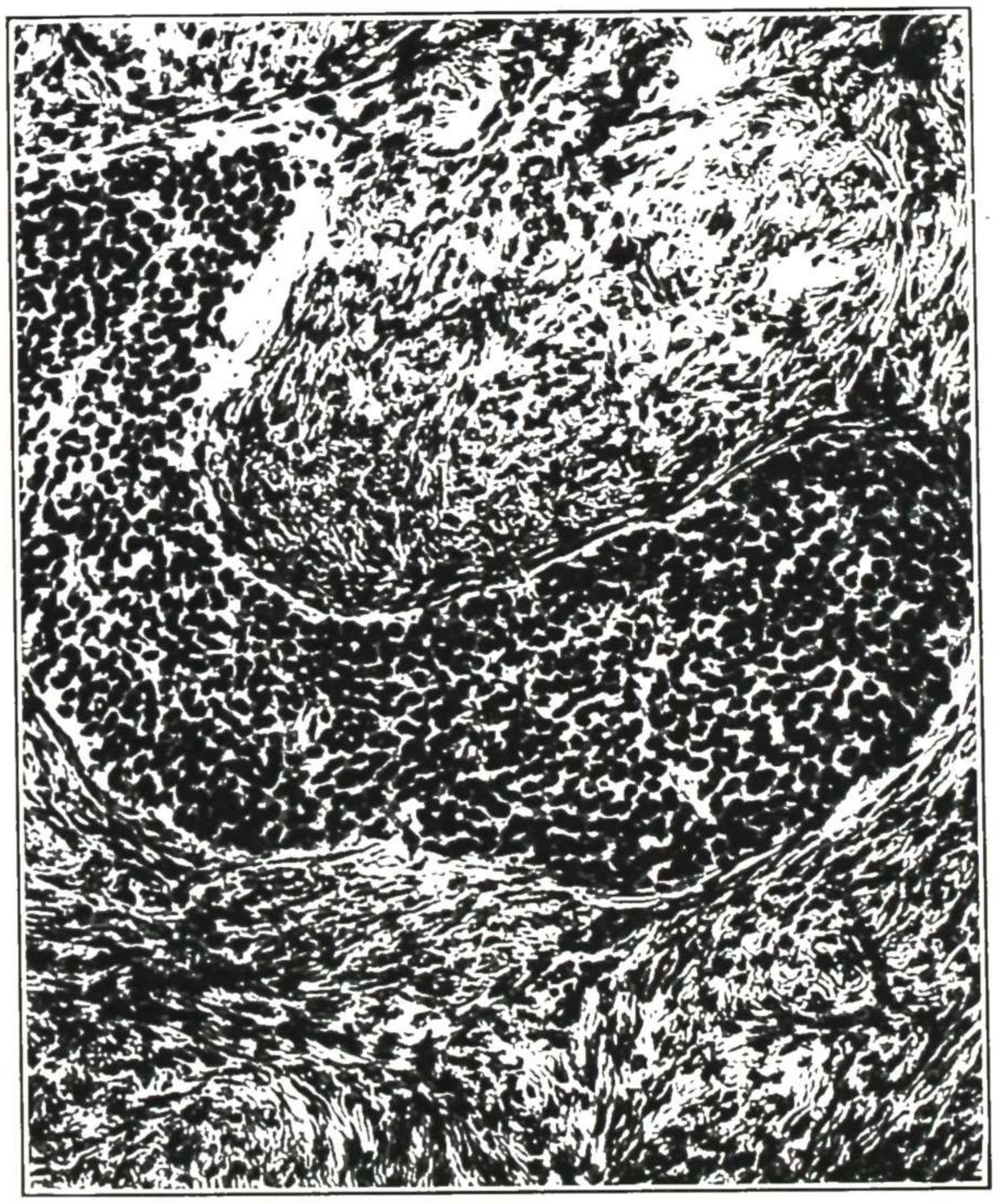


Fig. 878.

Fig. 877.—Brenner tumor, Type I. There are a few hollow spaces seen but no large cysts.

Fig. 878.—High power of the upper portion of the Y-shaped nest of cells seen in Fig 877, showing the character of the cells. Gyn. Lab.

size, in which case they produce discomfort or pain, with perhaps the presence of a mass noticeable to the patient herself. The pathologic characteristics have been described in the paper. The essential elements are (1) the presence of nests or columns, often partially cystic, of rather uniform size and appearance embedded in (2) a matrix of fibromatous tissue which is sharply marked off from the surrounding ovarian stroma though there is no definite capsule. The tumors probably arise from the so-called Walthard islands of indifferent cells which may at times occur in the ovary, though other explanations have been suggested.

The most interesting histologic characteristic is the frequently observed transition of the cells into a cylindrical type identical with that characterizing the ordinary pseudomucinous cystadenoma, so that large tumors of the latter variety may be produced, with only small nodular Brenner tumor vestiges in the wall to indicate their origin. There is logic, therefore, in the subdivision of Brenner tumors into the solid and cystic varieties. Three such tumors are included in our series. On the other hand, the fibromatous reaction may be so striking as to produce large fibromas of the ovary. In such cases, of which 2 are included in our group of cases, the origin is indicated by the finding of the typical cell nests scattered either sparsely or richly throughout the tumor. There is little or no evidence to indicate that Brenner tumors exert any such endocrine effects upon sex characters as those which characterize granulosa-cell carcinoma or arrhenoblastoma.

Because of the absence of any hormonal manifestations from these tumors, the diagnosis of the type of growth is made after removal.

MALIGNANCIES OF THE OVARY

The common forms of malignant disease of the ovary will be considered here: namely, carcinoma and sarcoma. The various special ovarian tumors now recognized as potentially malignant will be considered later.

Pathology

Of the two forms, carcinoma and sarcoma, carcinoma is by far the more frequent.

Carcinoma.—This form of malignant disease may be primary in the ovary or may be secondary to a growth in some other structure.

Primary.—Carcinoma developing with the ovary as the primary focus is found in from 10 to 12 per cent of ovarian neoplasms. Allan and Hertig, in a study of 1,740 proliferative tumors of the ovary, found that 265 were malignant. The malignant tumors were bilateral in 32 per cent of the cases, and of the bilateral cases 15 per cent were pseudomucinous and 37 per cent serous. Pfannenstiel in his series found that the carcinoma was bilateral in 90.9 per cent of the cases.

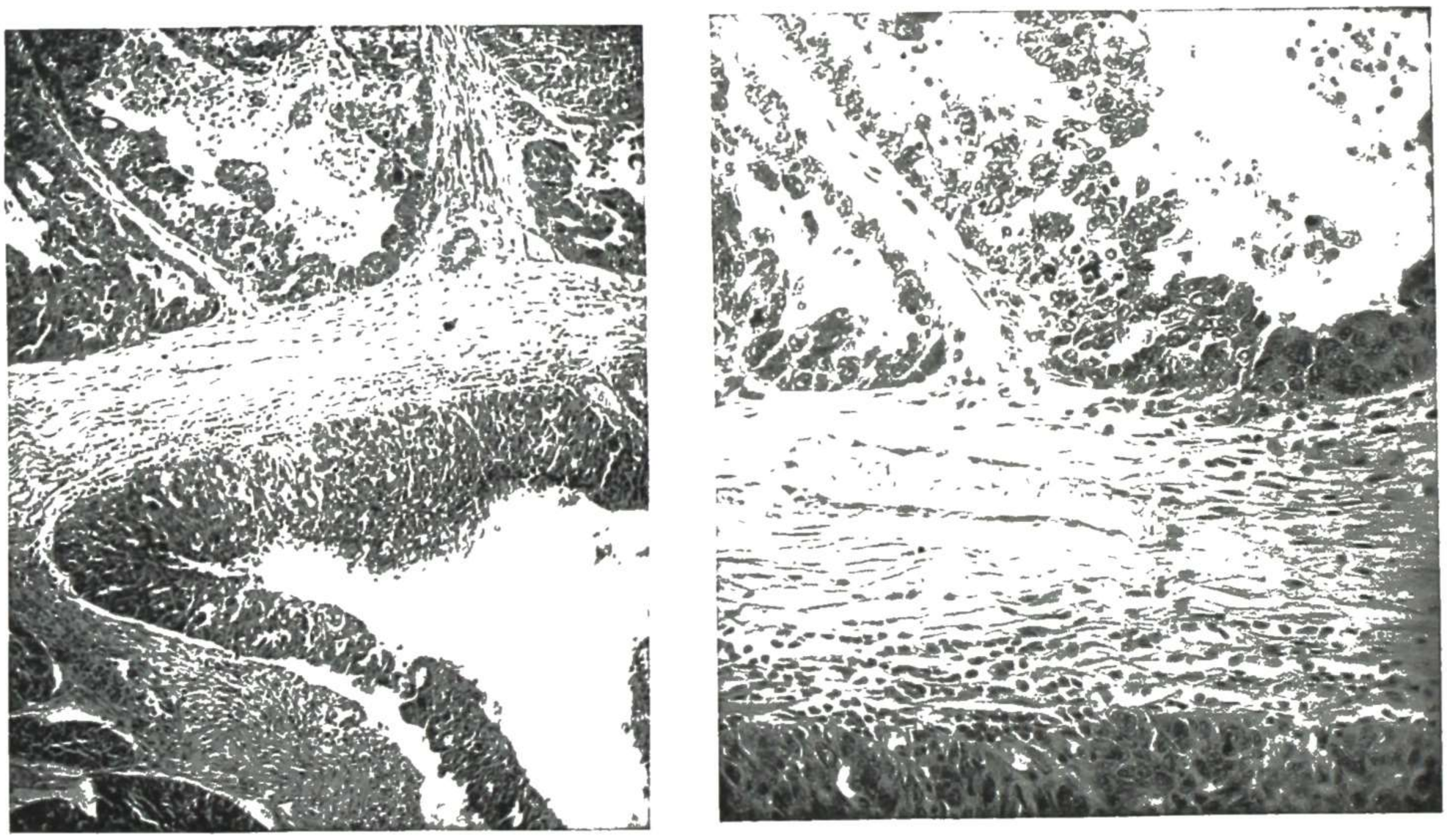
The greatest age incidence is between forty-five and sixty-five, and Marks and Wittenborg found the age specific incidence of ovarian cancer to fall in the sixth decade. There is an accompanying ascites in 78 per cent of the cases.

The gross appearance varies with the type of carcinoma. In the slower-growing type, secondary to a cyst, the surface of the cyst is usually studded with papillae. On opening the cyst the cavity is found to be filled with a granular cauliflower-like material. If proliferation is very rapid, the tumor may be solid, but they are usually soft. On opening this type of tumor, the inner pulp pouts out through the rent in the wall. In some specimens the solid areas resemble soft white brain tissue.

The microscopic examination of this tissue shows glandlike areas in the slower-growing tumors (Fig. 879), while in the more rapidly growing tumors there are solid interlacing cords of cells with no attempt at gland formation. Occasionally one can trace the epithelium in the glandlike structures from a single-layered benign epithelium to a frankly malignant multilayered polymorphous atypical epithelium.

Some are of the medullary type. They are of soft consistency as the result of degenerative processes, which are clearly shown on cross section.

Local metastases are the rule, especially to the surrounding organs and the peritoneum. The lymph glands commonly involved are the inguinal and lumbar and supraclavicular.



A. *B.*

Fig. 879.—Malignant papillary cyst. *A*, High power, showing the piling up of the epithelial cells and other characteristics of malignancy. *B*, Still higher power of the left central area in *A*, showing the individual cell characteristics. (From Erdmann and Spaulding: Surg., Gynec. & Obst.)

Pathologic Grading: Various groupings have been proposed with a view to definite pathologic classification of ovarian carcinomas, to aid in accurate recording and reporting of cases so as to permit analysis and comparison, as to prognosis in the different classes and as to results of various kinds of treatment. The following classification, suggested by Taylor, seems a practical and satisfactory one. It was used by Montgomery and Farrell in classifying their cases for clinical discussion, and the microphotographs showing a typical slide for each of the three grades are from their report.

Fig. 880 shows Grade I, which has well-marked glandular character, and represents the lowest grade of malignancy. .Fig. 881 shows Grade II, which has only imperfect gland formation, and represents increased malignancy. Fig. 882 shows Grade III, which has no gland formation, and represents the highest grade of malignancy.

For the reasons above mentioned, every specimen of ovarian carcinoma sent to the laboratory should have this grading recorded, and the classification in this respect should be included in the report to the physician.

Secondary.—Metastatic carcinoma of the ovary is not uncommon. In a series of 79 ovarian carcinomas secondary to primary tumors in the abdominal cavity reported by Schlagenhaufer, 61 were of gastric origin, 10 intestinal, 7 gall bladder, and 1 probably pancreatic. Handley in 442 autopsies on patients dying of mammary cancer found metastases to the ovaries in 13.4 per cent. Karsh in a study of 53 metastatic ovarian tumors found that the primary site was most frequently found in the breast (34 per cent) and the second most common site (15.2 per cent) was the stomach. Of the four Krukenberg tumors in his series, three were primary in the stomach and one in the gall bladder.

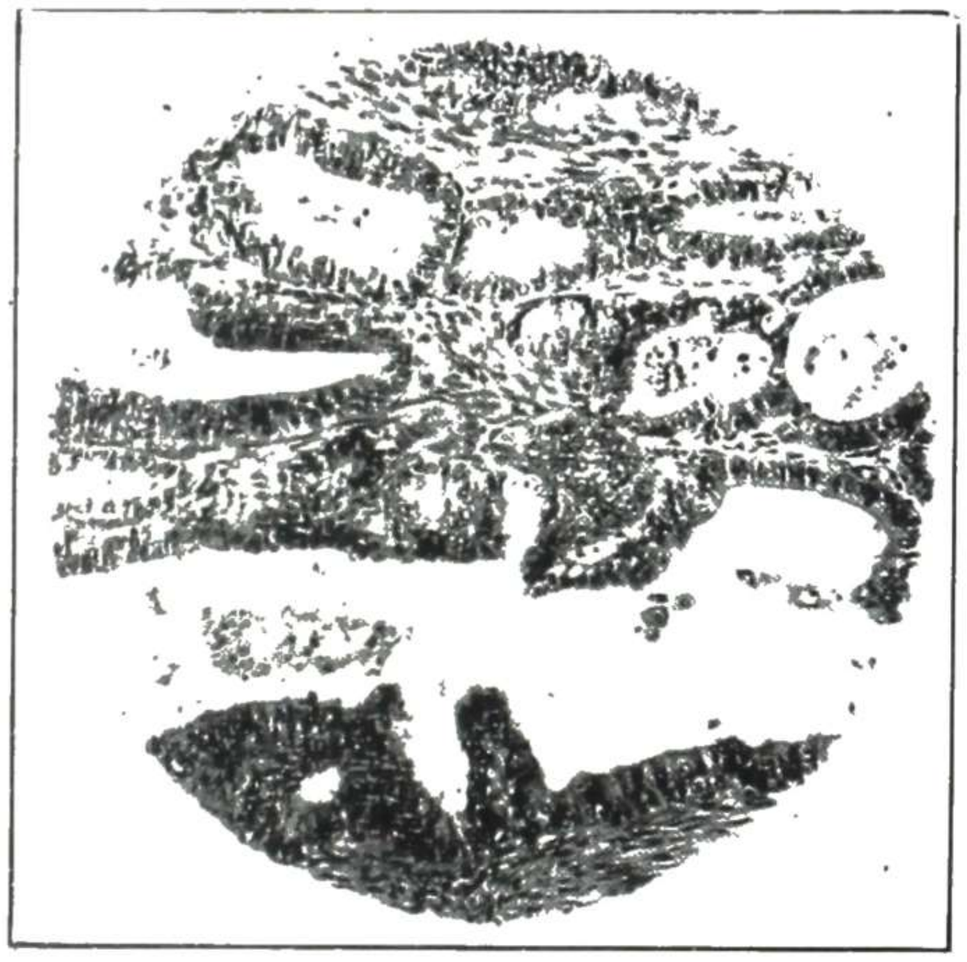


Fig. 880.

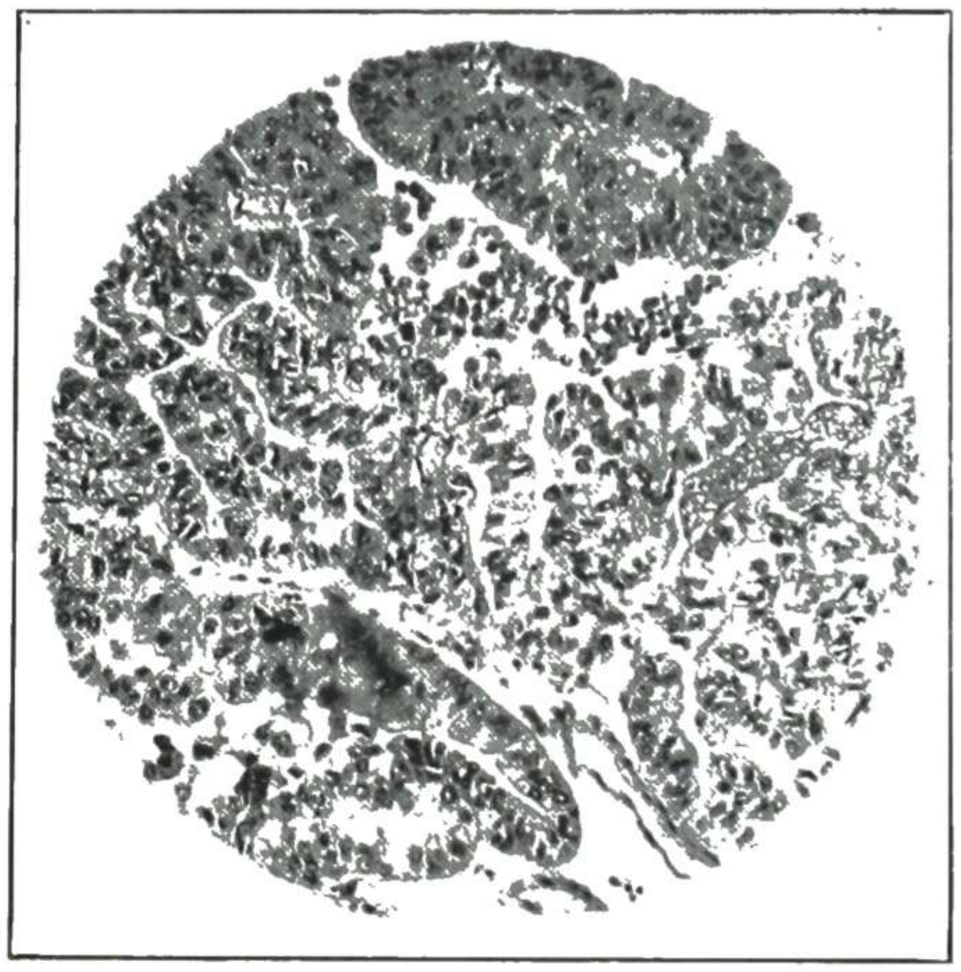


Fig. 881.

Fig. 880.—Ovarian carcinoma. Grade I. There is good glandular formation, with well-differentiated columnar epithelium. The mature type of structure is maintained throughout, except in occasional areas where early malignant changes are seen, such as the epithelial cells piling up in numerous layers in the glands or penetrating the stroma. This is the least malignant type.

Fig. 881.—Ovarian carcinoma, Grade II. Glandular and papillary structures are still present, but they are poorly developed. The columnar epithelium is not so well differentiated. There are moderate variations in the size and shape of the cells, nuclear changes, and more extensive infiltration. In this type the malignancy has increased very decidedly.

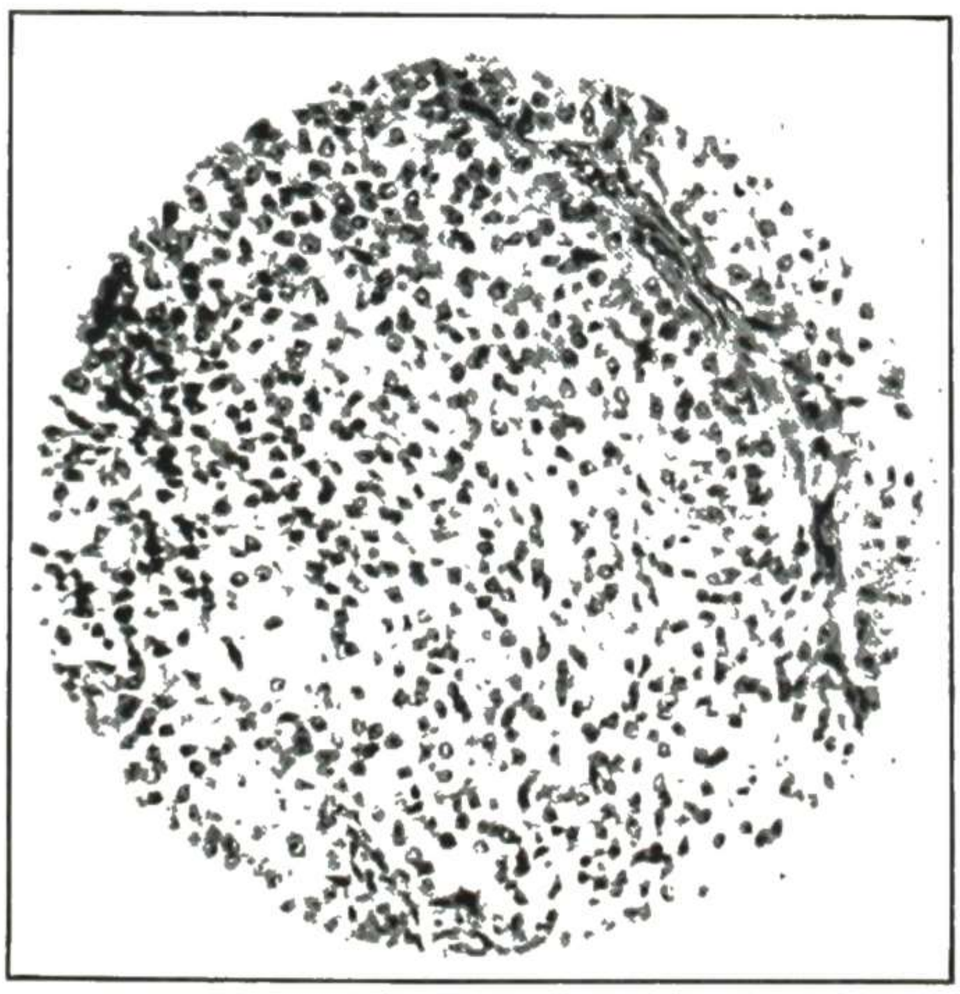


Fig. 882.—Ovarian carcinoma. Grade III. There is little evidence of glandular or papillary structure, the fields showing practically solid carcinoma. There are marked nuclear changes and undifferentiated epithelial cells. This is the most malignant type.

(Figs. 880 to 882 from Montgomery and Farrell: Am. J. Obst. & Gynec.)

Frankl divides the cases of secondary metastases into three groups: Those with no topical relation to the ovaries (breast); those having partial topical relationship (gastrointestinal tract, gall bladder, liver); those which have a close relation (uterus, tubes, rectum); and Karsh adds a fourth group which he designates as general (lymphosarcoma).

In the early stages the metastases appear as small circumscribed nodules on the surface or in the substance of the ovary. The lesions are usually bilateral and subsequent growth of these ovarian tumors is very rapid. Early death of the patient usually prevents the tumors from becoming very large, though some large ones have occurred.

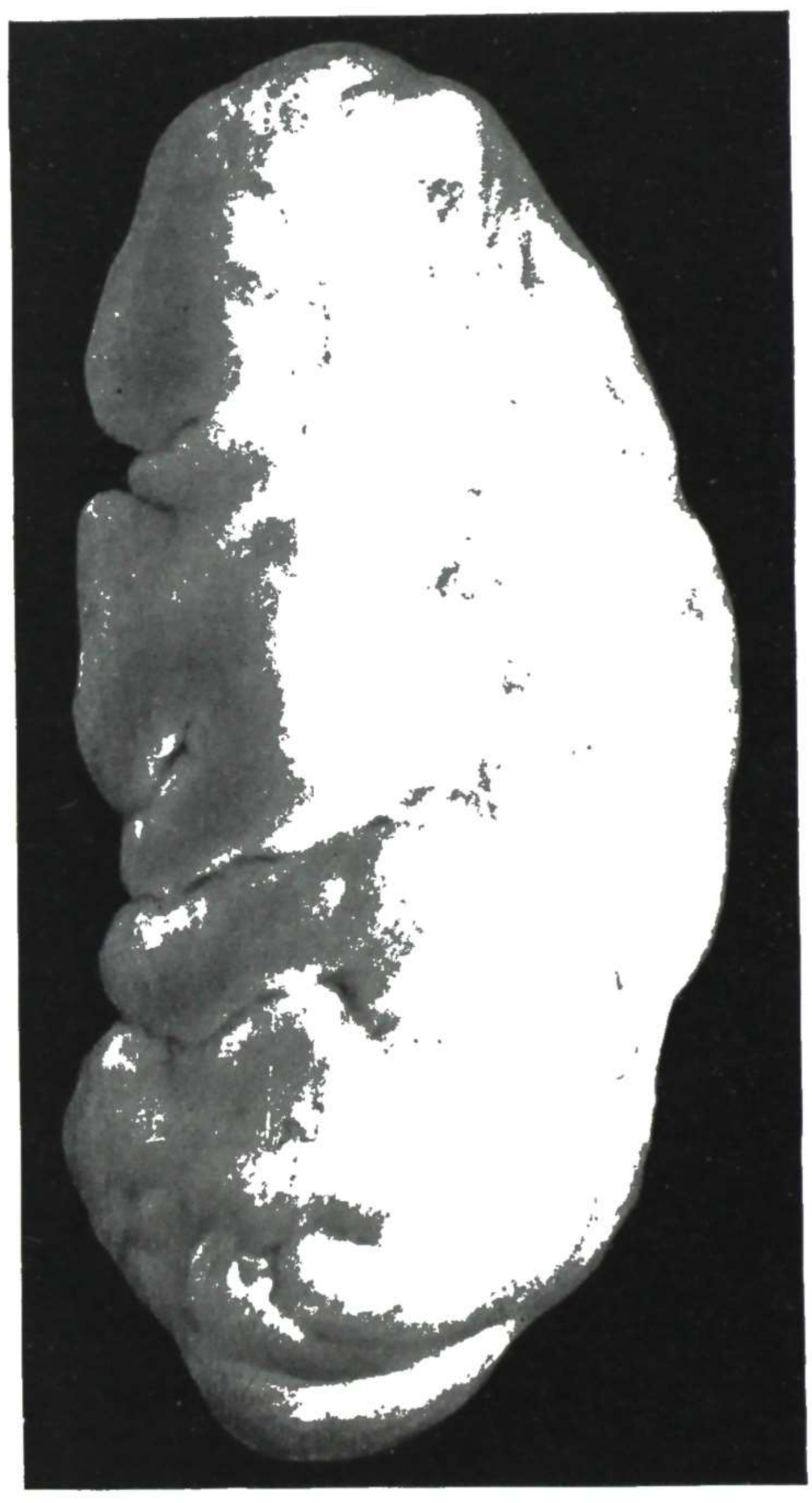


Fig. 883.

Fig. 884.

Fig. 883.—Krukenberg tumor of ovary.
Fig. 884.—Same specimen shown in section. Gyn. Lab.

The most typical of the metastatic ovarian growths is the Krukenberg tumor, which is usually secondary to a certain type of gastric and intestinal carcinoma, though as shown by Andrews and further substantiated by Novak, Bittman, and, more recently, by Schiller and Kozoll, the primary type of Krukenberg tumor does occur. Novak and Gray suggest that these primary types of tumors can be traced back to teratoid inclusions. These tumors are

fairly large, as a rule; are smooth, and have a glistening white surface. They are usually solid and are hence easily mistaken for sarcoma. The gross and microscopic characteristics of such a tumor are shown in Figs. 883 to 886.

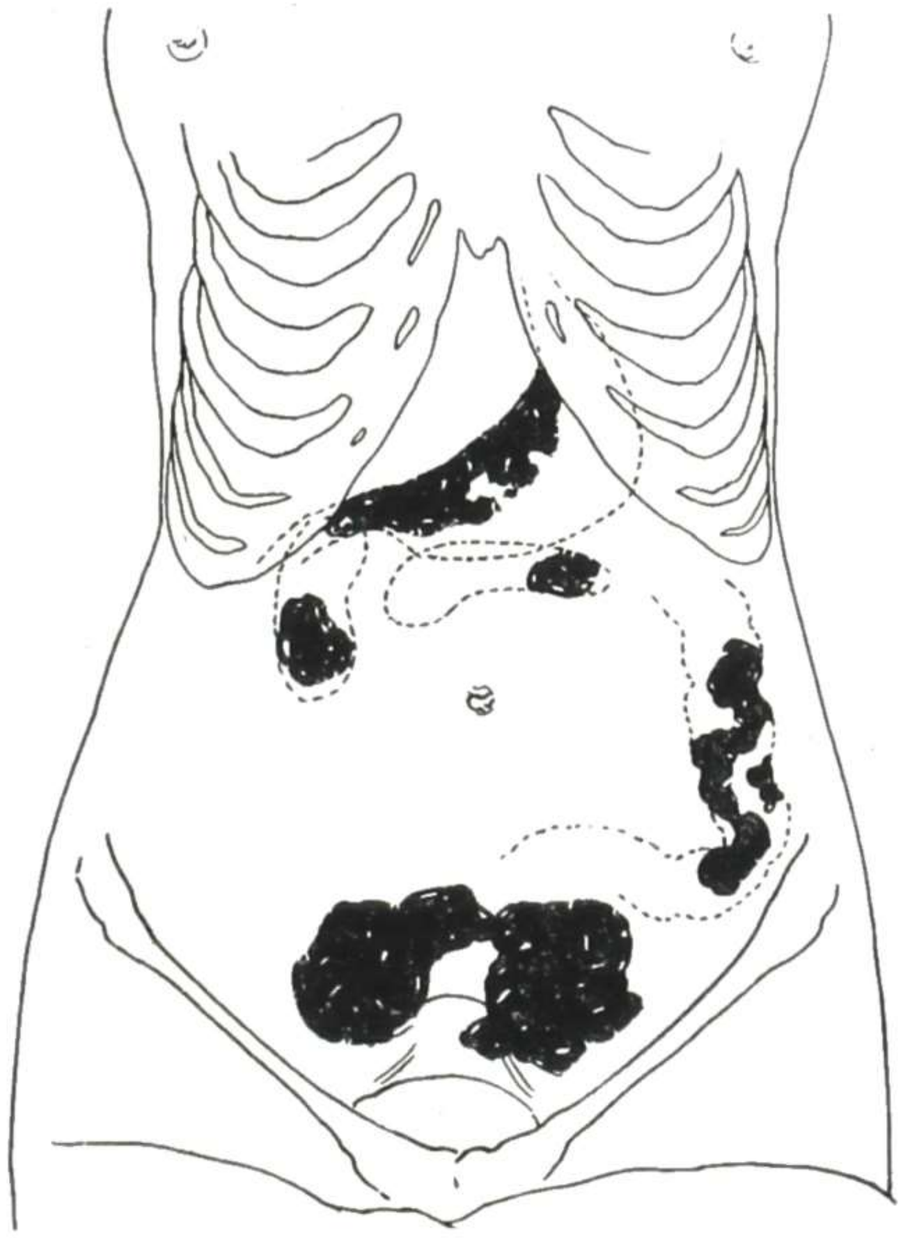


Fig. 885.—Krukenberg tumor, indicating the primary growth (in the stomach) and the distribution of the secondary growth in this case (both ovaries, right kidney, pancreas, and sigmoid flexure of the colon).

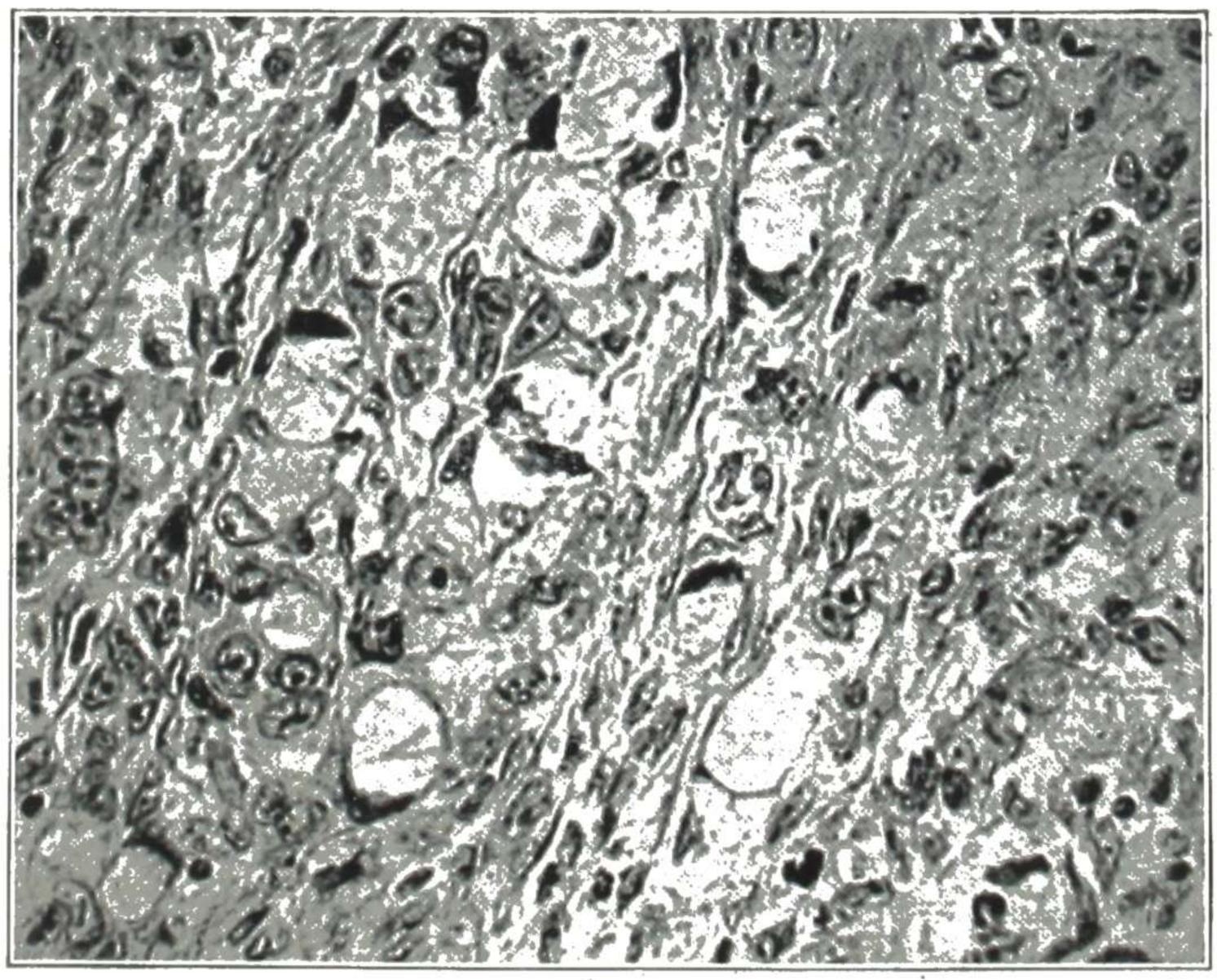


Fig. 886.—Krukenberg tumor of ovary. High power. The characteristic "sickle" or "signet ring" cells are well shown. Gyn. Lab.

The microscopic examination of the Krukenberg tumor shows an edematous connective tissue of spindle cells, of various sizes, shapes, and staining qualities, interspersed with areas of necrosis and myxomatous degeneration.

The cells which are characteristic of this tumor, however, are the large mucus-producing epithelial cells. These cells may be scattered through the connective tissue stroma or they may form alveoli. In the cells that are filled with the mucin the nucleus is pressed against the cell wall forming a crescent (Fig. 886). The names of "seal ring," "signet ring," or "sickle" cells have been applied to these cells, and their presence aids in the diagnosis of the Krukenberg type of tumor.

The other types of metastatic tumors reproduce cells similar to those of the primary carcinoma, as do also the growths reaching the ovary by direct extension.

There are four methods of spread commonly given to explain ovarian metastases: (1) lymphatic; (2) peritoneal sedimentation; (3) hematogenous; (4) direct extension; in any given case several of these methods may be present. In the Krukenberg tumors the fact that they usually maintain the contour of the normal ovary means that the carcinoma cells probably enter the ovary via the lymphatics through the hilum of the ovary. As evidence of this, Stone has reported finding the malignant cells in the retroperitoneal lymphatics in some Krukenberg tumors. The second method undoubtedly occurs in many of the cases.

In an excellent review of Krukenberg tumors of the ovary, Berens states that up to the time of his report (1951) there were 165 cases reported. He emphasizes the point that when this tumor is found in the pelvis, an intensive search must always be made for the site of the primary growth. With carcinomas of the intestinal tract the ovaries should be checked for metastases. Karsh found that the ovary containing the metastases was not enlarged in half of his cases, and hence gross inspection may be misleading. Copland and Colvin found bilateral Krukenberg tumors measuring 3 mm. in diameter; hence, even in cases where an ovary is sectioned at operation and examined, it is possible to miss a small tumor. This point is of great practical importance and justifies the stand taken by some that when one ovary is involved in primary carcinoma, the opposite ovary should be removed, though this dictum does not hold in all types of ovarian malignancies.

Sarcoma.—Sarcoma of the ovary may be of spindle-cell or round-cell variety and may be primary or secondary.

PRIMARY.—Between 2 and 5 per cent of ovarian growths are primary sarcomas. One has been reported by Doran in a seven months' fetus, and this is the one type of tumor which is more common in young people. Pfannenstiel states that 40 per cent of the patients are under twenty-five years of age and Hubert collected 200 cases in children. Frank states that in his series they were most frequent between the ages of eighteen and twenty-five years. Bloody ascites is almost always present.

These malignant tumors are usually secondary to a fibroma of the ovary.

The gross appearance and the consistency of these tumors depend upon the degree of maturity of the constituent cells and on the amount of fibrous tissue present. The soft friable tumors are the round-cell tumors while the spindle-cell variety is firmer and whiter in color. These tumors are usually bilateral and are shaped like a large kidney, due to the fact that the hilus

remains retracted while the rest of the ovary enlarges. Tumors of the round-cell type are so friable that they frequently fall apart when being removed at operation. The surface is usually irregular but fairly smooth, and there are necrotic areas present. On cut surface, one sees cystic cavities from necrosis or hemorrhage.

Frank divides the microscopic types into those in which unripe cells predominate and those in which the ripe cells make up the larger part of the tumor. The unripe types approach most nearly the embryonal types, and these include the round cell, the polymorphous and giant cell, and the myxosarcomas. The spindle cell, myosarcoma, chondrosarcoma, and osteosarcoma are made up of well-differentiated cell types. There is usually a mixture of these various types of cells in different parts of the tumor. In 100 cases of ovarian sarcoma, reported by Wolff, 44 per cent were spindle cell, 38 per cent round cell, 5 per cent mixed, and the remaining 13 per cent were osteo-, myxo-, and melanosarcoma (secondary).

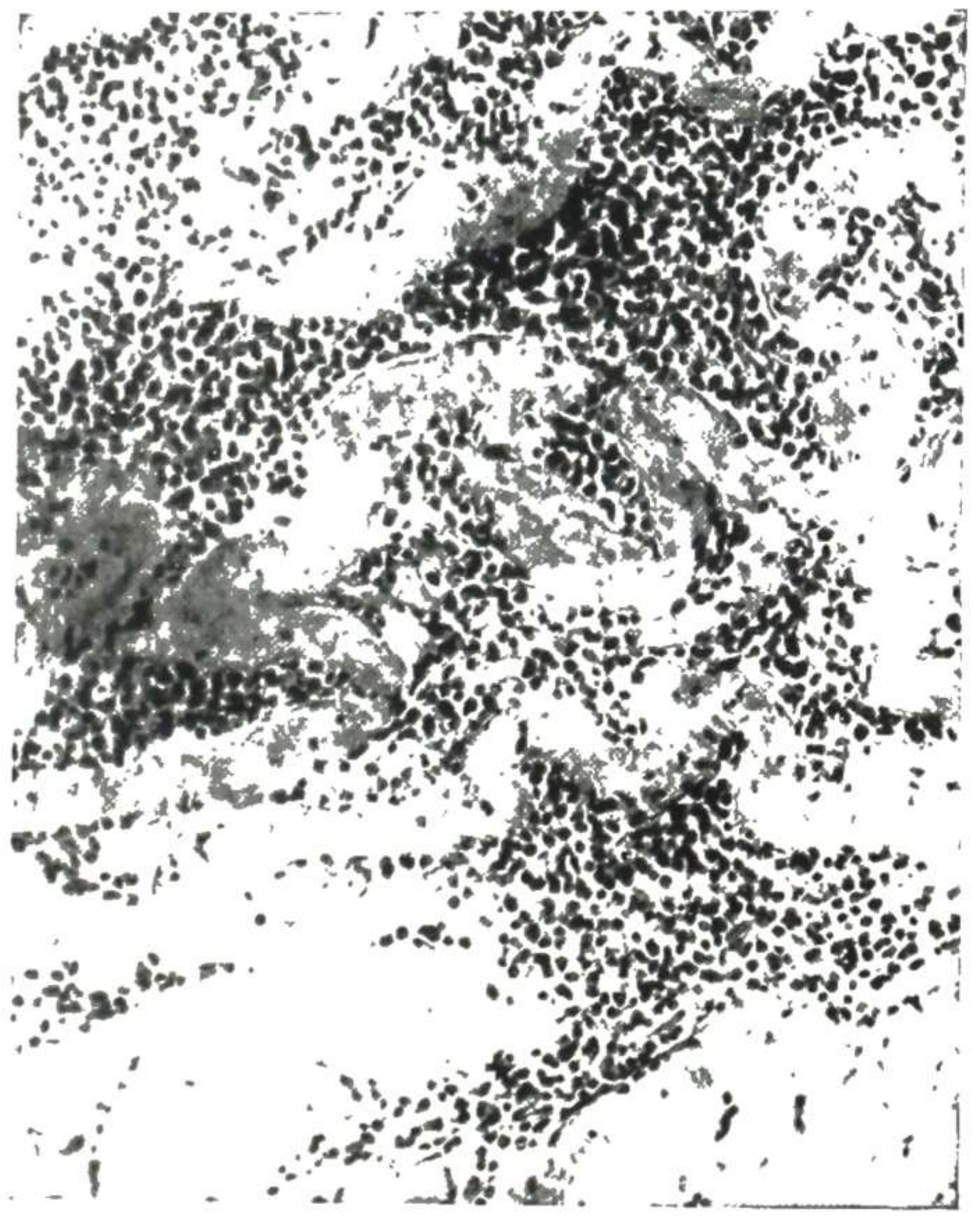


Fig. 887.

Fig. 888.

Fig. 887.—Sarcoma of the ovary secondary to a sarcoma, originating in a uterine myoma. The sarcomatous infiltration has involved old remnants of a corpus luteum. Gyn. Lab.

Fig. 888.—Mitotic figure in sarcoma cell. (From Caylor and Masson: Am. J. Obst. & Gynec.)

The spindle-cell tumors microscopically show a less differentiated fibrillar structure than do the benign fibromas. The cells are more ovoid, and the nuclei stain irregularly. Mitotic figures are frequently seen. Multinucleated cells are not uncommonly found. Areas of necrosis are common.

The round cell type may occur as either small round cells or large round cells. Occasionally they assume an alveolar arrangement. Necrosis and hemorrhage are very common in these rapidly growing tumors. The small cells somewhat resemble lymph cells.

Durfee, Clark, and Peers reported a primary lymphosarcoma of the ovary.

The polymorphous cell or mixed cell variety is characterized by the marked variation in the size and shape of the cells and by the frequent occurrence of giant cells. In the myxosarcomas the so-called star cells are present, containing flagella-like processes.

SECONDARY.—The melanosarcomas are usually secondary, though they may arise from a melanoma from skin in a dermoid cyst. These contain melanin and have the same characteristics as a melanosarcoma elsewhere. Other secondary sarcomas present the charcteristics of the growths from which they come. Fig. 887 shows a sarcoma of the ovary secondary to a sarcoma arising in a uterine myoma. A rapidly growing sarcoma furnishes good examples of mitosis (Fig. 888).

Teratomas

Dermoid cysts have been described under Benign Tumors, and in rare cases carcinoma may develop in the squamous epithelium present in a dermoid.

In certain of the tumors arising from undifferentiated somatic cells there is not so much development toward mature structures as in the dermoid cysts, but the growth is more solid and has more embryonic tissue. It is to such a tumor that the term "teratoma" is applied.

The cells being less developed and their activities more erratic than in the dermoid, there is a greater tendency to malignancy. There are usually small areas of partly mature tissues, such as bone, cartilage, hair, etc. There may be small cavities. Areas of hemorrhage are not uncommon. If the growth contains a considerable amount of thyroid tissue, it is designated "ovarian struma."

Teratomas of the ovary are rare in the first two decades, though at least five have been reported in the first seven years of life. The youngest patient was twenty months of age and was reported by Garrett. According to Lisa et al., they comprise the most common ovarian tumor of the premenstrual years.

Sarcomatous change is more common than carcinomatous change, and the tumors tend to metastasize early. Radical therapy followed by x-ray is the treatment of choice, but the prognosis is always poor and few patients live more than a year after the onset of symptoms.

Diagnosis and Treatment of Ovarian Malignancy

Owing to the rarity of solid tumors of the ovary and the absence of distinctive symptoms, the **diagnosis** is usually made only after the abdomen is open. In the case of a firm mass presenting the symptoms and signs already described for a small ovarian tumor (except fluctuation) a probable diagnosis of solid tumor of the ovary may be made.

If there is ascites, the fluid from tapping should be centrifuged and the residue fixed, cut and stained for microscopic examination. It may show cancer cells and even a special type of cancer cell, thus permitting a very definite diagnosis.

The great majority of ovarian carcinomas occur in the ages between forty-five and sixty-five. In Randall's series of 218 ovarian tumors first diagnosed in women over fifty, 60 per cent were malignant neoplasms. Unfortunately,

the onset of ovarian malignancy is not, as a rule, accompanied by any outstanding diagnostic symptoms, and symptomless progress to incurability is the rule.

The **treatment** for every solid tumor of the ovary is prompt removal by operation. Prompt removal is important because of the frequency of malignant development. If the growth is already inoperable, then deep x-ray treatment is advisable and may give considerable relief.

In regard to ovarian malignancy brought to light at operation, several important questions arise, including the following: What types of operation should be employed in the different conditions found? Is irradiation treatment of definite value? What is the prognosis (patient's life expectancy) in ovarian malignancy? Help on the problems in this connection has been given by several writers in reporting series of cases.

Types of Treatment.—In an interesting paper on ovarian tumors, H. C. Taylor, Jr., presents the following helpful suggestions as to the handling of patients with carcinoma of the ovary:

> At three stages in the treatment of a case of ovarian carcinoma, decisions must be reached as to the course to be followed. (1) When the patient is first seen, whether an operation is to be performed; (2) when the abdomen is open, how extensive an operation is to be undertaken; and (3) after the operation is complete, whether x-ray is to be given.
>
> 1. OPERABILITY.—In many cases of ovarian cancer a definite diagnosis is not arrived at till the abdomen has been opened, so that one must recognize laparotomy as usually the first procedure. This should not, however, be the invariable approach because the surgical exploration of advanced cases is accompanied by a high mortality rate.
>
> Attempt should be made, therefore, to eliminate two categories from the group to be operated upon. (1) In all cases of apparently malignant ovarian tumor the possibility of the growth being secondary in the ovary must be thought of. X-rays of the gastrointestinal tract should be made, and operation given up when any other lesion besides the ovarian is discovered. (2) Certain very advanced cases with ascites, cachexia, large pelvic tumors, and upper abdominal masses, are readily recognizable as inoperable, and these cases should have their treatment limited to external radiation.
>
> 2. THE EXTENT OF THE OPERATION.—When at the time of operation the growth is found apparently confined to one or both ovaries, there is a general agreement that a complete hysterectomy should be performed, with the removal of both appendages. The preservation of an apparently uninvolved ovary is rarely to be considered, for as Norris has shown, in 17.5 per cent of such cases the grossly normal ovary is later found in the laboratory to contain foci of cancer cells.
>
> The extension of the operation to the removal of single metastatic lesions from organs outside of the pelvis is a dubious procedure. Only in the case of an isolated metastasis in the omentum whose removal does not increase the severity of the operation to an appreciable degree, is such a procedure justifiable, and one patient so treated at the Roosevelt Hospital was in good health when last seen four years after her operation. Resection of part of the bladder or intestine was carried out in a few of the earlier cases but proved both futile and dangerous.
>
> When cancer is found widely disseminated on the pelvic or general peritoneum, a question arises as to whether any surgical procedure should be carried out. Such a condition was found in approximately half of the Roosevelt primary cases. It has been our practice under such conditions to remove as much of the tumor tissue as possible, partly because of the temporary palliation, partly because of the improved psychologic effect on the patient resulting from the disappearance of visible evidence of tumor, partly because of the possibility that x-ray may be more efficient when directed at smaller masses of tissue.
>
> 3. POSTOPERATIVE RADIATION.—In view of the bad results obtained by the simple surgical treatment of ovarian cancer, postoperative radiation therapy should be given in practically all cases. This opinion is held as a result of favorable reports from outside sources although

our own series shows no cures and no increase in the average duration of life attributable to x-ray or radium therapy. The relative failure in this series is very likely dependent upon inadequate dosage.

This corresponds with the experience here (Mallinckrodt Institute of Radiology, furnishing x-ray service to the Washington University Group of Hospitals), both as to our personal experience in having patients definitely benefited by the x-ray treatment and as to the general experience of the Institute.

When the diagnosis of malignancy is fairly certain and the patient is in or past the climacteric, it is advisable to give the radiation (deep x-ray therapy) before operation. This preliminary radiation checks the carcinoma activity temporarily and lessens the danger of spreading active malignant cells in the operative area. It is well to wait some weeks after the radiation before doing the operation—long enough to obtain the desired cancer-cell devitalization from the x-ray and for the patient to make good recovery from the digestive disturbance of this deep therapy.

When the diagnosis is doubtful and there is a fair chance of nonmalignancy, and especially in younger patients, operation at once is advisable, the question of radiation treatment being postponed till the diagnosis is settled at operation or by subsequent microscopic examination.

In inoperable cases or those in which most of the tumor is irremovable, it is sometimes wise to leave the uterus so that intrauterine radium may be used as a central source of radiation.

There are two excellent reviews on the value of x-ray in ovarian carcinoma, one in the British literature by Margaret Tod and another from Iowa Medical School by Kerr and Elkins.

In regard to prognosis, Allan and Hertig point out that long periods of observation are necessary to be sure of a cure, and recurrences have appeared as long as twenty years following operation. The results from surgery alone in their series at the end of five-, ten-, and fifteen-year intervals were 29 per cent, 20 per cent, and 14 per cent, respectively. The results of surgery with additional x-ray for the same intervals were 46 per cent, 20 per cent, and 14 per cent. These statistics are fairly typical of results in other series of cases of primary ovarian cancer, and an even more pessimistic recent report was given by Randall and Hall who had only 6.7 per cent five-year survivals in 89 primary carcinomas of the ovary operated upon during the years 1941 to 1946 inclusive.

The importance of clinical classification of the extent of the growth as well as the histologic grading of the tumor on prognosis has been emphasized by Taylor, Montgomery, and, more recently, by Cashman and Helsel. In general, localized tumors of low-grade malignancy give a much better prognosis than do disseminated tumors of high-grade malignancy.

Prevention of Ovarian Carcinoma

Ovarian cancer is the fourth most frequent cause of death from neoplasms in women over forty years of age. The clinical course of this disease is insidious and by the time well-defined symptoms bring the patient to the phy-

sician she is frequently in the hopeless stage. Shands and Clark, in 1,067 proved cases of ovarian cancer, found that 73.4 per cent occurred in women past forty years of age.

The excellent program of acquainting the public and the general practitioner with the importance of a pelvic examination has resulted in some improvement in early diagnosis of these tumors. We know that ovarian tumors in women past forty should be removed promptly. The difficulty is that in the general population a large percentage of women still do not come for examination until adverse symptoms compel them to seek advice, and, as mentioned, this procrastination usually leads to despair and death.

In spite of frequent repetition of statements in the many articles on this subject as to the apparent hopelessness of most cases by the time the malignancy is discovered and the poor results with all methods of treatment, few authors give any constructive advice as to how this situation can be improved.

In an article on "Silent Ovarian Carcinoma," in 1942, H. S. Crossen drew attention to the fact that in a large proportion of these cases the patient had no symptoms indicating the serious lesion present until she was in the inoperable stage. Taylor found that in over half of the cases at Roosevelt Hospital the carcinoma was widely disseminated in the pelvis or general peritoneum when first seen.

In his article H. S. Crossen advised as a preventive measure the removal of ovaries in cases in which the abdomen had to be opened for some pelvic procedure, in women over forty-three years of age. This age limit was not rigid (some authors prefer forty-five years) and in selected cases if the patient prefers to keep one ovary after explanation of our advice, we acquiesce to her desire in the matter but emphasize the necessity for six-month checkup examinations. Montgomery relates a case of his in which a far-advanced malignant tumor of the ovary was found within a year after hysterectomy, at which time the ovaries were examined and thought to be normal. Others have reported malignant tumors progressing to inoperability in the period between the sixth month checkup examinations. The difficulty of detecting an early ovarian enlargement or tumor in obese women or those who cannot seem to relax is evident to anyone who has done a large number of pelvic examinations.

The prophylactic removal of ovaries at operation for other pelvic lesions in women at or near the menopause, as suggested by H. S. Crossen, has been criticized by numerous authors in recent years because of statistical data which indicate that only three women per 1,000 at the age of forty-five will develop ovarian malignancy, even if they live another forty years.

Speert has shown that of 260 patients with ovarian cancer, 67, or 26 per cent, had previous surgery of one form or another. In forty-five, or 52 per cent; the patient was forty years or older at the time of her initial surgery. More striking is the fact that 25, or 29 per cent of these, were operated upon under two years prior to the discovery of carcinoma of the ovary. Montgomery's figures show 21 per cent incidence of previous relevant operations in a study of ovarian carcinoma in 99 patients.

Guerriero et al. found that, in a series of 75 cases, 36, or 47.4 per cent, had had a previous surgical experience. Astoundingly, 25 of these were beyond

forty years of age, and, of these, 17 had been operated upon less than two years previously. They conclude: "In view of the above findings, serious consideration should be given Crossen's suggestions. This is a decision which may well be as important a prophylactic therapy for carcinoma of the ovary as was the adoption of total hysterectomy in carcinoma of the cervix."

Thorp, during a five-year period, collected 276 pelvic tumors, most of which were ovarian, removed from women who had previously had a hysterectomy. Ten of these growths were malignant and five of these women were already dead as a result of the ovarian malignancy. The author stresses that the widely accepted conservation of the ovaries in women undergoing hysterectomy requires re-evaluation. He feels that since ovarian atrophy or cystic changes ensue following hysterectomy it is best to combine hysterectomy with a bilateral oophorectomy, and questions that the patient's future well-being can be defined in terms of freedom from hot flushes. Authors inconsistently observe that ovarian atrophy frequently or even invariably follows hysterectomy, while at the same time they also advise against removal of the gonads. This "touch-them-not" tradition stems largely from the false premise that women must invariably suffer distress with the menopause. Artificial menopause resulting from surgery and/or x-rays need be no more distressing than the symptoms of physiological decline in ovarian activity. There is no valid reason for leaving unpredictable organs like the ovaries, which later in life might produce serious disease.

In view of the above statistics, it seems to me that one should weigh the risk of losing even three women out of a thousand, against the hypothetical harm involved in removing ovaries when the abdomen is open, at a time in life when the ovaries either are, or soon will be, involuting. In order to determine what effect removal of the ovaries had on sexual reactions, Huffman questioned 68 women between the ages of twenty-six and forty-three who had had complete hysterectomy and bilateral salpingo-oophorectomy at least a year before, and, in 34 cases, three years previously. Of these 61 stated that the sexual relations were the same after as before operation, two who had been apprehensive concerning the loss of sex desire had a loss of libido, five lost their normal urge as a result of dyspareunia but were relieved by correction of this difficulty. Seventy-seven of 86 women between the ages of thirty-one and forty-nine who had had a complete hysterectomy with preservation of the ovaries experienced no change in sex response. In the first group 58 of the patients were receiving estrogens and, in the second group, 11 were receiving estrogens for menopause symptoms. Huffman concludes from this survey that the physician can assure the patient who is to have hysterectomy and/or bilateral oophorectomy that her sexual life after operation will probably follow the same pattern as before. Another important fact which seems to be frequently overlooked is that we now have adequate oral replacement therapy with which to tide the patient over the period necessary for adjustment to the complete cessation of ovarian function. As is well known, only about 15 per cent of women require therapy for the menopause. Hence our conclusions in this matter will remain unchanged until some better method of prevention is forthcoming.

MALIGNANT TUMORS ARISING FROM OVARIAN MESENCHYMA

WITH ENDOCRINE INFLUENCE

In the past few years interest has been aroused in the study of a group of tumors arising from early oophorogenic structures in the sex gland area. There are two general groups: (1) those which function and produce hormones and in this way determine certain secondary sexual changes, for example, granulosa-cell tumors and arrhenoblastomas, and (2) those which exert no endocrine effect, such as dysgerminomas. We are indebted to Robert Meyer of Berlin for his clear-cut classification of these confusing pathologic pictures. The endocrine group will be considered here, and the second group under the next heading.

Recently Schiller has differed in his explanation as to the origin of these tumors. As Schiller points out, the ovarian mesenchyma is a type of tissue found nowhere else in the body. It forms the unspecified stroma of the ovary, the part of the germinal cord which gives origin to the granulosa, and lastly the theca, which originates from the surrounding connective tissue and which, as explained in Chapter 1, is evoked by the granulosa as an organizer. According to Schiller, "remnants" of the cells which form the germinal cord; then later the granulosa of the follicles, when left behind from fetal times may preserve their prospective potencies. Also, if they do not find contact with an egg cell at the time of formation of the germinal cord, these cells, if awakened years later by an unspecific stimulus, may develop their prospective potencies; but since the organizing egg is missing the neoplastic growth shows poor organization. It is from this tissue that the granulosa-cell tumors are formed. If, on mitotic division, cells destined to become granulosa cells lose their female character by losing their two X chromosomes, they change from cells destined to produce the auxiliary tissue of the follicles (granulosa cells) into cells which play the corresponding auxiliary role of the testes. They thus give rise to a tumor which duplicates the fetal testicles minus the spermatogonia but contains the male hormone-producing Leydig cells (arrhenoblastoma).

The other type of tumor in which there is an error in the sex chromosomes is the dysgerminoma. In this type of tumor the cells of the mesenchymal core develop into sexually different cells and are neuter, having neither the male nor the female direction of development.

Granulosa-Cell Tumors, Thecomas, Luteomas

Granulosa-Cell Tumors.—These tumors, according to Meyer, arise from dormant undifferentiated embryonic tissue situated in the medullary portion of the ovary. Such tissue can be found in the fetus and in infants and even into adult life, and occasionally in the ovaries of women far past the menopause. These cells persist without differentiation into late life. Under conditions still unknown they may at any age produce granulosa-cell tumors. Schiller's ideas on the histogenesis of these tumors has been given above. Butterworth deduced from experimental production of granulosa-cell tumors in senile mice by irradiation that these tumors developed from the normal follicles after degeneration of the ova. Against this theory are at least five re-

ports on the extraovarian retroperitoneal occurrence of granulosa-cell tumors, the most recent being by Rottino and Crown. The detached location of these tumors support Schiller's idea of mesenchymal origin. Transplantation studies may prove valuable in studying histogenesis, morphology, and physiology of ovarian tumors. Li recently transplanted a malignant granulosa-cell tumor into the spleen of a castrated male mouse and it not only continued to grow but metastasized to the liver. Silberberg et al. studied the effect of anterior hypophyseal transplants on intrasplenic ovarian grafts in mice. They found that the intrasplenic tumors appeared early, and that there were more luteomas than granulosa-cell tumors. The cells of these tumors produce estrogen and the clinical changes caused depend upon the age of the individual. In young children there is a development of the secondary sex characteristics, enlargement of the uterus, and uterine bleeding; during the childbearing period there are frequently menstrual disturbances; in older women it may cause postmenopausal bleeding.

Fig. 889.

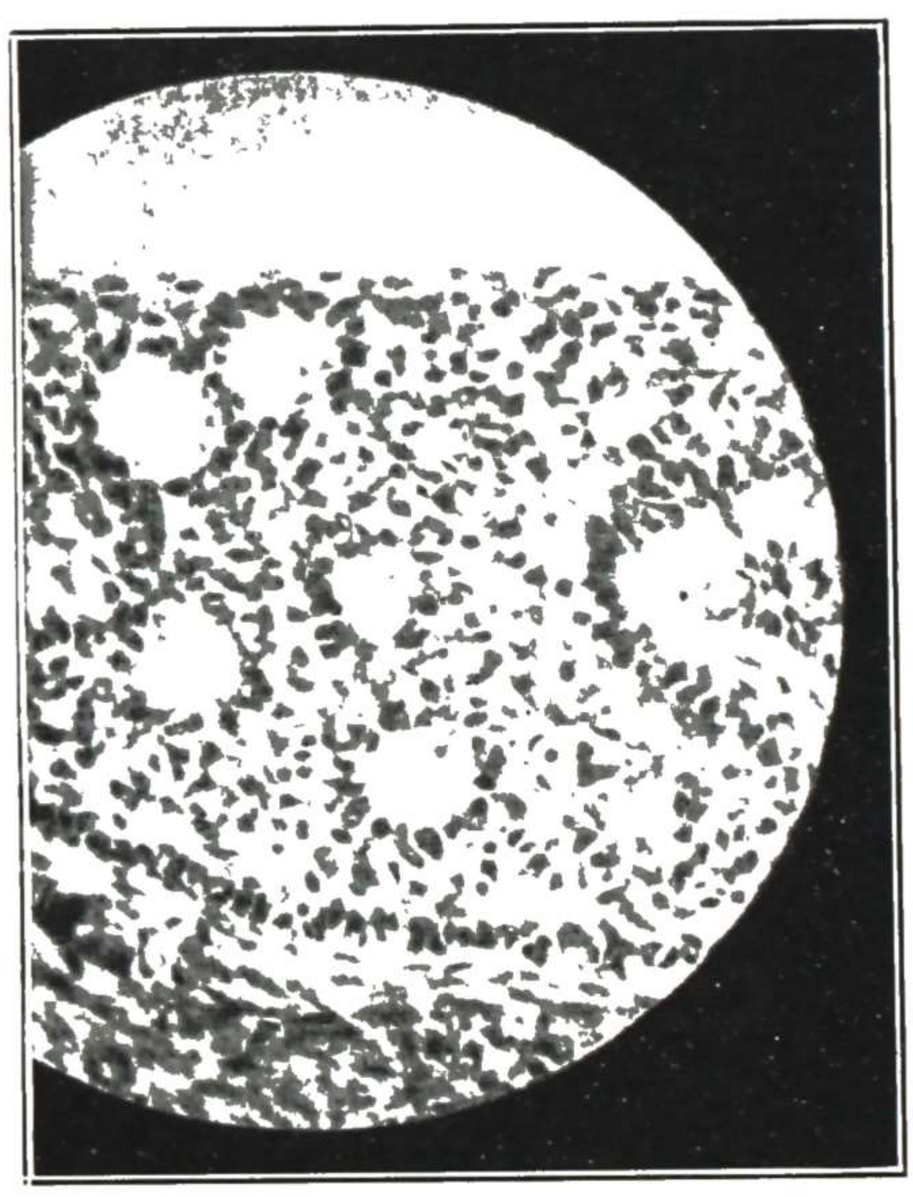


Fig. 890.

Figs. 889 and 890.—Small granulosa-cell tumors in the otherwise normal ovary of a woman, aged forty. Fig. 890, Higher magnification of a special area in Fig. 889, showing the resemblence to Call-Exnar bodies. (From Meyer: Am. J. Obst. & Gynec.)

Structural Pathology.—Meyer gives the following three histologic classifications according to the structure:

1. It may occur as a folliculoma, often associated with small cysts. The cells are arranged about a central liquefied area so that they resemble somewhat small primordial follicles (Figs. 889 and 890). The similarity to Call-Exner bodies found in rabbit ovaries is very striking. In the first few cases these were thought to be abnormal follicles, because the central cavity superficially resembled an ovum. Meyer stressed the fact that the cells around the small cystic cavities are arranged in a curious antipodal fashion, that is, the nuclei of the inner layer are placed close to the lumen while those of the outer layer are away from it, toward the periphery. Between these two layers there may be several layers of well-preserved cells, or only a thin zone of degenerated cytoplasm may remain. This so-called follicular type may contain small or large cavities (Figs. 891 and 892).

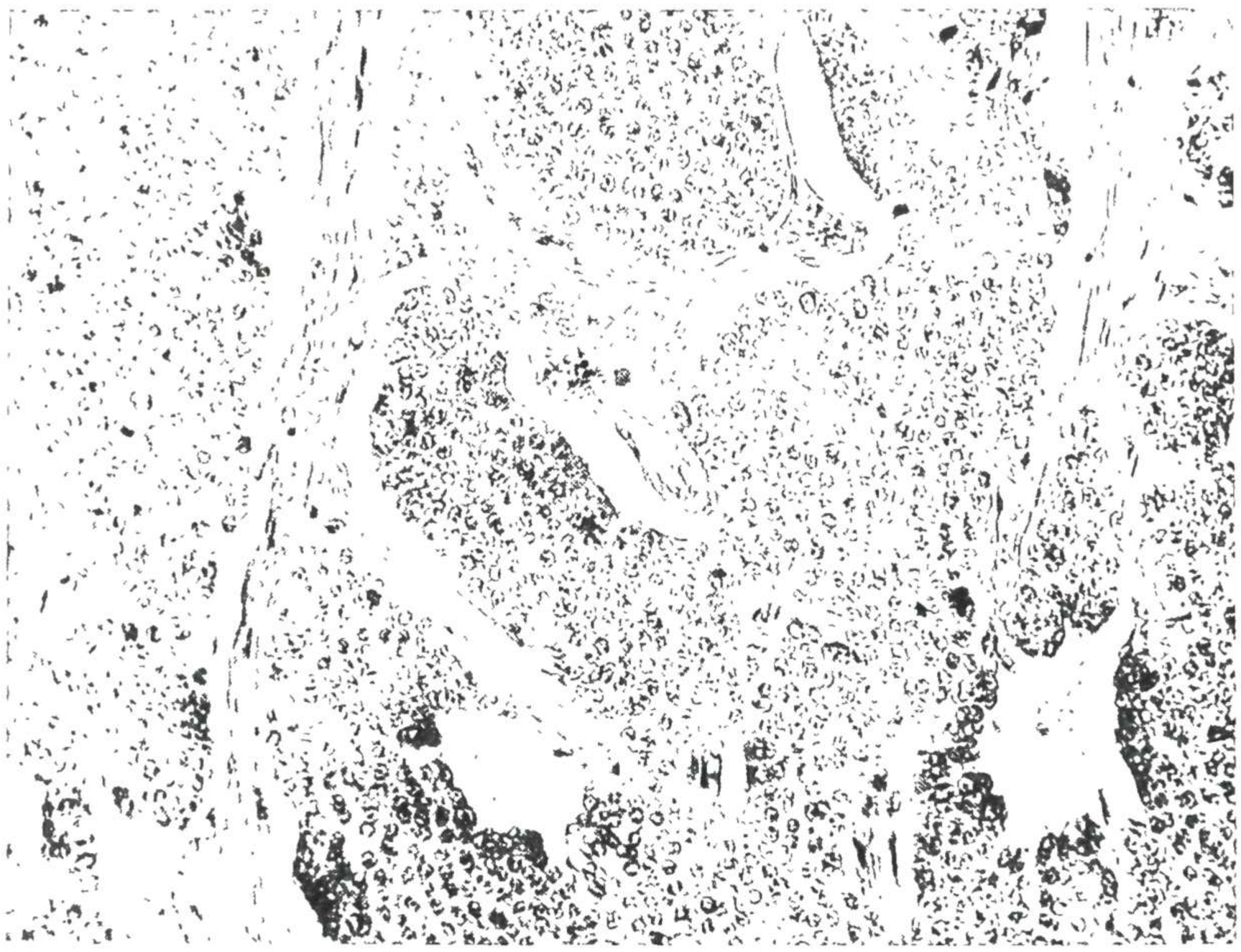


Fig. 891.—Parenchymatous masses of granulosa cells. Note the absence of Call-Exner bodies. (×400.) (From Haukohl: Am. J. Obst. & Gynec., April, 1949.)

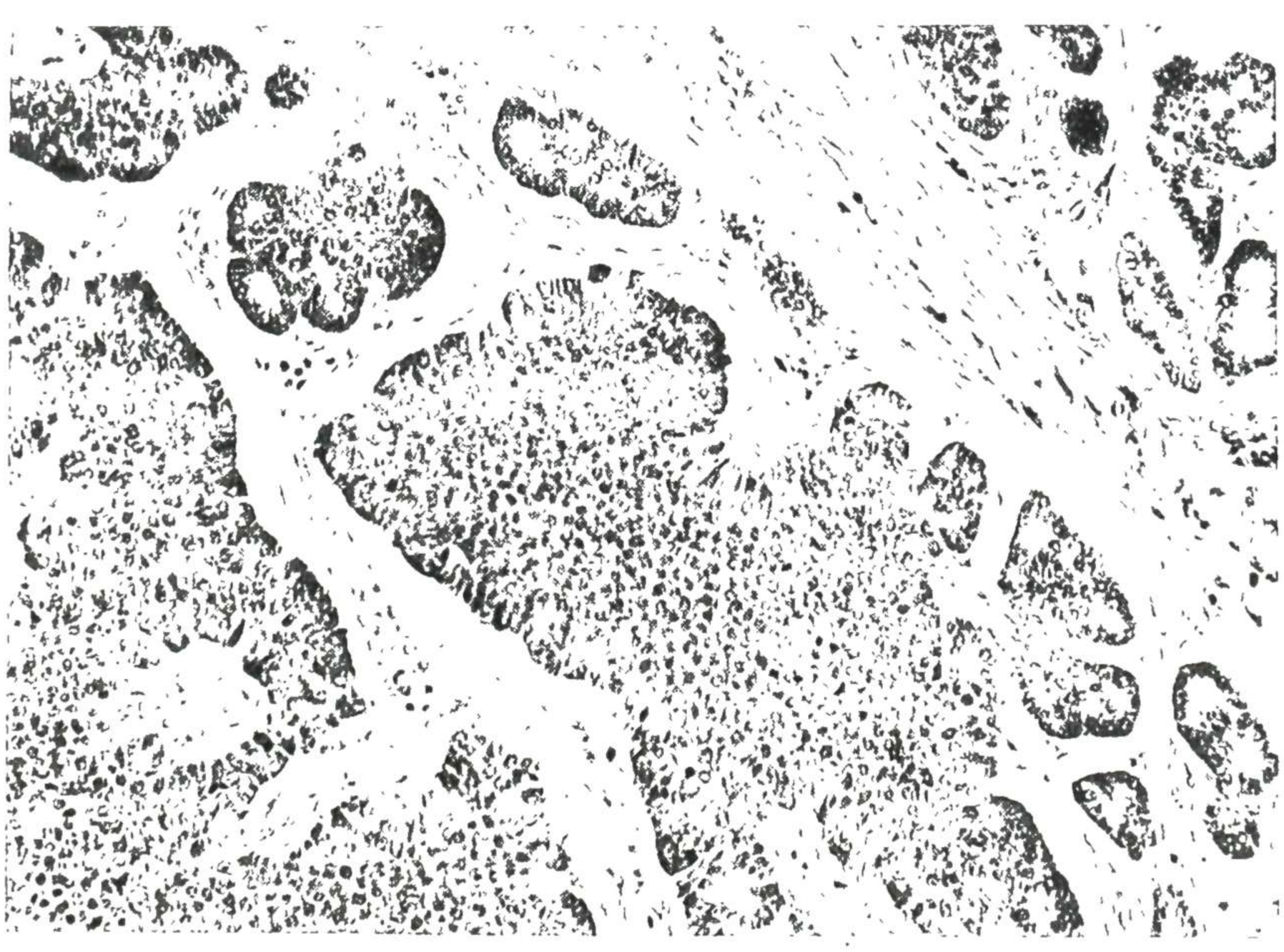


Fig. 892.—Masses of granulosa cells showing peripheral gland formation and glands in separate groups. (×400.) (From Haukohl: Am. J. Obst. & Gynec., April, 1949.)

2. The second and most common type is the cylindroid type, in which there are solid cords of cells or cylinders. Hyaline degeneration of the connective tissue stroma is commonly present. Many bizarre patterns are found, which have been compared by Novak to elaborate scrollwork or rippled water or the pattern of moiré silk.

3. Some cases show a diffuse structure which cannot be distinguished from sarcoma. All three varieties may be present in the same tumor.

In the gross these tumors have a friable or granular consistency and are usually gray but may have a yellowish tinge. They vary in size from a few millimeters in diameter to huge tumors filling the abdomen. An excellent example is shown in Fig. 893, taken from a case reported by Rowan, Schwartz, and Farinacci. Another is shown in Figs. 894 to 896 together with the microscopic findings and the patient.

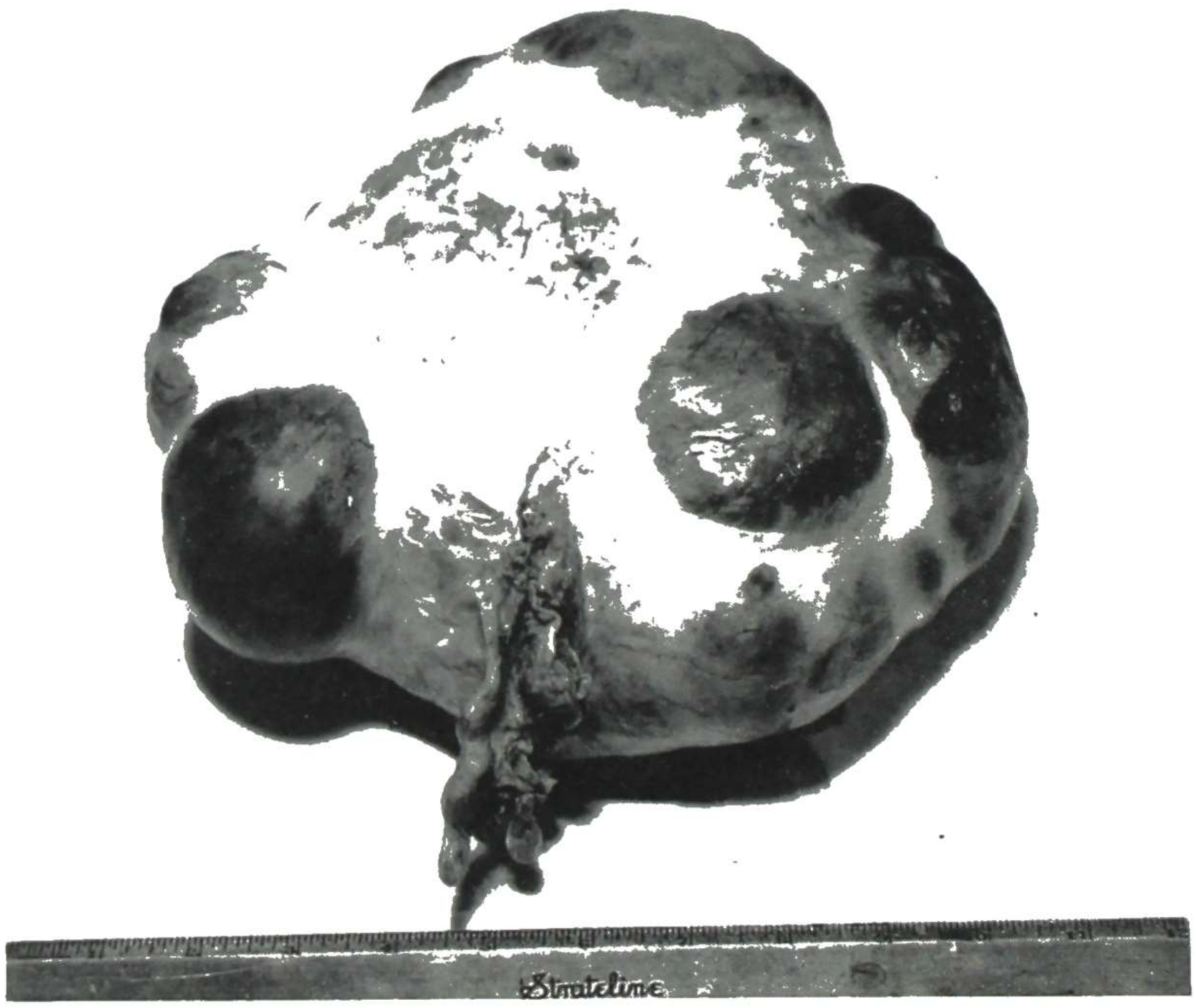


Fig. 893.—External view of granulosa-cell tumor with attached fallopian tube. (Courtesy Armed Forces Institute of Pathology.) (From Swartz and Farinacci: Am. J. Obst. & Gynec., June, 1951.)

Thecomas.—Before the report of Loeffler and Priesel in 1932 these tumors were classified as fibromas in which cystic or lipoid degeneration had occurred. The fact that true fibromas have a yellow color has been mentioned, and Novak and others have stated that the differentiation between this type of fibroma and a thecoma has to be made on a morphologic basis and that this is not always possible. McKay, Robinson, and Hertig, in a histochemical study of granulosa-cell tumors, thecomas, and fibromas of the ovary, concluded that one can differentiate active thecomas (functioning) from inactive thecomas and fibromas, but that differentiation between the latter two is not always possible. These workers reported a pure granulosa-cell tumor in which there was no evi-

dence of estrogen secretion, and they pointed out that this finding agreed with the histochemical studies of Dempsey and others that the theca cells and not the granulosa cells secrete estrogen (see Chapter 1). Other evidence for this conclusion is given by these authors, but there is not space here to discuss these interesting phases of the subject. Sternberg and Gaskill noted a high incidence of ovarian stroma hyperplasia in fibromas and in thecomas.

Microscopically these tumors show a mixture of both granulosa and thecal elements, and this helps in differentiation from fibroma.

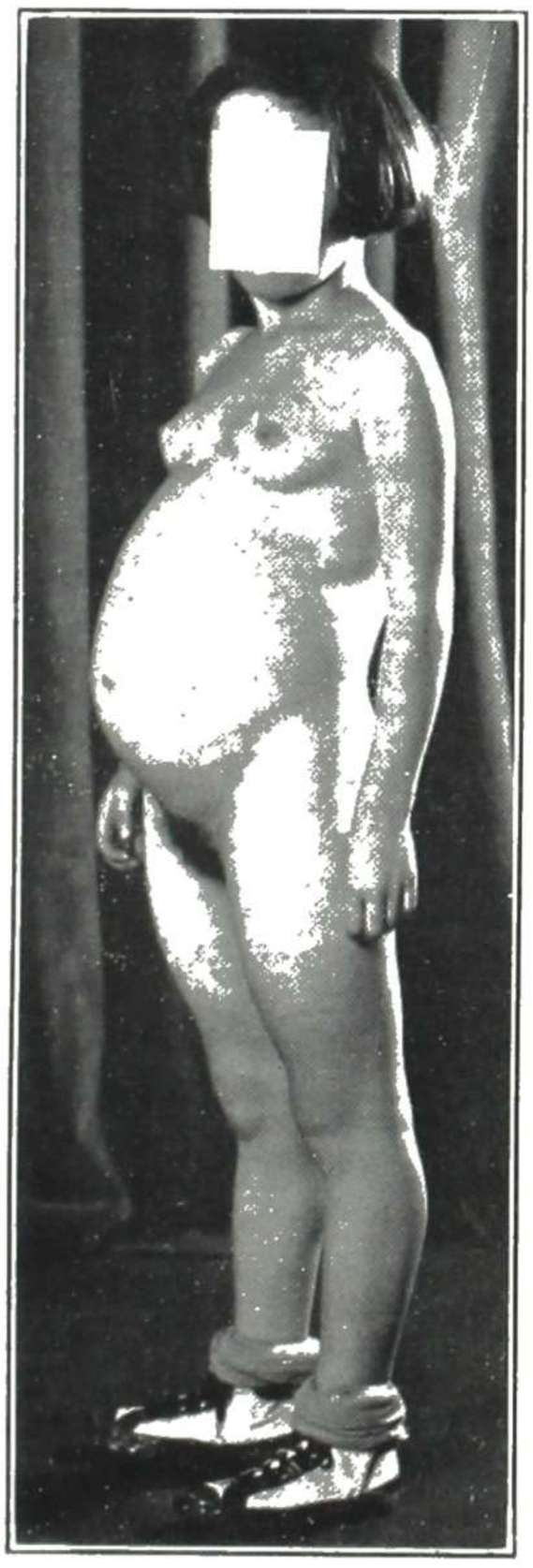


Fig. 894.

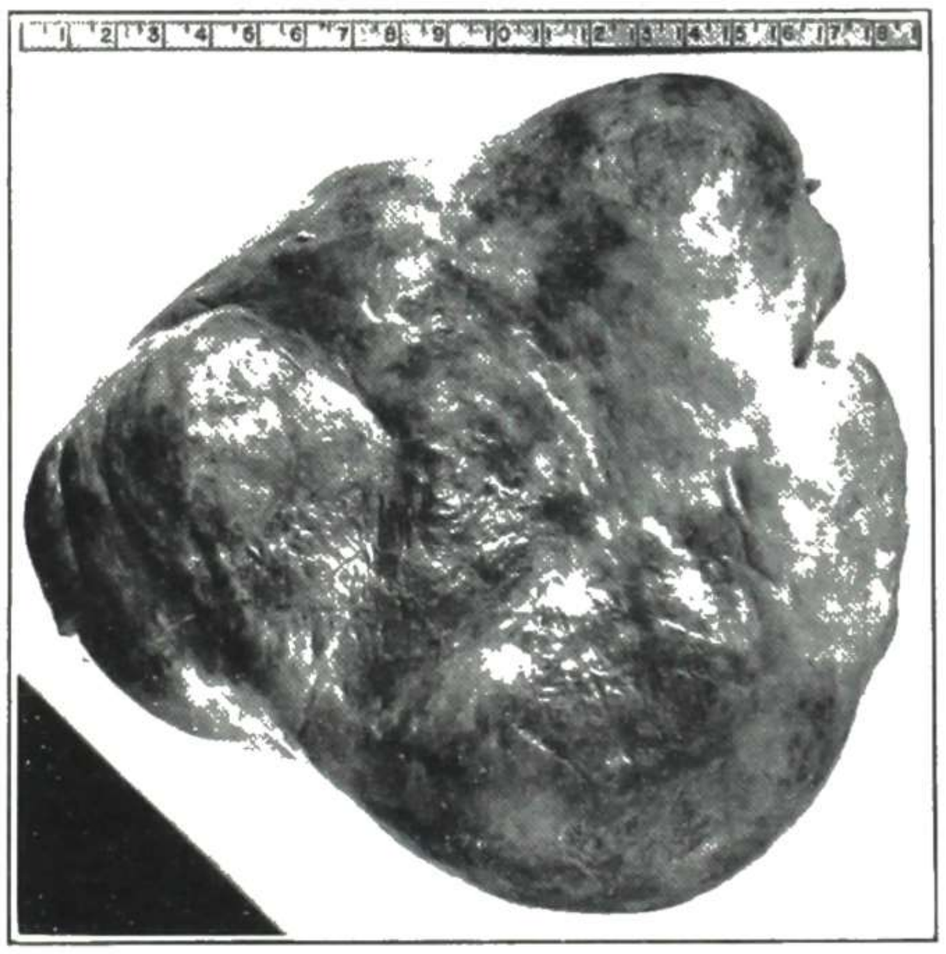


Fig. 895.

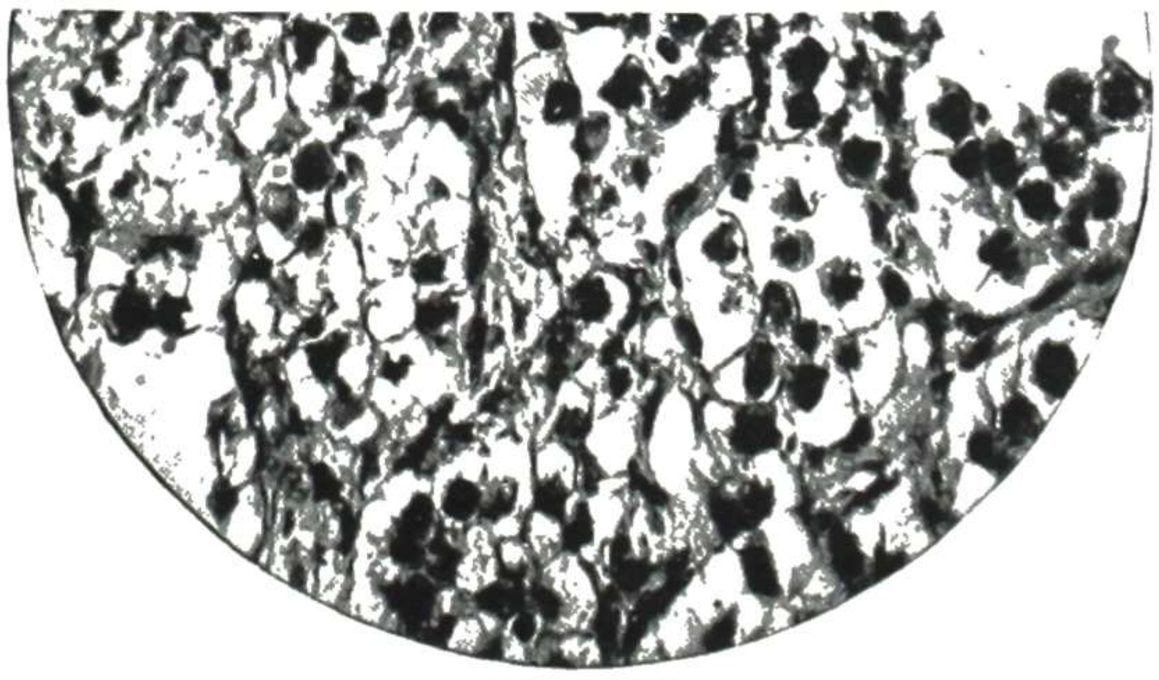


Fig. 896.

Fig. 894 to 896.—Patient, aged seven years, with a granulosa-cell tumor. Fig. 894, General view, showing the precocious sexual development, with a marked growth of pubic hair and hypertrophy of breasts. In this case there is also marked enlargement of the abdomen from the tumor. Menstruation began four months before the patient was brought for treatment. Fig. 895, The large tumor removed in this case. It involved the left ovary. After the operation, the precocious menstruation ceased and the patient was well for eighteen months, when she came again with a similar growth of the right ovary, which seemed normal at the first operation. The Aschheim-Zondek test was positive before each operation, and was negative within two weeks after each operation. Fig. 896, The microscopic structure of the first tumor. The structure of the second tumor was the same. (From Bland and Goldstein: Surg., Gynec., & Obst.)

Since the report by Loeffler and Priesel, close to a hundred cases of thecoma have been reported. The largest tumor, weighing 7,727 grams, was reported by Knight. These tumors comprise 3 to 5 per cent of solid ovarian tumors.

The tumor has never been found in young children; 35 per cent occur between puberty and the climacteric, and 65 per cent occur after the menopause.

The predominant hormone secretion in these cases is estrogen, though there are a few in which there is also a progesterone secretion associated with a progestational effect on the endometrium. About 65 per cent of the cases have an associated hyperplasia of the endometrium, and in patients over fifty years of age one-fourth had an associated cancer of the uterus, usually of the endometrium. A recent endometrial carcinoma case was reported by Sparling.

Five cases of malignant thecomas have been reported, the most recent one by Proctor et al. It is probable that the malignancy rate of these tumors will eventually be found to approximate that of granulosa-cell tumors.

Luteomas.—These tumors are considered by Novak to be merely luteinized granulosa-cell tumors. In some of these there is a progesterone effect on the endometrium, suggesting functionally active lutein cells; in others there is no effect on the endometrium; hence, these are designated as pseudolutein cells since they are not functionally active. The "folliculome lipidique" of Lecène falls into this category.

Fig. 897.—Appearance of patient with bilateral granulosa-cell tumors. Ages from left to right: Seven and one-half, sixteen, and thirty-three months. (From Zemke and Herrell: Am. J. Obst. & Gynec., April, 1941.)

Symptoms of Feminizing Ovarian Tumors.—As mentioned, the symptoms caused by these various types of mesenchymes depend on the age of the patient and the amount and type of the hormone secreted. Granulosa-cell tumors when they occur in children cause the child to mature and become an adult as far as her sexual development is concerned. The youngest case was a fourteen-week-old child reported by Zemke and Herrell. In this case (Fig. 897) bilateral tumors were removed by bilateral oophorectomy.

Menstruation may occur at two or three years of age, the breasts enlarge, and pubic and axillary hair appears; with the removal of the tumor these signs and symptoms regress, as shown in Park's case (Figs. 898 and 899). The fact that precocious puberty can occur at a very early age, with menstruation, in perfectly normal children was emphasized by Novak; Fig. 900 shows one of his patients who started menstruating at fifteen months and was still menstruating regularly at fifteen years of age. In this type of case pregnancy can occur; the earliest pregnancy reported was in a five-year eight-month old girl. Operative interference in children showing precocious development should be based upon the finding of pelvic tumors; in cases of doubt, re-examination

at frequent intervals will usually help to separate the tumor cases from the constitutional types. Ovulation never occurs (in young girls) with granulosa-cell tumors.

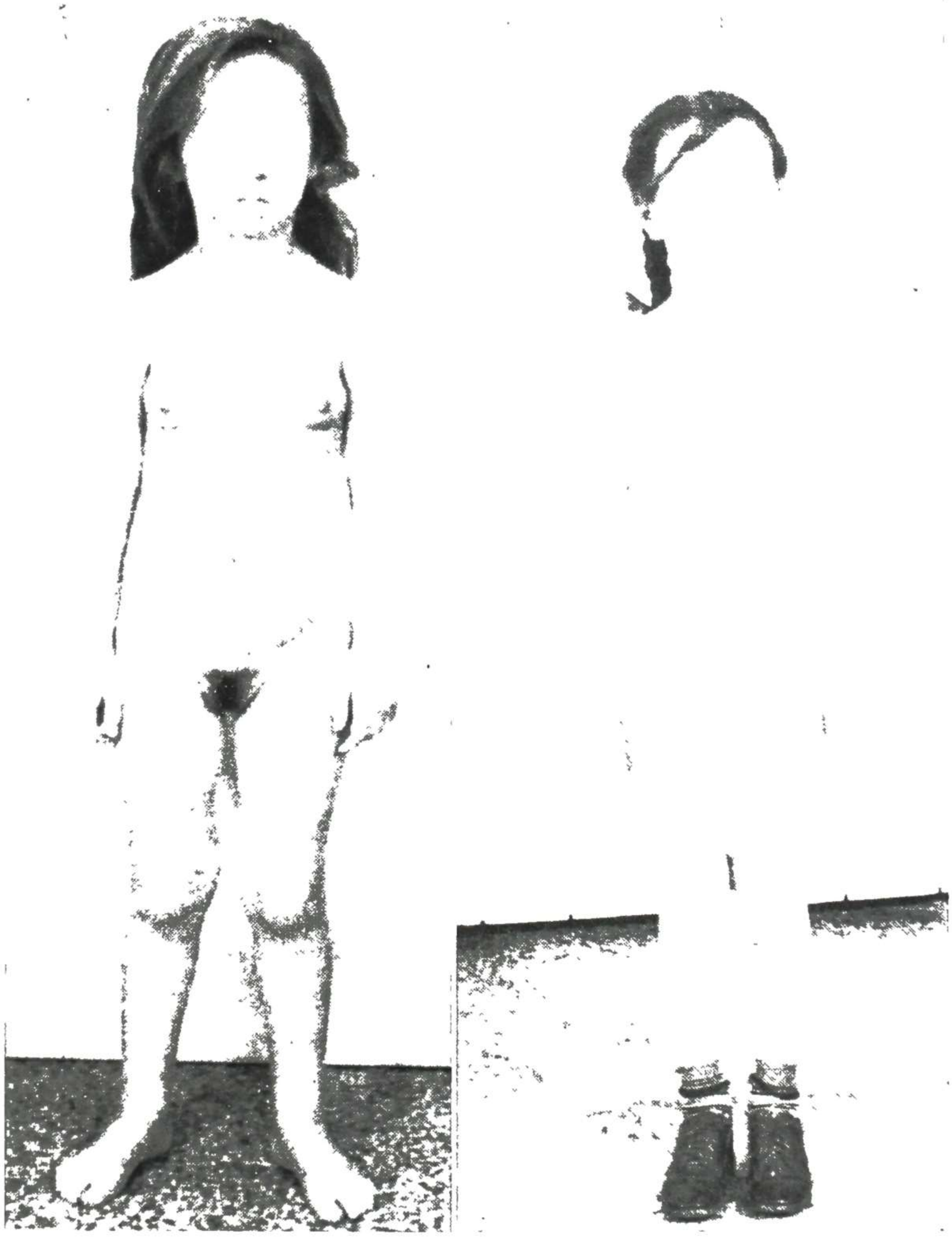


Fig. 898. Fig. 899.

Fig. 898.—Precocious secondary sex characteristics in a 5-year-old girl with a granulosa-cell tumor of the right ovary.

Fig. 899.—Recession of secondary sex characteristics fifteen months after removal of a granulosa-cell tumor of the right ovary.

(From Parks: Am. J. Obst. & Gynec., October, 1938.)

In the cases in which the tumor does not begin until adult life, when the person is already menstruating, the symptoms are frequently masked. There may be an increase in the amount of the menstrual flow, and nothing else to indicate the tumor. Occasionally there are periods of amenorrhea interspersed with periods of menorrhagia. There have been so few of these cases diagnosed

before operation that the number in which hormone tests have been run preoperatively is not sufficient to permit detailed deductions.

After the menopause the tumor is likely to cause a return of menstruation or prolongation of menstruation if it becomes active before menstruation ceases entirely.

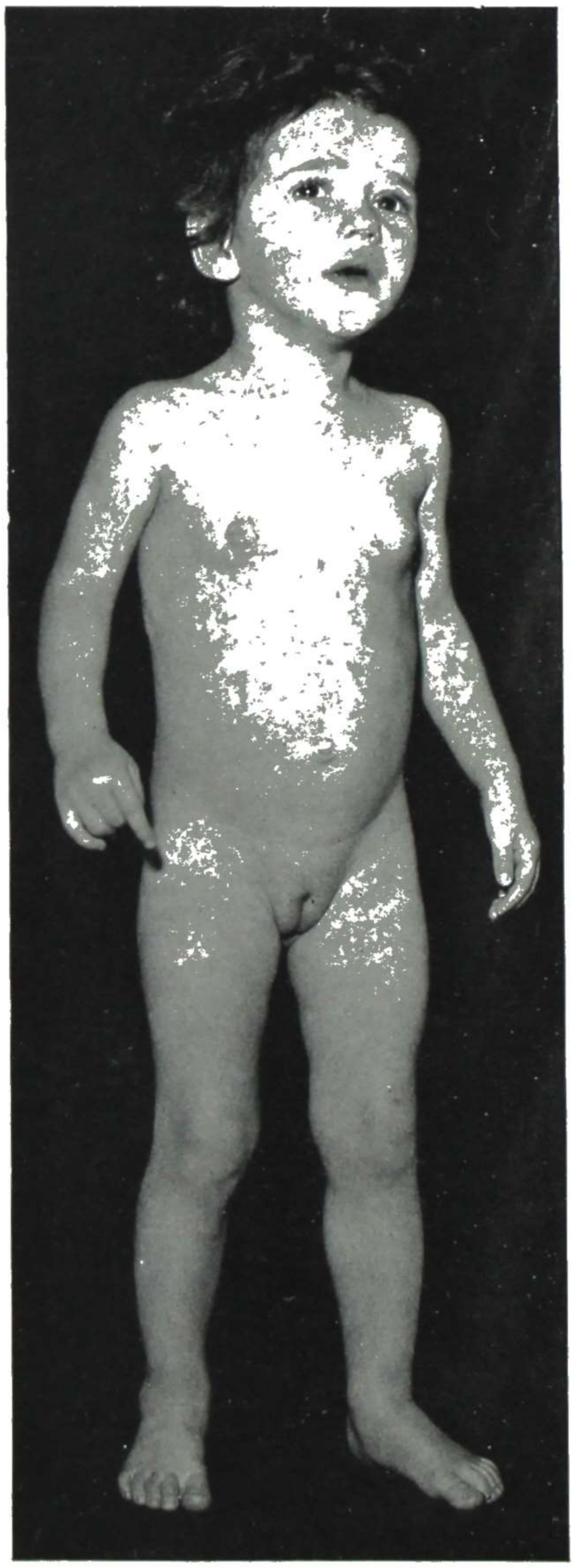


Fig. 900.—Precocious puberty in a child of twenty-two months, with no discoverable cause. This girl, now twenty-two years of age, began to menstruate at the age of fifteen months, and is still menstruating regularly. No clinical evidence of any endocrine tumor has ever been discoverable. (From Novak and Novak: Textbook of Gynecology. The Williams & Wilkins Co.)

Novak in a series of 33 cases of granulosa-cell tumors found the following age incidence: first decade 15 per cent, second decade 3 per cent, third decade 12 per cent, fourth decade 21 per cent, fifth decade (ages forty to fifty) 36 per

cent, sixth decade 9 per cent, and seventh decade (ages sixty to seventy) 3 per cent. The tumors, while not common, are not nearly as rare as was formerly thought.

The association of adenocarcinoma of the corpus uteri with granulosa-cell tumor has been more frequent than to be expected from mere coincidence, and this is an additional indication that excess estrin is a factor in the development of endometrial carcinoma.

Pregnancy associated with mesenchymal ovarian tumors is rare. Diddle and O'Connor reviewed the case reports of 1,193 women with theca-cell (263) or granulosa-cell (930) tumors and found 37 instances, including two of their own, in which there were sufficient data to evaluate the relation of these neoplasms to pregnancy. Parity was known for only 25 of the women, sterility was high for the group as a whole, and abortive tendencies were the rule. Some patients continued through the pregnancy only to die later with recurrence of the malignant tumor; others with medium-sized tumors had the complication of torsion of the pedicle and rupture of the tumor.

Malignancy.—Henderson, in a follow-up of 40 cases of feminizing ovarian tumors, found a recurrence rate of 35 per cent; half of these occurred within five years, and two cases recurred more than ten years after removal of the tumor. Diddle found that in 343 cases of granulosa-cell tumor which were followed a fifth of the recurrences occurred after ten years. This again emphasized the need for a prolonged follow-up.

Treatment.—In view of the evidence that these tumors are malignant, bilateral oophorectomy and complete hysterectomy should be done in an adult. Henderson found that all of the recurrences in his series occurred in women past thirty-nine years of age, and in five patients with recurrences after five years, the tumor at operation had an intact capsule and was freely movable. In younger individuals with well-encapsulated tumors, unilateral salpingo-oophorectomy will frequently result in cure, though these patients should be followed carefully.

Moreton and Leddy, in a study of the radiosensitivity of granulosa-cell tumors, concluded that the best results were obtained by surgery. In inoperable cases and in those where the operation has to be incomplete, radiation should be tried.

Arrhenoblastoma

The second type of tumor producing endocrine effects is the arrhenoblastoma. According to Meyer, these tumors arise from undifferentiated germ cells which are not utilized during embryonic development but nevertheless retain their sexual potency. Under certain conditions they begin later in life to proliferate and then exert an influence toward maleness. Some types of this neoplasm exert no hormonal effects. The following quotations are from Meyer:

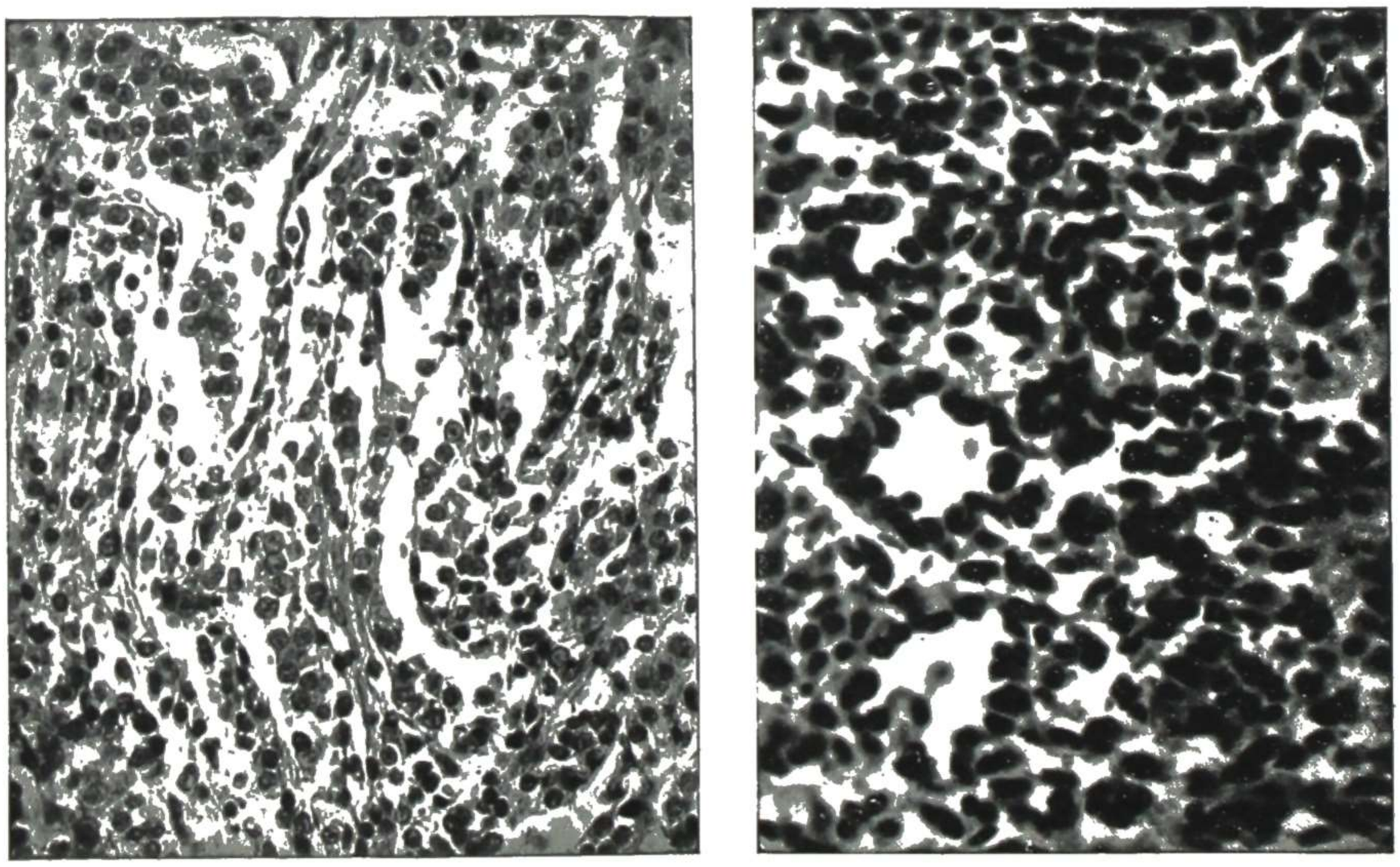
> In every embryonic sex gland undergoing development into an ovary, cells at the hilum remain for some time in an undeveloped state (blastema). This blastema under normal conditions later on produces the rete ovarii and some medullary cords or tubules which are homologues of the rete testis and tubuli afferentes of the testicle in the male. The future sexual character of the young embryo is not unalterably determined from the beginning, at least not in all instances, but does depend upon determining factors in the genes in the

chromosomes. A priori every embryo and also every embryonic sex gland has the potential faculty of developing in either direction—male or female.

The rete ovarii and the medullary tubules, which do not exert any functional influence on the female sex gland, prove the normal bisexual anlage of the gonad. If these structures then persist in part in an undifferentiated state, and later for unknown reasons begin to proliferate, they may induce the male direction of development and thus change the sexual characteristics by creating bisexual stimulation like an ovariotestis.

In the hilum of the adult ovary, I found a small tubular adenoma in a very young stage attached to the rete, which proves this type of neoplasm may have its origin just in this location. Therefore, it is not the hormonal effect alone which justifies the name arrhenoblastoma but the fact that the resulting masculinization confirms the theory of the origin of this new growth.

As mentioned in the opening paragraph, Schiller feels that these tumors are formed from the same cells as are found in the granulosa-cell tumors except that the cells destined to become future granulosa cells lose two of their X chromosomes and are hence converted into cells which play an auxiliary role in the testicle, or Leydig cells.



A. *B.*

Fig. 901.—Arrhenoblastoma, atypical group. *A*, Showing the irregular epithelial cord-like structures. *B*, Showing the sarcoma-like structure of these tumors. Some tendency to tubule formation is seen. (From Taylor, Wolfermann, and Krock: Surg., Gynec. & Obst.)

Structural Pathology.—The tumors are usually unilateral and seldom get very large. On cut surface they have a soft consistency and are pale yellow in color. There are two distinct morphologic forms and a third which holds an intermediary position.

1. The type described by Pick and named by him "adenoma testiculare ovarii" consists of an adenomatous structure made up of tubules resembling seminiferous tubules of the testis. It is not only similar to the adenoma developing in men but also contains some of the same structures. Masculinization occurs only occasionally in these cases.

2. The intermediary group shows a sarcoma-like tendency but usually rudimentary cords or irregular tubules could be found (Fig. 901, *A*). Women with this type showed a little more tendency toward masculinization, amenorrhea, hirsutism, etc.

3. Atypical variety, resembling sarcoma with little to suggest its origin. Most of these patients showed marked masculinization. Fig. 901, *B* shows such a growth.

Teilum suggests the term "androblastoma" for all tumors of the ovary or testicle which have their origin from male-directed cells and the use of arrhenoblastoma for those tumors in this group which are characterized clinically as virilizing. In a discussion of this whole problem of classification, Marchetti and Lewis conclude that although Teilum's concepts are thought-provoking, much remains to be settled before they can be completely accepted.

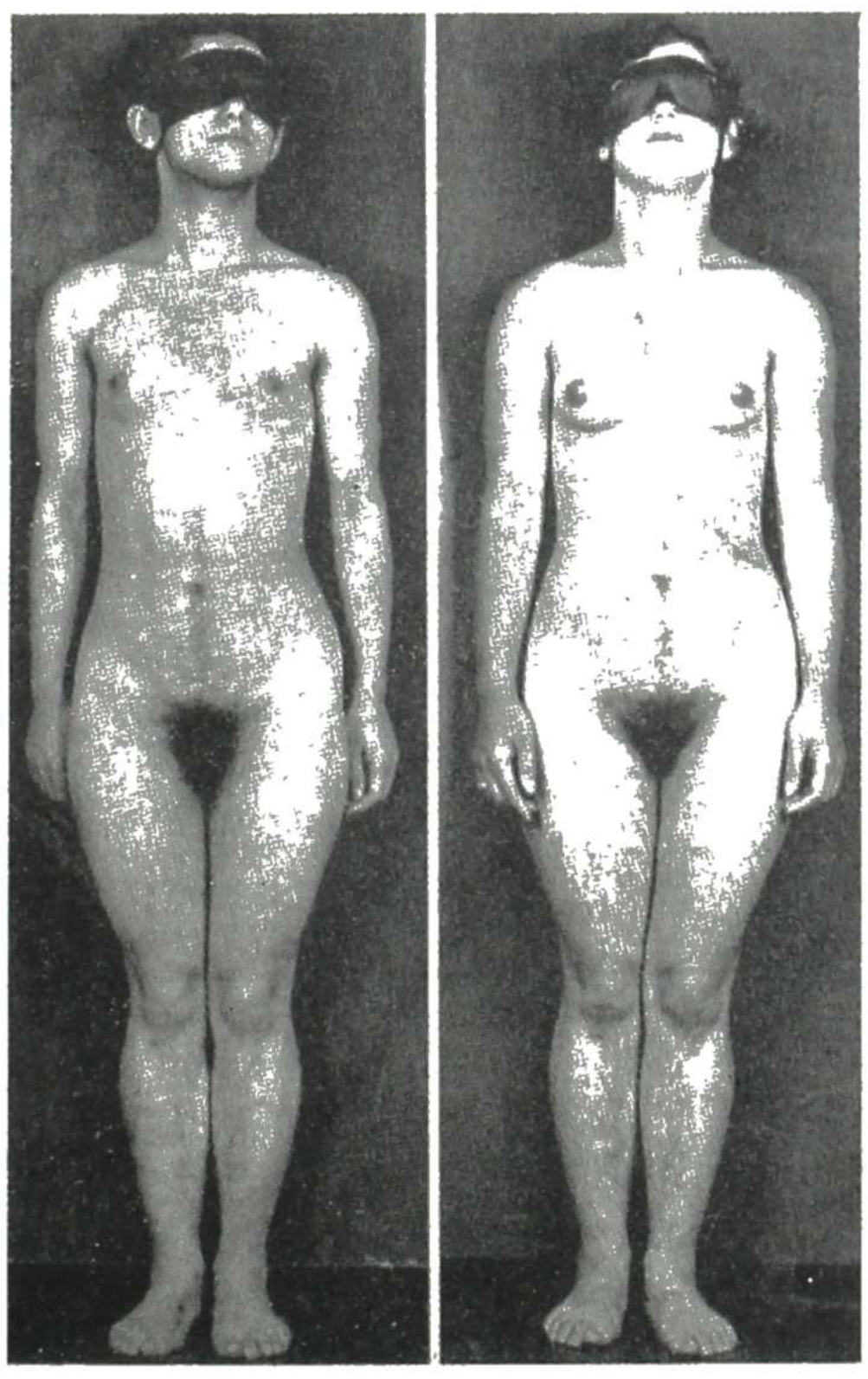


Fig. 902.—A case of adrenal cortical tumor before operation and two and a half months after operation. Changes in the body contour, breasts, and hair distribution are evident. (From Cahill, Loeb, Kurzrok, Stout, and Smith: Surg., Gynec. & Obst.)

Arrhenoblastoma is a much rarer tumor than is granulosa-cell tumor, and Henderson was able to collect only about 78 cases from the literature. Zelle places the number at 98 cases, but some of his cases may not have been properly classified.

The youngest patient was reported by Flannery; the symptoms began in his case at thirteen years, four months of age. It is most frequent during the childbearing age and is rare past the menopause.

Symptoms.—Patients harboring this type of tumor usually pass through two phases: first, defeminization and, second, masculinization. The early symptoms are amenorrhea, decrease in the size of the breasts and flattening, and a change in the feminine contours toward the masculine type due to a loss and a shift in the deposits of subcutaneous fat. Later the voice deepens, clitoris enlarges, and the body hair gets heavy and is prominent in the male distribution.

The diagnosis is made from the appearance of the patient, the history, and the finding of an ovarian tumor. In the differential diagnosis one must rule out basophilic adenoma of the anterior pituitary, adrenal cortex lesions, especially cortical hyperplasia, and pineal tumors.

In basophilic adenomas, the patients are usually very fat, and they have other symptoms referable to a pituitary lesion. Hirsutism is usually not a marked feature.

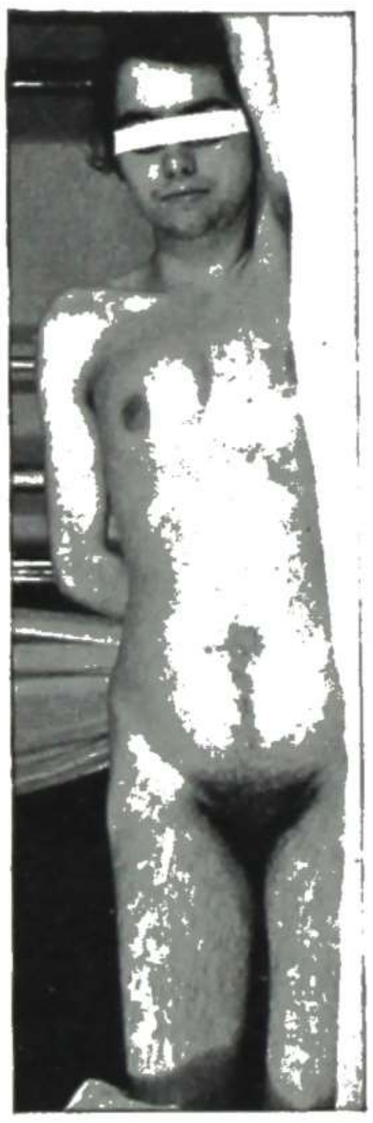


Fig. 903.

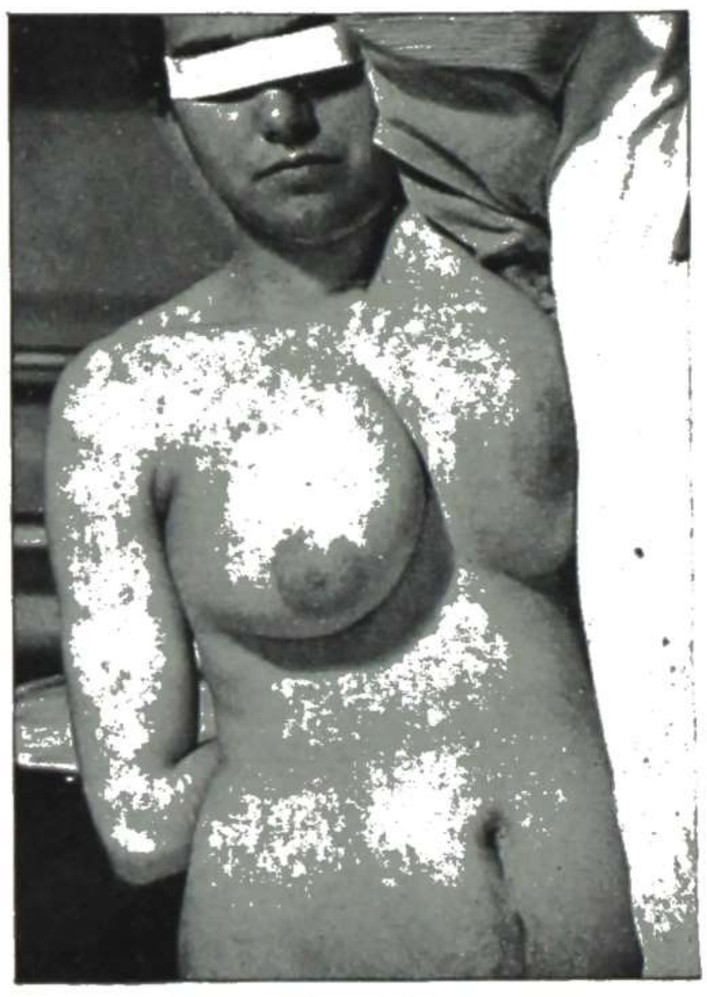


Fig. 904.

Figs. 903 and 904.—Patient with an arrhenoblastoma of the ovary, showing the masculinity the tumor caused and its subsidence after removal of the growth. Fig. 903, Showing the development of hair on the face and the developing masculine type of public hair growing upward toward the navel, and the flatness of the breasts as compared with Fig. 904. Fig. 904, Six months after removal of the tumor. Note the return of the feminine type of breasts and hip-outline, and the lessening of the hypertrichosis on the face. (From Taylor, Wolfermann, and Krock: Surg., Gynec. & Obst.)

In adrenal disorders there is a marked hirsutism, and the breasts usually remain of normal size. A tumor may occasionally be felt in the kidney region and there may be other adrenal symptoms (see Fig. 902).

Adrenal tissue may occur in the ovary and produce a tumor there. Such an ovarian tumor has much the same masculinizing influence as an arrhenoblastoma, so the differentiation has to be made by microscopic examination after removal of the growth.

In pineal tumors there is frequently calcification of the gland which can be seen in the x-ray. There is usually some evidence of increased intracranial pressure with an internal and external ophthalmoplegia and an impairment of the upward gaze. Secondary sex characteristics need not be changed.

The treatment for an arrhenoblastoma is removal. This causes a complete reversal to the feminine type. The abnormal hair drops out, the menses reappear, and the breasts assume the normal fullness. Figs. 903 and 904 show such a patient in the childbearing age, before and after operation.

Novak, in his article on masculinizing tumors of the ovary, calls attention to the occasional occurrence of adrenal adenoma in the ovary and in the broad ligament. The endocrine effect, when present, is toward masculinization, and hence the adrenal tumor may be mistaken for an arrhenoblastoma till removed and sectioned.

The microscopic picture, particularly the large lutein-like cells, has caused confusion with corpus luteum growths. Novak agrees with Schiller that most of the so-called luteomas of the ovary are really tumors of adrenal tissue. Rests of adrenal tissue occur in the ovary, and this fact must be taken into consideration in interpreting the microscopic pictures in uncertain conditions.

Treatment.—The treatment of arrhenoblastoma is removal. In young women unilateral removal is indicated, but in women near the menopause both ovaries should be removed if the nature of the tumor is recognized. Because of the relatively low-grade malignancy expectancy, treatment should be used when the condition has not been recognized until after operation, and if recurrences occur after removal of both ovaries, radiation is indicated. Henderson found recurrence and death in 12 to 15 per cent of the cases. Javert and Finn found the incidence of malignancy in 122 collected cases to be 22 per cent.

Gynandroblastoma

Robert Meyer described a tumor in which both the male- and female-directed cells were present and functioning in the same ovary. The clinical picture of these patients is that of acquired virilism, as it is with arrhenoblastoma. This is due to the fact that the androgens hold the balance of power, inhibiting the estrogens and giving a masculine clinical picture. About twenty-two cases have been reported, the most recent one by Hobbs. These tumors are so rare that little is known of their potential malignancy.

WITH NO ENDOCRINE INFLUENCE

Dysgerminoma Ovarii (Seminoma)

The dysgerminoma arises, according to Meyer, from undifferentiated germinal cells which have lost their power of becoming either masculine or feminine and therefore can develop into identical pathologic structures in either the testis or the ovary. They are very common in pseudohermaphrodites, in ovariotestis, and in poorly developed sex glands of otherwise normal persons. They are devoid of any specific sex influence and exert no hormonal action either toward masculinization or feminization. The growths are rather rare generally but are common in pseudohermaphrodites. They usually appear in the second or third decade of life. Meyer states that these tumors may attain enormous size, destroying the ovary and adjacent uterus. They are usually unilateral, though there are a number of cases, including one of our own, in which the tumor involved both ovaries (Fig. 905). They are usually solid, grayish white, and of a doughy consistency.

In a few cases some endocrine activity has been reported. In a case of Hain's an eight-year-old girl had signs of a precocious puberty which disappeared after operation. A number of cases have been reported with an excess of anterior pituitary-like substances in the urine, giving a positive pregnancy test. Burge reported two such cases. Mueller et al., in an analysis

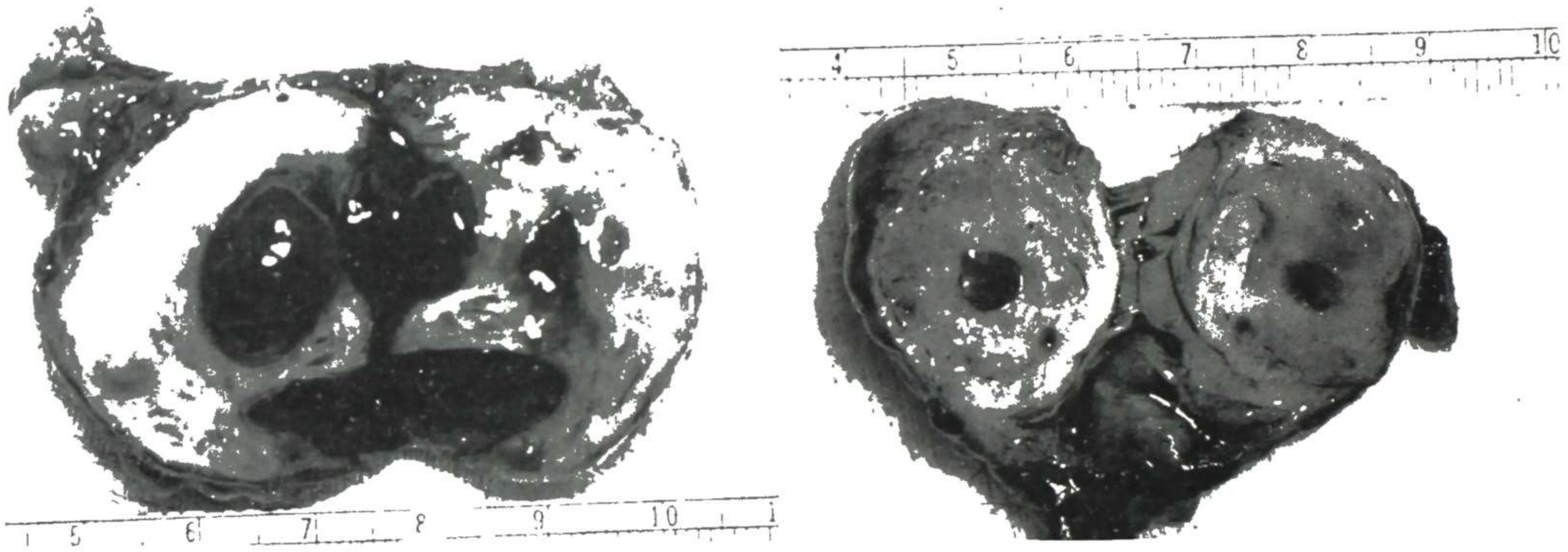
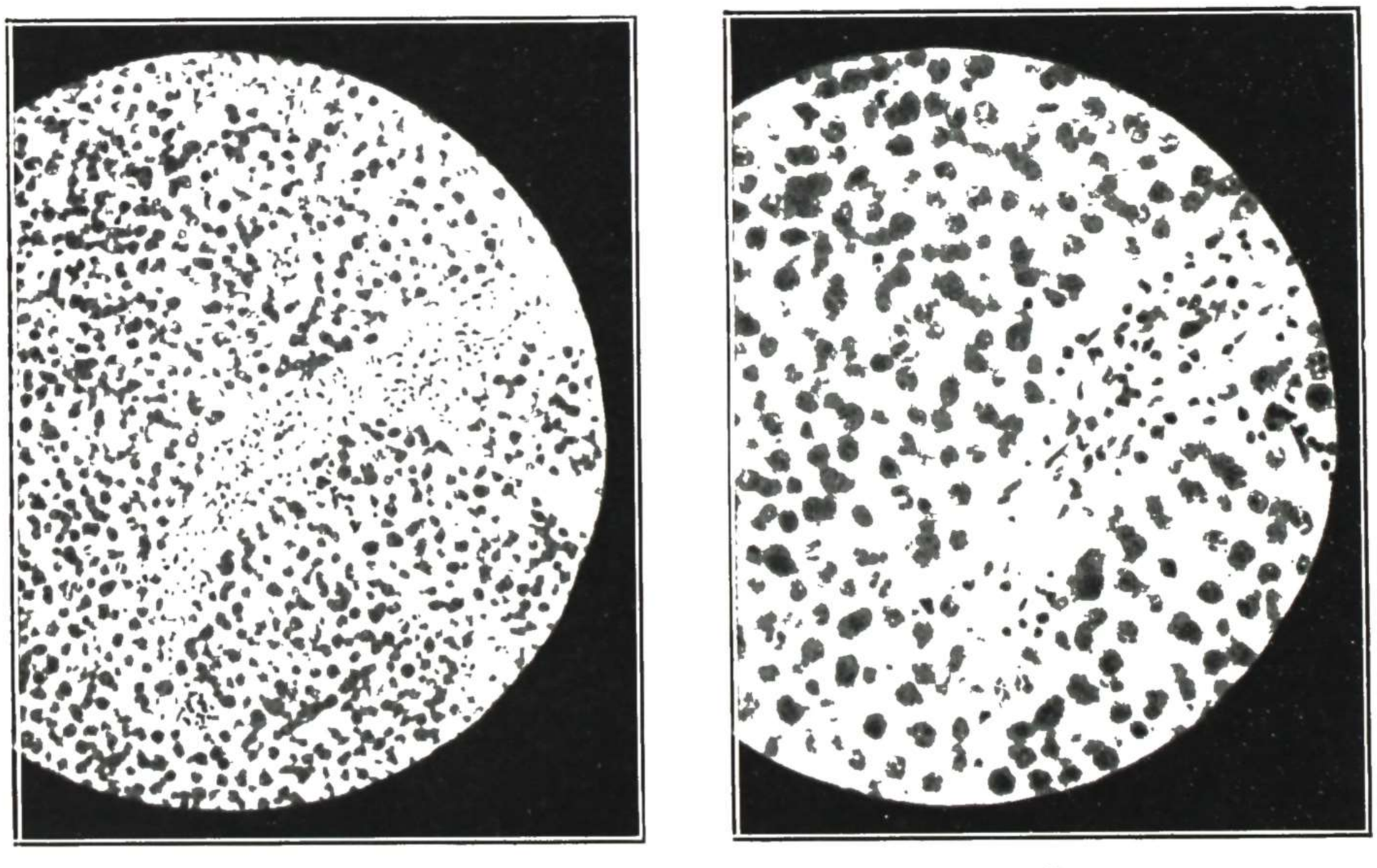


Fig. 905.—Bilateral dysgerminoma of the ovaries in a case of ours. This patient had had a previous abdominal operation elsewhere and a plastic operation had been done on both ovaries. Re-examination of the slides of the tissue removed proved the condition to be dysgerminoma; hence on the second operation both ovaries were removed and deep x-ray therapy was given. There has been no recurrence to date, two years after the last operation.



A. *B.*

Fig. 906.—Dysgerminoma of the ovary. *A*, Shows the resemblance to dysgerminoma of the testicle. *B*, High power of A. (From Meyer: Am. J. Obst. & Gynec.)

of 427 cases of dysgerminoma, found that 45 per cent occurred before twenty years of age and an additional 46 per cent between twenty and forty years of age. They found that over 89 per cent of the patients in whom the lesion was confined to one ovary and the capsule was intact were alive five years later,

whereas in those cases which were bilateral or extension was present only 25 to 30 per cent were alive after five years.

These tumors in the ovary have the same microscopic characteristics as they do in the testis, with the exception that there are no tubules present in the ovary. There is an alveolar arrangement of the large epithelial cells of the new growth. In some cases there is a cordlike arrangement of these large cells. There is a marked infiltration of the connective tissue. Fig. 906 shows the microscopic structure of a dysgerminoma of the ovary.

It was formerly thought that these tumors were relatively benign, but it is now known that they are as malignant as granulosa-cell tumors. Novak states that somewhat over 30 per cent recur. The knowledge of this malignant potential of the tumor has led to a more radical approach to the treatment; Pedowitz and Grayzel advocate "radical surgery in all patients, regardless of age, size of tumor, and degree of encapsulation," and they advise subsequent radiation in all cases. Mueller et al. make an exception in young women with a well-encapsulated, unilateral tumor but note the necessity of a careful follow-up.

In a discussion of Henderson's paper, Morton reported on the use of nitrogen mustard in a case of recurrent dysgerminoma, and another case was reported recently by Anderman et al. These cases indicate that nitrogen mustard may have a place in the treatment of recurrent cases along with radiation.

MISCELLANEOUS RARE TUMORS

Under this heading we will include adrenallike tumors which produce masculinization; other names which have been given to these tumors by various authors are hypernephroma of the ovary, adrenal rests, luteoma, Leydig cell tumors, luteinoma, and masculinovoblastoma. In a recent report of a case, Rhoads et al. state that Iverson found only 15 authentic cases up to 1947, but at least three additional cases have been reported. The symptoms are those of masculinization, amenorrhea, hirsutism, and hypertrophy of the clitoris, which are always present, and in addition to these some show hypertension, polycythemia, and glycosuria. They are usually found in women in the period of menstrual activity.

There are several theories as to their origin: one is that they get pinched off from the adjacent adrenal cortex during early embryologic life. A teratomatous derivation is also possible. Microscopically these resemble the adrenal cortex.

Another tumor probably developing from the adjacent mesonephric structures resembles the immature glomeruli. Schiller designates these as mesonephroma ovarii, and about 79 have been reported. In a recent case reported by Anderson et al., the mesonephric origin is questioned.

A lymphangioma was reported by Siddall and Clinton, a ganglioneuroma by Schmeisser and Anderson, and a primary melanotic sarcoma by Otken. Adenoacanthoma of the ovary has been reported in association with endometriosis and adenoacanthoma of the uterus, but since the original report on primary adenoacanthoma of the ovary by Melody et al., there have been three additional reports, the most recent one by Epperson and Benson.

The ovary is the source of so many different kinds of tumors that every specimen should be submitted to microscopic checkup, and every atypical specimen should be carefully studied as to exact type and probable origin. When we can substitute demonstrated facts for the present interesting but uncertain theories, we shall have attained the long-sought goal of a comprehensive satisfactory classification of ovarian tumors. To assist in this direction a responsible American Registry of Ovarian Tumors has been established, for special study of specimens and slides sent to it, as explained by Novak.

Before closing this discussion of mesenchymal tumors I want to pay tribute to the outstanding contributions on this subject by Emil Novak. With due credit to Meyer, Schiller, Teilum, and others who have done fundamental work on the histogenesis and classification of these unusual tumors, the clarification of the complex subject for many of us in this country has come through the many concise articles on the subject by Novak, and we owe him a debt of gratitude.

TUMORS OF THE UTERINE LIGAMENTS

Growths of this class are represented principally by the tumors of the broad ligaments arising from the parovarium, which consists of remnants of structures which served their purpose during embryologic development and then largely disappeared.

Parovarian Cysts

The tumors of the parovarium (broad ligament tumors) are almost invariably cysts, and they are of two kinds: simple and papillary.

The **simple cysts** are single cysts containing clear fluid resembling water. On account of their confined position they produce very troublesome symptoms while still small. They arise from various parts of the remains of the wolffian body—parovarium, paroophoron, and Gartner's duct (vestigal wolffian duct).

The lining of these cysts consists, as a rule, of a single layer of flattened epithelium resting on a fibrous stroma. They rarely become malignant.

The **proliferating papillary cysts** arise also from the remnants of the wolffian body and their characteristic is the development of papillary growths in the interior of the cyst, which fill the cyst and grow through its wall, and spread to the peritoneal surface and the adjacent organs (uterus, ovaries intestines). The whole pelvis may be filled with these warty cauliflower-like growths and, having spread to all the adjacent structures, they often give rise to an erroneous diagnosis of cancer.

In the majority of cases they are bilateral and usually rupture before attaining a large size. Though they grow rapidly and spread to adjacent organs, where they implant themselves on the peritoneal surfaces and grow freely, they do not have the fatal infiltrating and destructive tendency of malignant disease, and many patients recover when the abdomen is opened and the larger part of the growth removed. Later they may undergo malignant change, and then they present the usual characteristics of carcinomas.

These proliferating papillary cysts arise from the parovarium. As most parovarian tubules lie in the broad ligament, the papillary cysts are usually

broad ligament cysts. · But they may also arise from that part of the parovarium which is prolonged into the hilum of the ovary. It is from that location that the papillary cysts of the ovary arise. The papillary cysts of the ovary are usually bilateral and present all the characteristics of the broad ligament papillary cysts, except that they arise from the ovary instead of from the broad ligament.

Symptoms and Diagnosis.—In the clinical history and in the signs obtained by examination, broad ligament tumors resemble ovarian tumors very closely. Practically the same symptoms and signs which serve to distinguish an ovarian tumor from other diseases serve, also, to distinguish a broad ligament tumor from the same diseases. So that, as a rule, in this condition, when there is trouble in diagnosis, the difficulty is to tell whether the tumor present is a broad ligament tumor or an ovarian tumor.

The characteristics of the ordinary parovarian cysts, or "broad ligament cysts," as they are usually called, are as follows:

1. They grow into the broad ligament, separating its layers and displacing the adjacent organs. The uterus is pushed far to one side, and the tube is usually stretched over the cyst, being much lengthened and flattened (Figs. 907 to 910). The ovary also may be flattened out on the surface of the cyst. There is more or less fixation of the cyst and also of the displaced uterus. They may grow under the peritoneum and separate it from the rectum, bladder, and abdominal wall.

2. They produce serious symptoms much earlier than ovarian cysts. This is due to their being confined within the broad ligament and the pelvis, and hence making serious pressure on surrounding organs while they are still small. For this reason they cause more pelvic pain and more menstrual disturbance than ovarian cysts of the same size.

The papillary cyst, after rupture and spread of its papillary growths, may produce a clinical picture very much resembling tuberculous peritonitis or chronic pelvic inflammation. It then usually gives rise to marked ascites, and the fluid returns repeatedly after tapping.

The **rapidity of growth** of the broad ligament tumors depends somewhat on the character of the growth. Those of slow growth are usually simple cysts. The papillary cysts grow rapidly at the last, though the growth may be slow while confined within the broad ligament.

Treatment.—The treatment for broad ligament tumors is the same as for ovarian tumors—that is, removal by abdominal section. In some cases of simple cyst, very low in the pelvis, with the patient in bad condition, it is better to open the cyst from below, drain away the fluid and pack the cavity, keeping the wound open until the cavity is obliterated, the same as in the treatment of pelvic abscess. Some cases may be permanently cured in this way with much less danger than by abdominal section.

Ordinarily, however, the preferable operation is abdominal section. The operation for a parovarian cyst is somewhat more difficult than for an ovarian cyst owing to the fact that the parovarian growth lies between the layers of the broad ligament. This necessitates opening the broad ligament to extract the cyst and also necessitates careful closure of the remaining broad ligament cavity to prevent oozing or secondary hemorrhage.

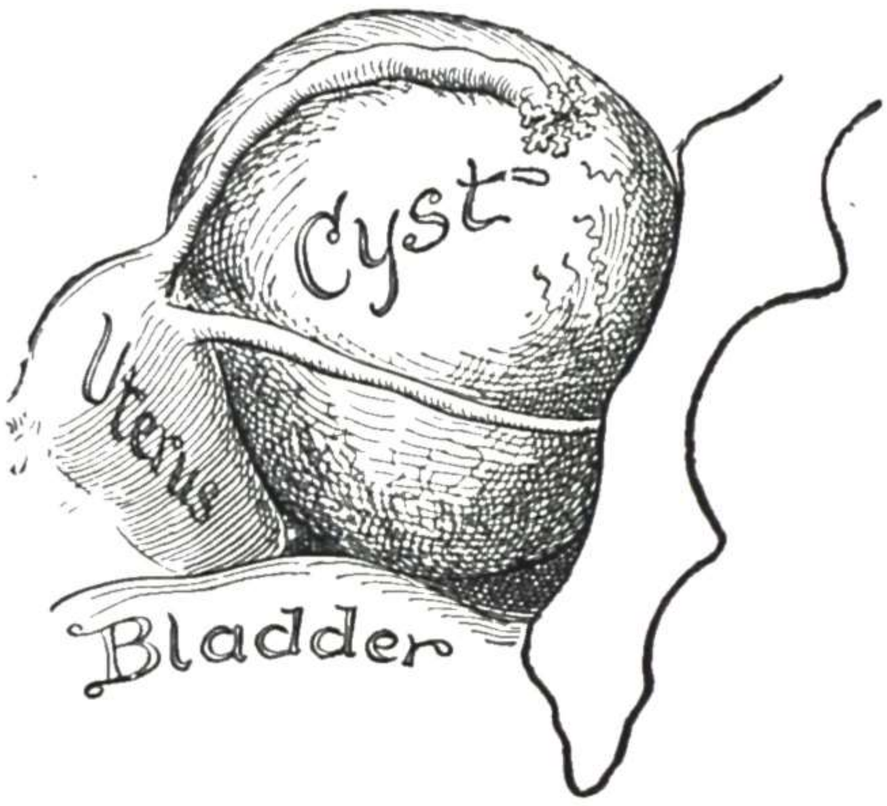


Fig. 907.

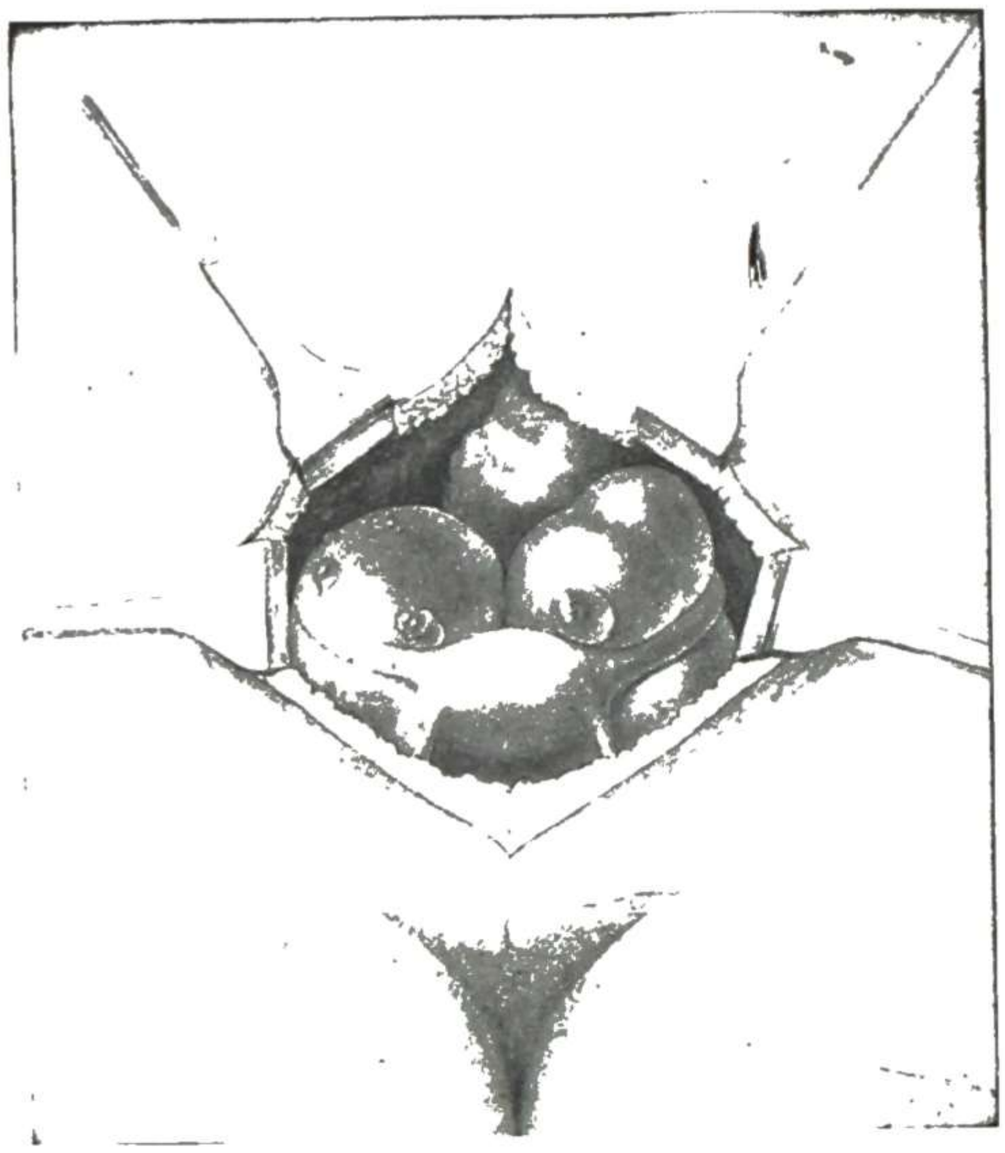


Fig. 908.

Fig. 907.—A parovarian cyst, forming a large mass and displacing the uterus. (From Ashton: Practice of Gynecology, W. B. Saunders Co.)

Fig. 908.—Graafian-follicle cysts of the ovaries, which have become intraligamentary. (From Kelly: Operative Gynecology, D. Appleton-Century Co.)

Fig. 909.—Parovarian cyst from left side, view from above. The ovary is seen at the upper left portion. Just below it to the left is the severed uterine end of the tube, from which the flattened tube may be traced under the peritoneum to its fimbriated end near the center of the drawing. As the cyst grew in its situation between the layers of the broad ligament and sides of the ligament were spread apart, the ovary was raised, and the tube was stretched out and flattened. Gyn. Lab.

Fig. 910. - A parovarian cyst of the broad ligament. Drawing from fresh specimen. Notice how the tube is stretched out over the mass and how the peritoneum extends from the tube out over the cyst in all directions.

Downing and Otoole, in their study of parovarian cysts complicating pregnancy, collected sixty-two reported cases, but in only seven did the cyst produce dystocia. They report a case causing dystocia and requiring aspiration of the cyst to permit delivery.

Myoma and adenomyoma sometimes occur in the uterosacral or round ligaments. In one of our cases a kidney-shaped myoma arose from the round ligament at a point just to the abdominal side of the internal inguinal ring.

Peritoneal bodies of the broad ligaments originally described by Walthard have been reviewed recently by Greene et al. They feel that these solid and cystic structures arise from the peritoneal mesothelium in response to inflammatory reaction. Nace recently reported a carcinoma of the mesonephric duct near the cervix in the broad ligament.

TUMORS DUE TO TRANSPLANTATION OR HETEROPLASIA

Pelvic Endometriosis and Endometrial Cysts

This type of tumor is represented by endometrial cysts of the ovary and of other pelvic structures. Since 1921, when Sampson first called attention to the condition, its importance in gynecology has increased until now it is considered not only one of the commonest lesions of the childbearing age, but also in extensive cases one of the most difficult to treat. It derives its name from the fact that it contains tissue which resembles the endometrium.

Definition.—In regard to terms used, "pelvic endometriosis" is the general term used to designate the appearance of endometrial tissue outside its usual location. If it appears in the ovary, it is likely to form a cyst, which is designated an "endometrial cyst" of the ovary. If the glands penetrate the uterine muscle, the process with the resulting condition is called "adenomyosis." If the adenomyosis causes a distinct tumor formation, that is called an "adenomyoma." This is also sometimes designated as internal endometriosis, and that occurring in the ovary and abdominal cavity and other locations outside of the uterus, as external endometriosis. As Novak and Alves de Lima have brought out, the histogenesis of these two types is entirely different though they have many points in common. Adenomyosis has been discussed under Myoma of the Uterus.

Spontaneous endometriosis has been reported in monkeys, and two cases were reported in dogs by Letulle and Petit. Two excellent reports on the condition in monkeys appeared in 1951, one by Klüver and Bartelmez and the other by Krohn.

Etiology.—There are several theories as to the etiology of this condition.

1. Transtubal implantation (Sampson). This is the first theory offered. Sampson thought that in certain cases during menstruation some of the blood and endometrial tissue passed out through the tubes into the peritoneal cavity. This endometrial tissue became implanted and grew at the point where it happened to fall. Any condition causing obstruction to the free cervical exit of the menstrual blood was presumed to be a factor in this transtubal implantation. This tissue after becoming implanted continues to function as endometrium and, as a result, menstruates. After a number of menstrual periods the transplant becomes a blood-filled cyst.

Owing to the increasing pressure within and the endometrial growth penetrating the wall, there is some leakage of cyst contents into the peritoneal cavity. This endometrial

leakage causes adhesions of the cyst to surrounding structures with endometrial penetration of the adherent area. Very frequently there is gravitation of material to the posterior peritoneal cul-de-sac with adhesions and penetration and infiltration there. This process of leakage and growth may continue, forming dense adhesions throughout the pelvis.

The arguments for the transplantation theory of the origin of endometrial ovarian cysts are: (a) in endometriosis the tubes are usually patent, (b) the islands of endometrial tissue are found where one would expect them if they were secondary to endometrial spill from the tubes, (c) endometrial tissue has been successfully transplanted in the peritoneal cavity of animals (Jacobson, and Crossen and O'Keefe), (d) blood has been observed coming from the fimbriated end of the tube at operation, and (e) the tissue seems to menstruate with each period similar to endometrial tissue, indicating that it is real endometrial tissue. (f) Te Linde and Scott in a study of experimental endometriosis performed an operation on monkeys which resulted in the menstrual flow being extruded from the uterus into the abdominal cavity. In some of their animals typical pelvic and abdominal endometriosis resulted from the desquamated endometrium. They conclude that at least some portion of the endometrium cast off with menstruation was viable.

The arguments against this theory are that this theory does not explain aberrant endometrial tissue occurring in distant structures, for instance, in the umbilicus or the inguinal canal, and it does not explain such tissue found in the depth of the ovary without surface contamination.

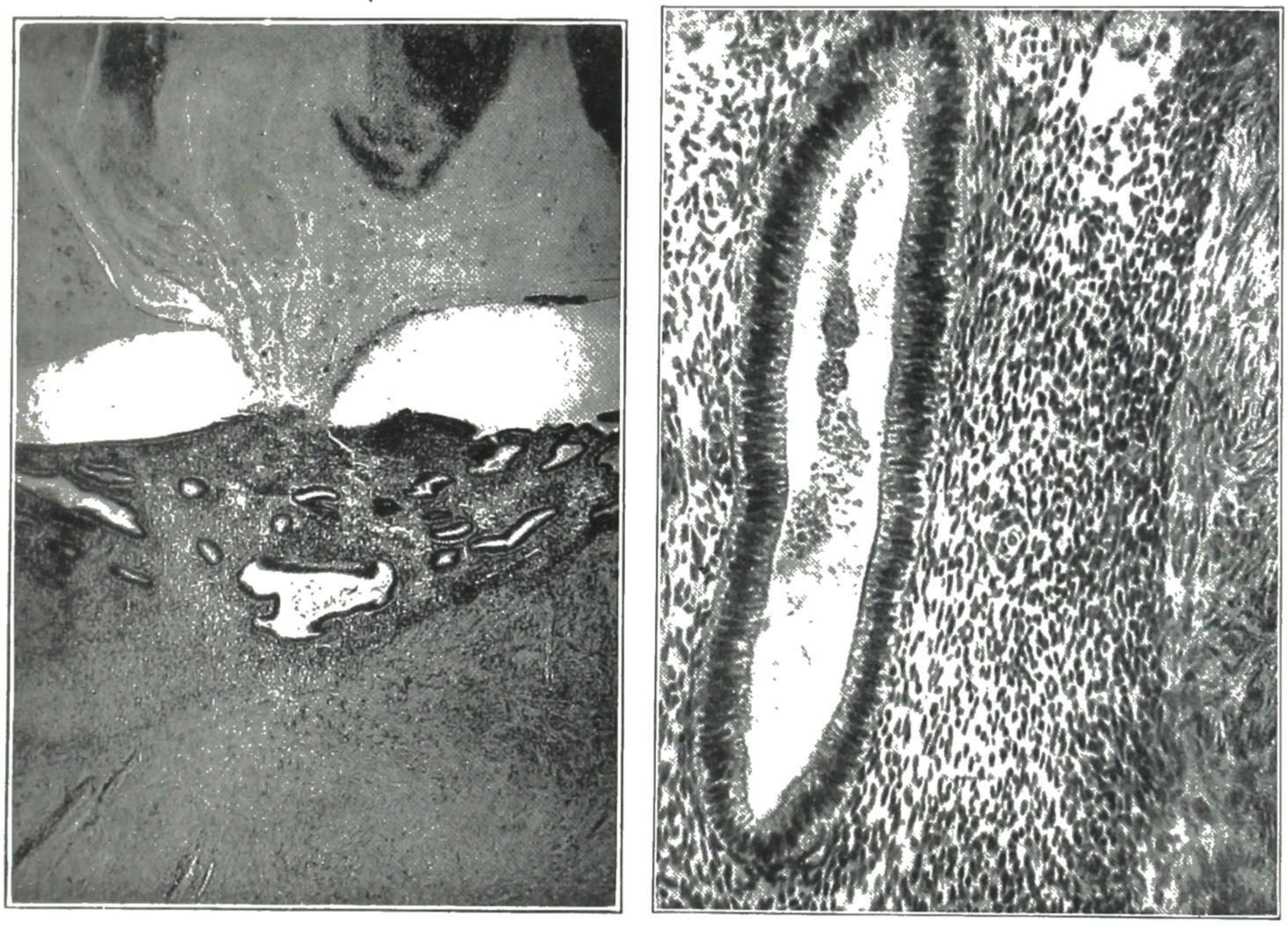
2. Heteroplasia of the serosa or celomic epithelium (Iwanoff, Meyer, Fischel, Novak). This theory of the origin of the endometrial cysts of the ovary is based on the embryologic fact that the lining mucous membrane of all parts of the müllerian canal (tubes, uterus, vagina), as well as the germinal epithelium covering the ovary, and the pelvic peritoneum, are all derived from the same parent tissue, namely, the celomic epithelium. The müllerian mucous membrane in all its varied forms is merely an invagination of the celonic epithelium, showing varying degrees of differentiation according to its location. Some of the less highly differentiated portions retain the power of further differentiation later in life, so that they may, under the influence of unknown stimuli, develop into differentiated tissue, such as tubal mucosa or endometrium. Whether this stimulus is of endocrine origin or whether it is due to some substance coming from the tubal ostium is still undecided. Also, there is the unsolved question as to whether all peritoneal cells or only certain ones, such as the "basal" cells (Meyer), have the power of differentiating.

In favor of this theory is the fact that it offers an explanation for all forms of endometriosis, for it is well known that remnants of peritoneal epithelium are frequently present in the inguinal canal and in the umbilicus. Against this theory must be counted the fact that the adequate stimulation is still unknown. Also, the known tendency to wide vascular dissemination of bits of tissue from the uterus, particularly during pregnancy, might account for subsurface endometriosis in various situations.

3. Halban suggested metastases by way of the lymphatics and blood stream, and this idea has recently been revived by Javert, combined with exfoliation and implantation. Javert has recently studied the pelvic lymph nodes removed in cases of endometriosis and found benign endometrial tissue in two of the thirteen cases in which an accompanying lymphadenectomy was done. He feels that the lymph node involvement is more common than we realize. Hobbs and Bortnick obtained endometriosis of the lungs in rabbits by intravenous injection of rabbit endometrium.

4. Meigs in 1948 emphasized that among his private cases where childbearing is usually delayed and fewer children are born, the incidence of endometriosis was 30 per cent, while in a similar group of clinic cases where the childbearing started early in life and the families were larger, the incidence of endometriosis was 5.75 per cent. He feels that the early initiation and frequency of the pregnancy cycle is an important factor in the prevention of endometriosis. The recent report of Scott and Te Linde confirms this idea.

Sampson does not hold that the transtubal transplantation is the only etiologic factor in endometriosis, but that it is the most important factor in causing the common clinical type. His indefatigable search for factual knowledge of this serious disease has resulted in one of the most comprehensive and helpful and beautifully illustrated studies in the history of medicine.



A. *B.*

Fig. 911.—Endometrial cyst of ovary. *A*, High power from the wall, showing typical uterine glands and stroma. *B*, Higher power, showing details of a gland and the surrounding stroma. The solid tissue about the two cysts is hyperplastic ovarian stroma. Gyn. Lab. (From Schwarz and Crossen: Tr. A. Obst. & Gynec.)

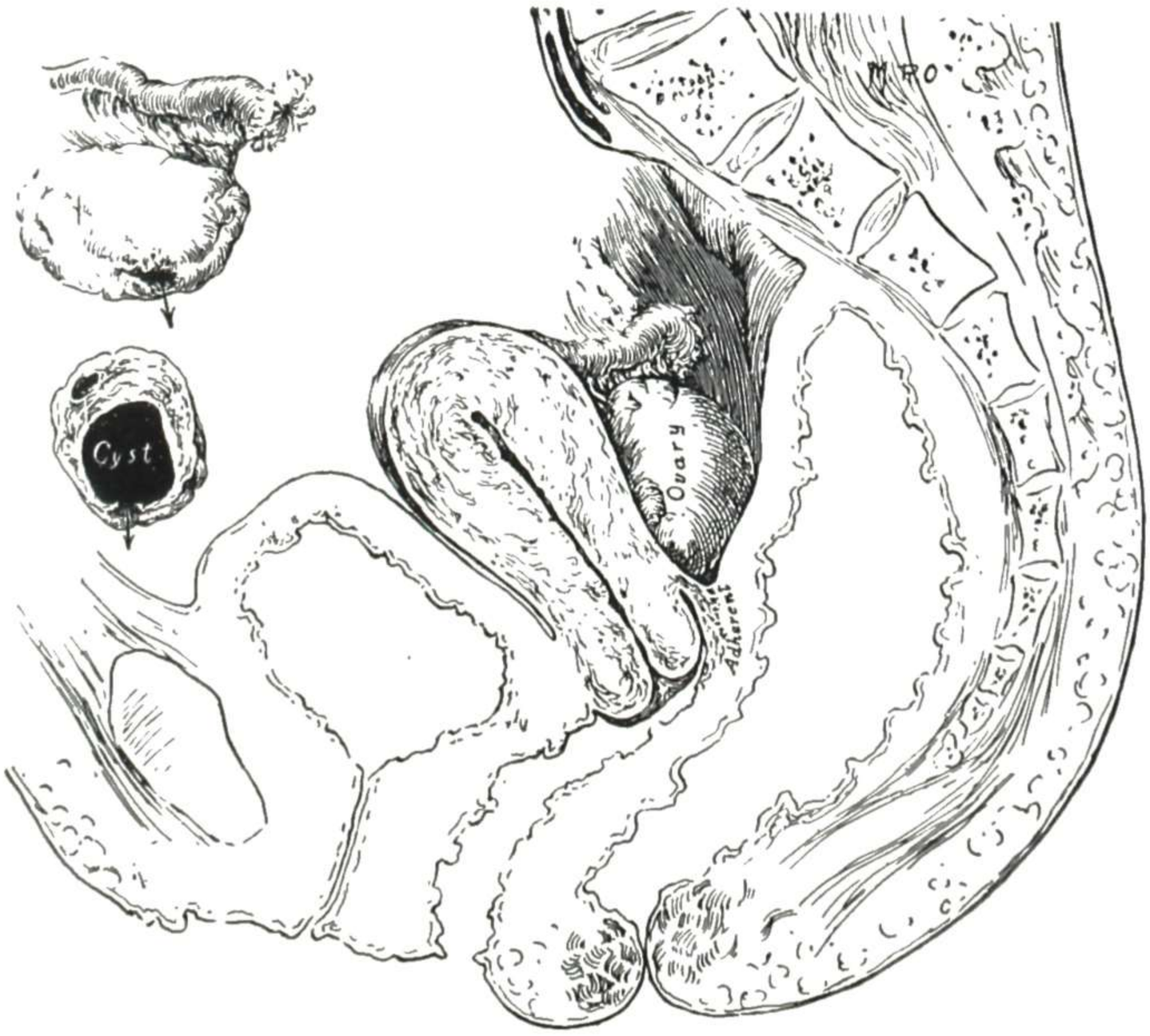


Fig. 912.—Endometrial cyst of ovary. The ovary is prolapsed and adherent. Perforation of the cyst wall has taken place, with gravitation of contents to the cul-de-sac and the formation of adhesions there. The insert shows the ovary sectioned and, also, the perforation through the cyst wall and ovarian surface. (From Sampson: Arch. Surg.)

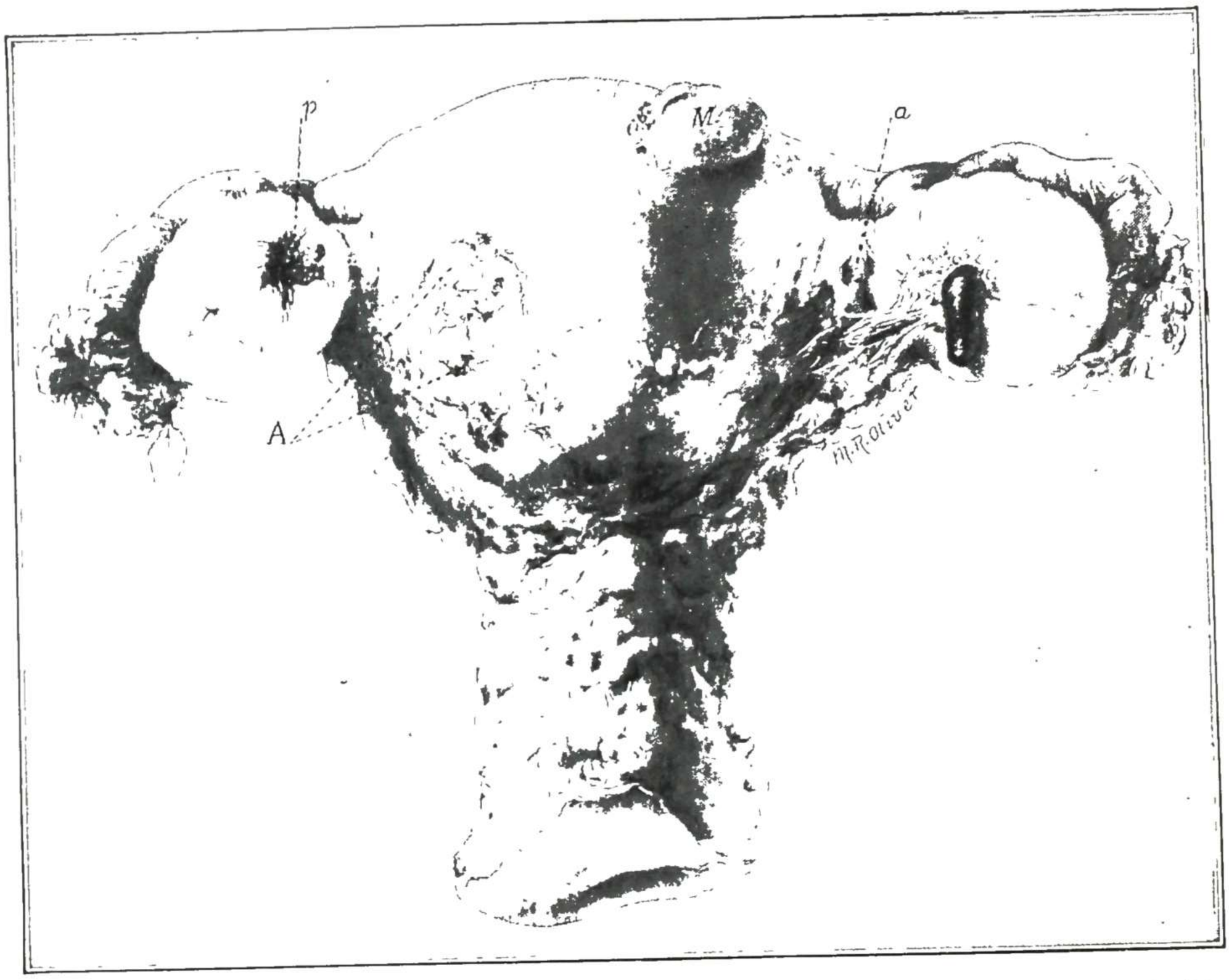


Fig. 913.—Endometrial cysts of ovary with peritoneal involvement (pelvic endometriosis). A cyst in each ovary has perforated, and from the cyst in the right ovary the contents are leaking out. At operation both ovaries were found adherent to the posterior surface of the uterus. Where the left ovary was adherent (*A*), a superficial adenomyosis is developing in the uterine wall. (From Sampson: Arch. Surg.)

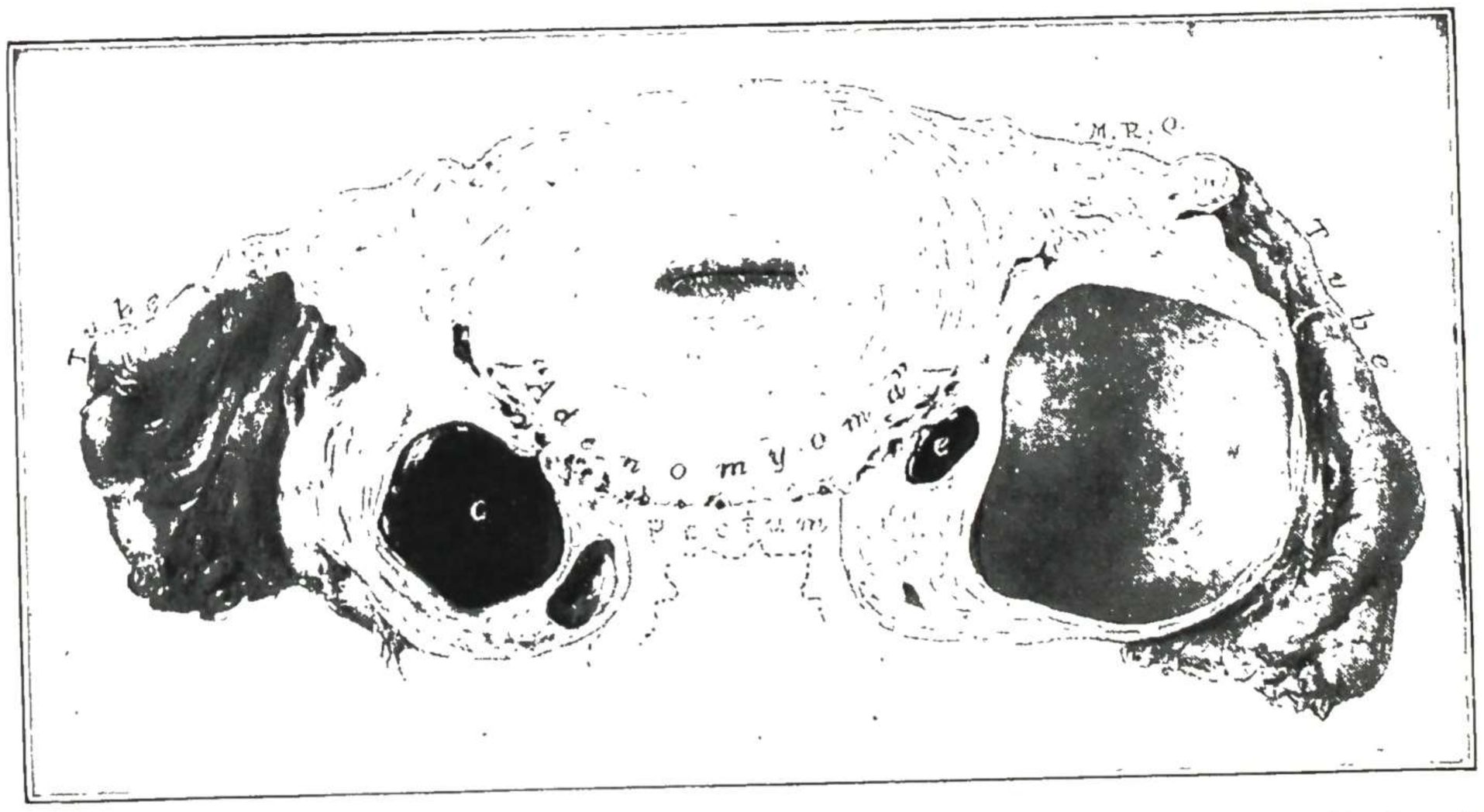


Fig. 914.—Pelvic endometriosis. Cross section of the uterus and ovaries, indicating the condition found at operation. Both ovaries were adherent to the posterior surface of the uterus and the implanted endometrial cells have grown into the uterine wall, forming superficial adenomyosis. Sections of the uterine wall showed no endometrial tissue between this area and the normal endometrium. The larger cavity in the right ovary is a simple follicluar cyst. (From Sampson: Arch. Surg.)

Incidence.—Sampson from several series of endometriosis cases concluded that pelvic endometriosis occurs in 10 to 20 per cent of all women between thirty years of age and the menopause. In 31,663 cases at the Ochsner Clinic, Tyrone and Weed found an incidence of 2.6 per cent, and Beecham in 1,000 consecutive gynecologic cases found an incidence of 5.8 per cent. Haydon found an incidence of 10 per cent in 4,500 gynecologic operations; Meigs in 400 abdominal gynecologic operations in private cases found 28 per cent to have endometriosis, whereas in an equal number of operations in clinic patients the incidence was 5.8 per cent. Blinick and Merendino on the gynecologic service of the Harlem Hospital, where nearly all of the patients are Negro women, found an incidence of 0.1 per cent. The fact that there was a high incidence of inflammatory disease at this hospital tends to confirm Sampson's finding that endometriosis is rare in association with inflammatory disease. Te Linde and Scott state that at Johns Hopkins Hospital the incidence is approximately 20 per cent of laparotomies in private patients.

Fig. 915.

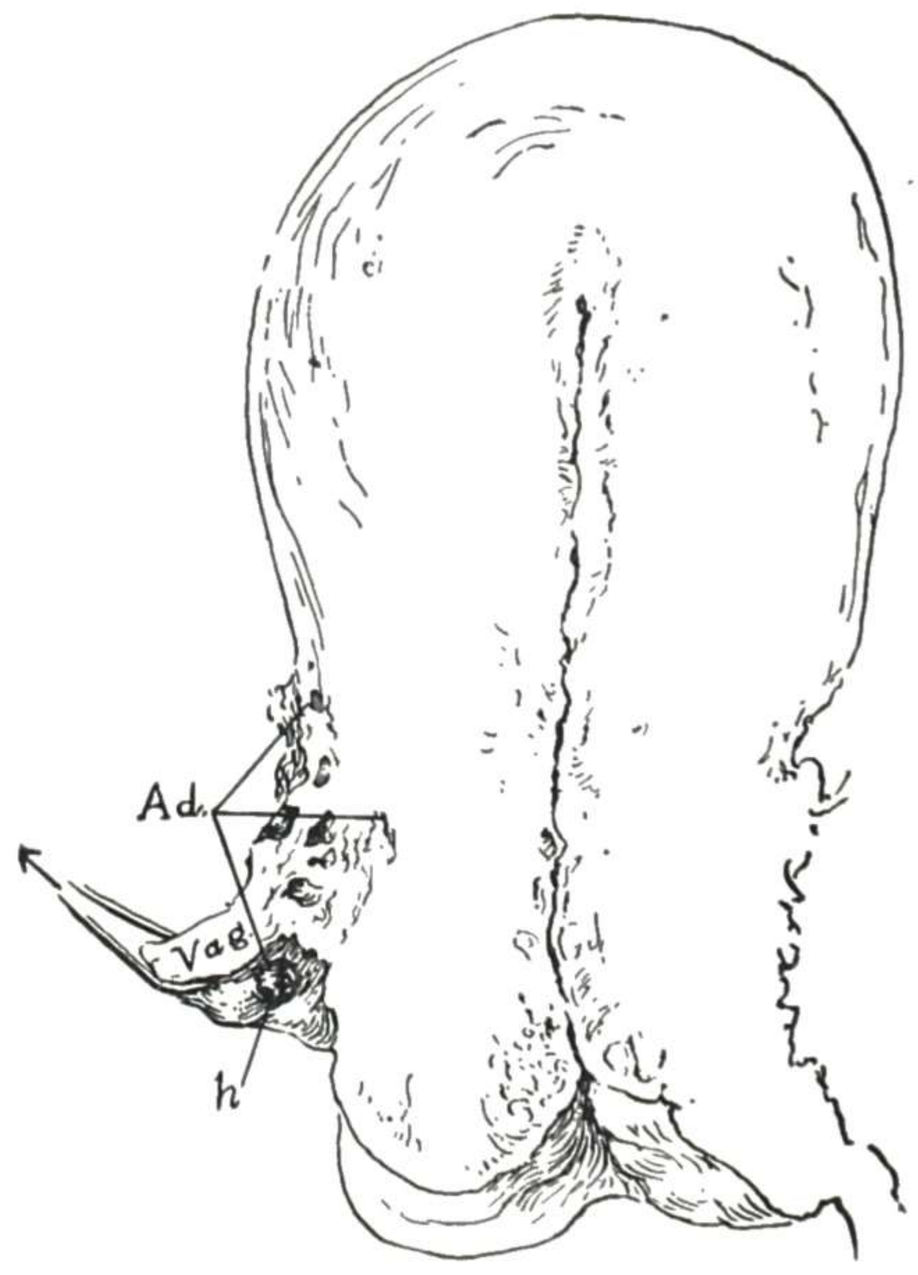


Fig. 916.

Figs. 915 and 916.—Endometrial cyst of ovary. Fig. 915, A small cyst of the left ovary has perforated and become adherent high up to the round ligament. The omentum also is adherent over it. On separating the adhesions, dark chocolate-like fluid escaped. Fig. 916, Section of the cul-de-sac area in the same case. Gravitations of leakage material have caused an implantation endometriosis at the bottom of the cul-de-sac. A small, blood-filled cyst of this endometriosis of the rectovaginal septum may be seen projecting into the vaginal cavity at the posterior vaginal vault. Compare with Fig. 917. (From Sampson: Arch. Surg.)

Pathology.—Since the attention of the profession has been drawn to the occurrence of this condition, it has been found to be fairly frequent. This process varies in extent from tiny "spots" on the surface of the ovary to tumors as large as a uterus at the sixth month of pregnancy. Usually these cysts are ruptured in removal, the reason being that the adherent structure comes in time to form a part of the wall of the cavity, and the cavity is necessarily opened when the separation is made. These cysts contain a thick chocolate-colored liquid, hence the term "chocolate cysts."

The epithelium lining these cysts varies a great deal. In some specimens the epithelium is strikingly similar to that of the endometrial glands. These glands are also surrounded by stroma similar to endometrial stroma. In other specimens the epithelium is not at all typical of endometrial glands, and indeed may resemble epithelial cells from any part of the body. Also, the stroma may be very scanty or missing entirely. There is usually evidence of old blood

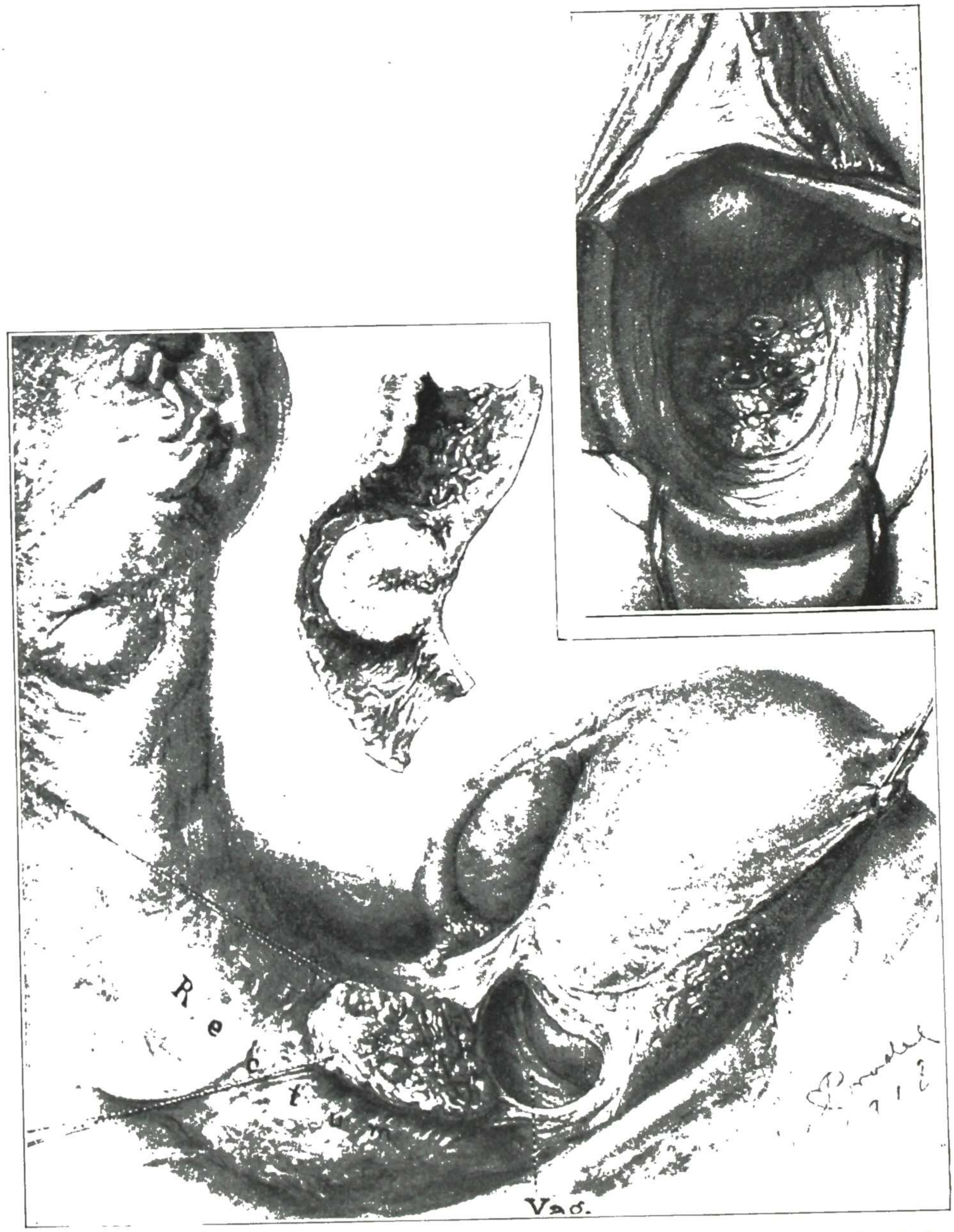


Fig. 917.—Endometriosis of rectovaginal septum, with coincident endometriosis of the sigmoid flexure which almost completely blocked the bowel. The inset at the upper right corner gives an excellent reproduction of the appearance through the vagnial speculum. (From Cullen: Arch. Surg.)

in the cavity and walls of these cysts. Fig. 911 shows typical characteristics of the endometrial cyst. The leaking cyst contents may gravitate to the posterior peritoneal cul-de-sac, where they form strong adhesions and ingrowths, binding the rectum to the posterior surface of the uterus. The various resulting conditions are shown in Figs. 912 to 920.

The dense adhesions to the small intestinal coils and sigmoid and rectum and other structures seriously complicate the operation for removal. The early perforation with adhesions and the chocolate-like contents are the striking clinical features of these cysts, and Sampson designated them as "perforating hemorrhagic cysts" and also as "chocolate cysts." As the essential pathologic feature is the endometrial tissue in the wall, the term "endometrial cyst" has now been widely adopted. As previously mentioned, in many cases the aberrant growth of endometrial tissue is not confined to the ovarian cyst, but spreads to various other structures throughout the pelvis. This condition of widespread growth of aberrant endometrial tissue is appropriately designated "pelvic endometriosis."

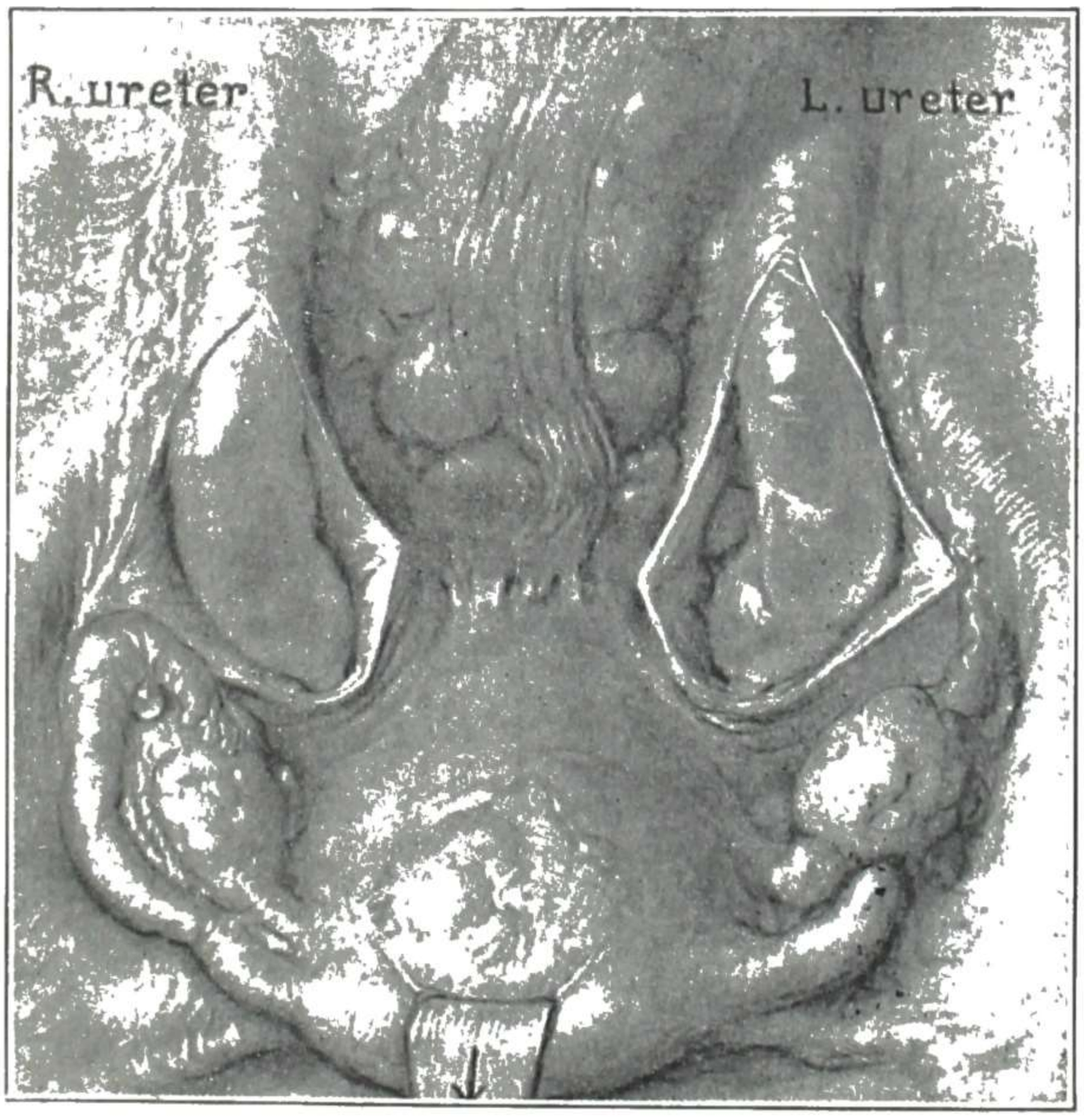


Fig. 918.—Remote results of an endometrial cyst of ovary. Patient aged twenty-five years, suffered at menstruation with pain in rectum and radiating down left thigh to knee. Trouble persisted. At operation, August, 1914, a cyst of the left ovary, size of an orange and filled with old blood, was removed. Some blood free in cavity. (Cyst had evidentally perforated long ago with the formation of implantation endometriosis in cul-de-sac.) Some temporary relief from operation, but in February, 1916, polypi appeared at the vaginal vault, connected with an induration in the rectovaginal septum. Polypoid masses were removed but recurred, and microscopic examination showed them to be endometriosis. Operation in November, 1916, revealed the condition shown in the above drawing. The endometriosis of the rectovaginal septum had extended into the parametrium, constricting the ureters until they were both dilated as here shown. Uterus was removed but not all of the rectovaginal growth could be removed. Later, radium treatment. Improvement. July, 1917, patient was doing well, no pain in kidney regions. (From Cullen: Bull. Johns Hopkins Hosp.)

Diagnosis.—In the first place, endometriosis is a disease of the age of ovarian activity, for its development and progress are dependent on the same ovarian hormones that cause the normal menstrual changes in the uterine endometrium. As the initial lesions are minute and their progress slow, it probably takes several years for the process to reach the stage of clinical

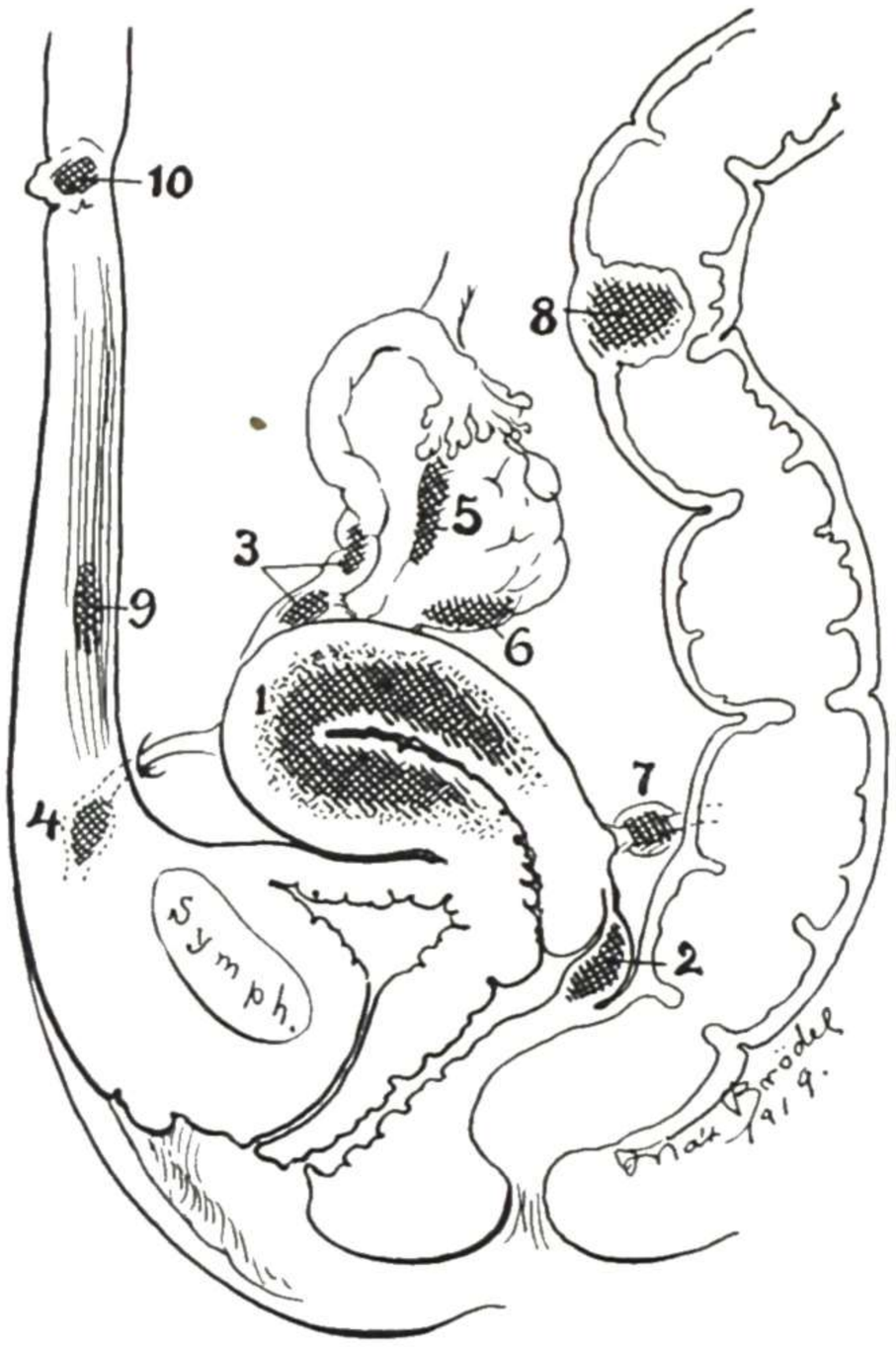


Fig. 919.—Sites at which endometriosis has been found. (1, Uterus; 2, rectovaginal septum; 3, tube; 4, round ligament; 5, ovary; 6, uteroovarian ligament; 7, uterosacral ligament; 8, sigmoid flexure; 9, rectus muscle; 10, umbilicus. As explained at the beginning of the chapter, when endometriosis occurs in a muscular structure, it is called adenomyosis, and if such growth develops in a way to form a distinct tumor it is called an adenomyoma. (From Cullen: Arch. Surg.)

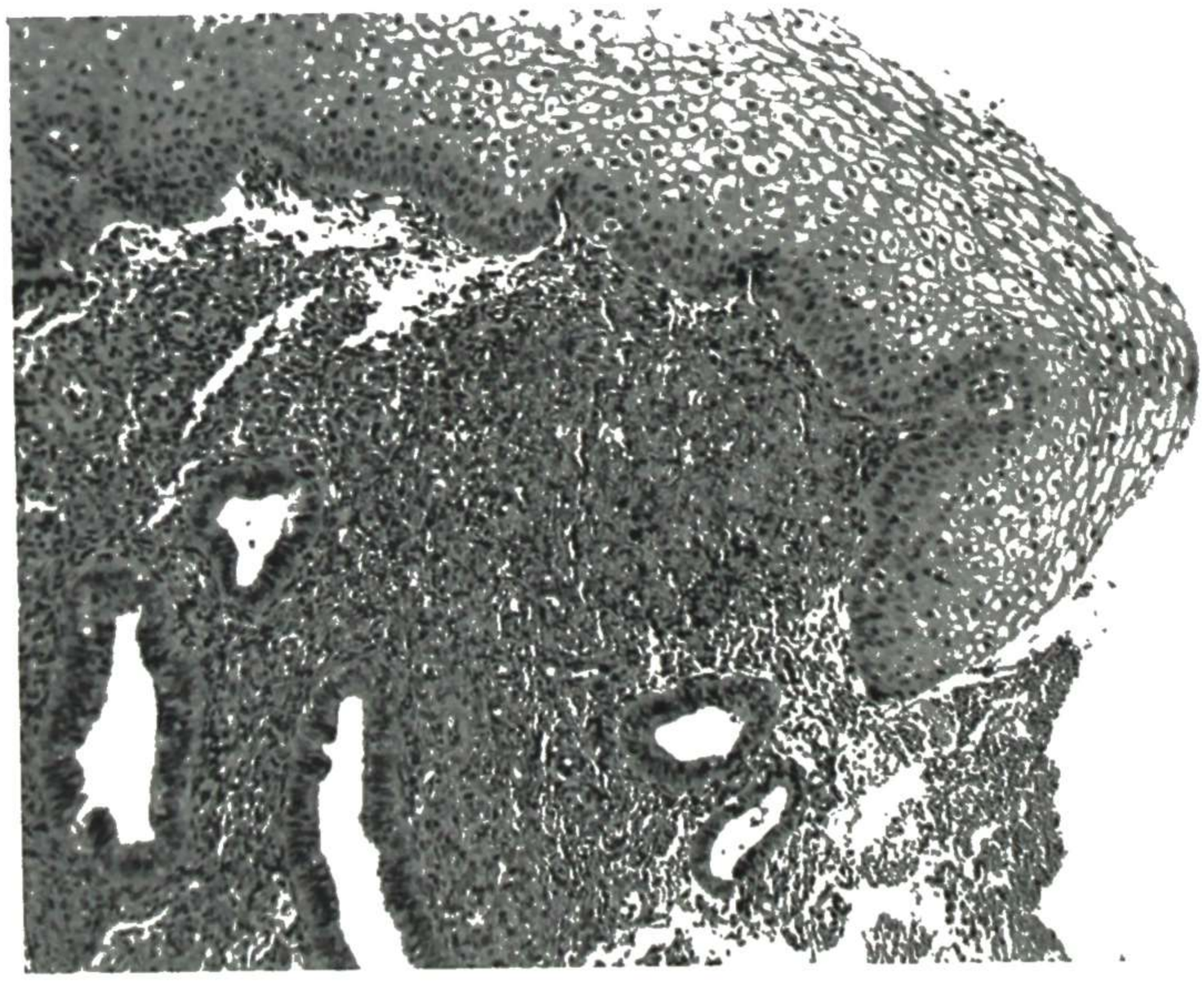


Fig. 920.—Endometriosis of the cervix showing the squamous epithelium of the portio above and the endometrial stroma and glands underneath it. This patient had a small bleeding area on the surface of the cervix from which I took this biopsy. She was two days premenstrual at the time of the biopsy. Gyn. Lab.

symptoms. Consequently the lesions which have advanced sufficiently to cause pain and disability are found principally in individuals from thirty to forty-five years of age.

Even with the progressive lesions there may be but few symptoms. It is surprising what extensive adhesions may form without symptomatic disturbance. For example, an ovarian cyst that has given the patient very little discomfort may at operation show extensive and dense adhesions. On the other hand, some patients suffer much pain and disability, the progressive pathologic process giving rise to marked symptoms and examination signs.

The bedside recognition of pelvic endometriosis is not as easy as might be inferred from the clear-cut pathologic changes. The difficulty in diagnosis comes from the fact that, though there may be definite symptoms and examination signs, these same symptoms and signs occur in other more common diseases. Consequently, the more common disease is usually decided on as the diagnosis, and endometriosis is encountered unexpectedly at the operation.

It may be said in a general way that endometriosis gives rise to the symptoms of chronic inflammation, without the infection and pus formation. There are present fixation of structures and induration and tenderness, and usually a definite mass as in inflammation. There is exacerbation of the pain and distress at the menstrual time with subsidence between, as often happens in chronic pelvic inflammation.

The following are the items likely to arouse such suspicion:

1. Absence of Definite Evidence of Infection.—As the patient tells her story of pain and disability with fairly comfortable intervals, we naturally think of chronic pelvic inflammation. But when the attempt is made to determine the time of infection and its character, we are not successful. The history gives no definite indication of gonorrheal infection nor of puerperal infection. The objective findings also include nothing that might not be due to non-inflammatory irritation and infiltration. There is no telltale focus of chronic inflammation in the vulvovaginal glands or in Skene's glands or in the cervix. There is nothing in the temperature or leukocyte count definitely indicating infection. Forman has called attention to the fact that in an occasional patient a significant elevation of temperature is present without accompanying infection.

2. Fixation Without Evident Cause.—As mentioned under Pathology, fixation of adjacent structures by ingrowths is a marked feature of endometriosis. This may take place so gradually and with so few symptoms that it is encountered as a surprise at the examination. When extensive fixation is found in the pelvis without a history of inflammation or preceding operation, endometriosis is to be suspected.

One very common form of this fixation is adherent retrodisplacement. There may be simply the fixation of the retrodisplaced uterus or there may be also the characteristic infiltration of the cul-de-sac area under the displaced uterus. This infiltration if at all extensive is likely to present a nodular "shotty" feel due to irregular islands of epithelial growth. When the areas of endometrial growth advance to the stage of menstruation, small collections of blood form in them. These feel hard at first but as they become larger or nearer the vaginal surface, their cystic character may be recognized.

Another form of fixation is adherent ovarian cyst. A small or medium ovarian cyst, which should be freely movable in the absence of inflammation, is found adherent, without any history of infection or other adequate cause for the fixation.

3. Disproportion Between the Pain and the Palpable Lesion.—This disproportion may be in either direction. As previously mentioned, there may be no pain or history of disability, in spite of the fact that examination shows a marked lesion with extensive fixation. This in itself indicates that the fixation is due to some process different from inflammation.

On the other hand, there may be marked pain and disability, much more than to be expected from chronic inflammation without abscess formation. In endometriosis marked pain is usually due to tension from extrusion of blood into a filled cavity or to peritoneal irritation from leakage. Consequently it presents certain characteristics, which are taken up later.

The important feature here emphasized is that the pain bears no definite relation to the size of the mass, often being very severe with only a small mass. In fact, severe pain has been reported in cases of endometriosis not yet advanced sufficiently to give any palpable mass. On this account, endometriosis is recognized as one of the causes of dysmenorrhea without palpable lesion—the diagnosis depending on the time and character of the pain.

4. The Time and Character of the Pain.—Keeping in mind the pathology of the disease, the characteristic feature being a closed sac with menstruating endometrium, the relation of the pain to menstruation becomes clear. It starts with the premenstrual swelling some days before menstruation and continues severe till practically the end of menstruation. The pain from tension of the sac will continue as long as additional blood is being extruded into the sac from the aberrant endometrial tissue lining.

With a chronic inflammatory mass or a tumor, the discomfort is likewise more marked at the menstrual time, but there is a difference in two particulars. First, the pain of ordinary menstrual swelling about an inflammatory mass or tumor usually becomes less as the flow is well established, while the pain of endometriosis is likely to continue severe all through the flow. Again, with ordinary menstrual swelling, the discomfort is only moderate and is diminished by rest and other measures that diminish general pelvic congestion, whereas the pain of endometriosis may be severe in character and persistent in duration in spite of palliative measures.

In cases of obstructive dysmenorrhea from cervical stenosis the pain may be very severe, but it comes only with the onset of the flow and disappears as soon as the flow is well established. Also, it is likely to be more intermittent and cramplike than the persistent pain of increasing tension in a closed cavity. Again, dysmenorrhea from cervical obstruction usually dates from the first menstruation, whereas that from endometriosis is an acquired dysmenorrhea coming on later.

5. Miscellaneous Points.—In regard to the history, sterility, rectal pain, and dyspareunia are of rather frequent occurrence in endometriosis.

The *sterility* may have been absolute or there may have been children years before. Usually several years have elapsed since the last pregnancy. Evidently impregnation is interfered with in endometriosis a long time before the process reaches the stage of pain and disability that calls attention to it. Te Linde in endometriosis cases found an absolute sterility of 32 per cent and a relative sterility of 41 per cent. Counseller found almost the same percentages, while those of Payne and of Haydon were somewhat higher.

The incidence of *rectal pain* or pressure discomfort is due of course to the frequent involvement of the cul-de-sac area. When the cul-de-sac endometriosis extends to the connective tissue and the rectal wall, there is very likely to be deep rectal discomfort, off and on, especially at the menstrual time.

Occasionally *dyspareunia* appears, and gradually increases. This pain in coitus is more likely to be present when endometriosis involves the cul-de-sac area, though it may be absent with extensive involvement of this region. Dyspareunia due to endometriosis appears without any apparent cause, such, for example, as infection. It is usually slight at first and increases gradually with the increasing infiltration and fixation of the tissues about the cervix. It is likely to vary considerably at different times, being most marked usually near menstruation.

In addition to the special points in the history there are also certain special examination findings that are frequently associated with endometriosis.

Cul-de-sac infiltration, causing palpable induration of the vaginal wall just back of the cervix, is a distinctive feature in certain cases of endometriosis. Involvement of the vaginal wall in this situation in the childbearing period is nearly always due to plevic endometriosis or to inflammation. Consequently if infection can be excluded, endometriosis becomes probable. This probability is increased if there is evidence of endometrial involvement higher in the pelvis. In some cases the process in the posterior vaginal wall goes on to the formation

of distinct "shotty" nodules. If these approach the surface so that the bluish color of the contained blood can be seen in the speculum examination (Figs. 916 and 917), the diagnosis becomes positive.

Retrodisplacement of the uterus is found in a large proportion of cases of endometriosis. This may be because retrodisplacement favors the development of endometriosis or because endometriosis adhesions tend to pull the uterus into backward position. Perhaps both factors enter into the matter—the first in some cases and the second in other cases. At any rate, adherent retrodisplacement is found so frequently in endometriosis that that disease is to be suspected, especially if there is no history of infection to account for the fixation of the displaced uterus.

Fibroid tumor in the uterus is found in 55 to 60 per cent of the cases. Such a nodule may be an ordinary encapsulated myoma or it may be an adenomyoma. Endometriosis is to be suspected in any case of small uterine myoma with marked fixation without a history of infection.

An *associated endometrioma* of the umbilicus or of the inguinal region or in an abdominal operation scar indicates the nature of the process going on deeper in the pelvis.

Occasionally *cystoscopic* examination will show the characteristic small blood cysts in the bladder wall. Such an examination is especially helpful in differentiating between endometrial infiltration and carcinomatous infiltration in patients approaching the menopause.

Proctoscopic examination is useful in patients with perirectal involvement. The induration from involvement of the cul-de-sac and rectovaginal septum may bring up the question of carcinoma of rectal origin. In endometriosis proctoscopic examination will show normal rectal mucosa, except where the hemorrhagic cystic process has extended through the rectal wall.

Culdoscopy is useful in doubtful cases.

In addition to differentiation from ordinary chronic inflammation, pelvic endometriosis must be differentiated from a tumor with complicating inflammation, from pelvic tuberculosis, and from ectopic gestation.

Areas in which endometriosis have been found are shown in Fig. 919, and, in addition to these locations, it has been found in the following: (1) Cervix (review by Siddall and Mack); it may simulate carcinoma (McGuff and Lovelady) or, form a large cyst (Plager et al.). Fig. 920 shows a case of ours in which the cervix was involved. (2) Scars: abdominal (Sampson), episiotomy (Catherwood and Cohen), after vaginal hysterectomy (Reich et al.). (3) Bladder and ureter (O'Connor and Greenhill).

Endometriosis and pregnancy were reviewed in 1944 by Scott and in 1946 by Lock and Myers. The most recent report, in 1950, is by Ware. There may or may not be a decidual reaction in the ectopic tissue. In twelve of Ware's thirteen cases the pregnancy occurred after conservative surgical procedures for the endometriosis. The symptoms usually disappear and in some the lesions recess during pregnancy.

Treatment.—The treatment of pelvic endometriosis requires careful individualization and evaluations of the pelvic findings and the symptoms. Many cases have no symptoms and the decision for operation is made on the pelvic findings (ovarian cyst), and, as Novak noted, many patients are operated upon because of an acquired dysmenorrhea or other symptoms and no endometriosis is found. Fallon collected nine cases in which the patient was under twenty; the youngest patient, eleven years of age, was reported by Clark; but most patients are first seen between the ages of thirty and forty, and hence this is a disease of the childbearing age.

In many cases concomitant lesions are determining factors in favor of operation; in Dannreuther's series 40 per cent had fibromyomas, and in others 50 per cent was reported.

Huffman suggested the following working classification, consisting of four stages of involvement:

Stage I.
- a. Limited to uterosacral ligaments and/or
- b. Limited to one ovary and/or
- c. Superficial peritoneal implants.

Stage II.
- a. Extensive involvement of one ovary, plus lesser involvement of second ovary and/or
- b. Superficial implants both ovaries and/or
- c. Superficial bowel implants and/or
- d. Infiltrating lesions of uterus or uterosacral ligaments.

Stage III.
- a. Extensively infiltrating both ovaries.
- b. Bilateral ovarian endometriotic cysts.
- c. Deeply invading rectovaginal lesions.
- d. Infiltrating nonobstructing bowel implants.

Stage IV.
- a. Vesical invasion.
- b. Intestinal invasion, obstructive.
- c. Ureteral involvement.

This organized system of staging is helpful, but we still have many other factors to consider. In general, conservative treatment is indicated in young women and radical treatment is indicated in women around forty. The problem will be discussed under the following divisions: (1) no treatment; (2) endocrine treatment; (3) conservative operation; (4) radical operation.

1. As mentioned, in many cases there are no symptoms and the lesion is found on pelvic examination. Many patients can obtain adequate relief of symptoms by sedatives with the period. C. T. Beecham found that 50 per cent of his cases required no treatment; in the series reported by Scott and Te Linde this was true of 30 per cent, and in that of Counseller and Crenshaw 75 per cent. The conclusions of these latter workers are given:

> "In summing up the data herein presented, the problem seems to be one of selection of patients for surgical treatment. At the clinic we have reduced this problem to 25 per cent of all of the patients presenting evidence of endometriosis. Of this 25 per cent, the number of patients who are treated conservatively has been gradually reduced in the past ten years. The reasons for this seem obvious. In our hands, at least, the results do not justify the extension of surgical procedures to more young people. If we submitted more younger women to surgical exploration for endometriosis, we would secure some relief from pain, the possible correction of some of their menstrual irregularities, and possibly they would have some children after operation. It seems to us, however, that the same group of patients if they are treated medically, or have no treatment at all, would have just as many children and perhaps be just about as comfortable until they reached that age at which surgical treatment of a radical nature would be required either for the endometriosis or for associated lesions of the uterus and adnexa."

2. Endocrine therapy has in recent years been advocated for relief of pain, and in some cases where the periods are prevented over a period of many

months the lesions are reported to have been reduced in extent. Hirst suggested large doses of testosterone; Dannreuther found that progesterone contributed to the comfort of some of his young patients. Hoffman obtained relief in some patients who had failed to respond to stilbestrol or testosterone, by using progesterone. In 19 cases of extensive endometriosis Karnaky used 5 mg. stilbestrol daily from the fifth to the twenty-fifth day of the cycle, for three consecutive months, and obtained relief of symptoms and in some cases disappearance of lesions in the rectovaginal septum. In a later report he uses larger doses (100 to 200 mg. daily) and tries to keep the patient amenorrheic for six to nine months.

His treatment schedule is as follows:

"*Micronized stilbestrol 0.05 mg.*—Prescribe one tablet at 9 P.M. for the first two nights. Increase this dose by one tablet every third night until 10 tablets are being taken at 9 P.M., then

"*Micronized stilbestrol 1.0 mg.*—Prescribe one-half tablet at 9 P.M. for the first two nights. Increase this dose by one-half tablet every third night until six tablets are being taken nightly, then prescribe

"*Micronized stilbestrol 25 mg. tablets*—

For 3 days	¼ tablet	(take medication at 9 P.M.)
3 days	½	
3 days	¾	
3 days	1	
3 days	1¼	
3 days	1½	
3 days	1¾	
3 days	2	
3 days	2¼	
3 days	2½	
3 days	2¾	
3 days	3	
3 days	3¼	
3 days	3½	
3 days	3¾	
Then	4	

"The dosage is held at 100 mg. daily for three months or longer according to the severity of the symptoms. If spotting or bleeding ever occur during the treatment period, give two to four 25 mg. des® micronized stilbestrol tablets every fifteen minutes until symptoms are controlled.

"When des® micronized stilbestrol has been given for the desired period, it is decreased in the following manner:

2 tablets for one night
1 tablet for one night
½ tablet for one night
¼ tablet for one night
Stop"

He was able to reduce the side reactions by combined therapy, using micronized stilbestrol, testosterone, and vitamin B complex with folic acid and vitamin C. His routine for elimination of nausea and vomiting from diethylstilbestrol is as follows:

"Fifty to 100 milligrams of testosterone propionate are given intramuscularly and 1 cubic centimeter of soluble B complex is given intravenously on the day before the 9 P.M. dose of stilbestrol (¼ of a 25 mgm. desplex tablet).

"If the patient ever experiences stilbestrol side reactions, soluble B complex is repeated and the stilbestrol dose is reduced by ¼ tablet and increased ¼ tablet every seventh instead of every fourth day."

3. Selection of patients for conservative surgery is dependent upon many factors, and, in general, any operative work should be delayed as long as there is response to medical therapy. The factors concerned are: age of patient, marital status, fertility or infertility, severity of symptoms. In every patient where conservative operation is contemplated, it must be made clear that the procedure may have to be more radical than planned; also, if the conservative operation can be done, some of the symptoms may not be relieved, and radical therapy, either by operation or radiation, may be needed later in life. The percentage of conservative operations done varies with different workers: Counseller's opinions are given above; in Beecham's series of operative cases 70 per cent were conservative, that is, ovarian function and, where possible, the childbearing function were conserved. Te Linde feels that in sterility cases where the usual sterility procedures have been unsuccessful after a two-year trial, operation is indicated, and that this should be done while there is still some hope for success with conservative operation. In cases in which the childbearing function was preserved, the percentage of full-term children subsequently born was 31.8 in the series reported by Scott and Te Linde. The percentage of conceptions following such conservative therapy was as follows: Tyrone and Weed, 32; Siegler and Bisaccio, 28; Huffman, 47; and Bacon 26.8. Counseller states that the tendency at the Mayo Clinic is to defer surgery if possible, but if necessary then it is to be radical; in the 155 cases in which conservative operation was done, 20.8 per cent conceived afterward.

The type of conservative therapy to be employed must of course be determined at the time of operation after exploration. The question of presacral sympathectomy is one on which the authorities differ. Willard Cooke advocates it in almost every case and states in his discussion of a paper by Schmitz and Towne that he feels that it is so valuable that he has not done radical extirpation in any case. In seven cases of massive endometriosis in which the pelvic viscera were indistinguishably merged, the follow-up showed that not only was the pain relieved but there was almost complete disappearance of the mass in every case and three of the patients had borne children. He emphasizes the necessity of extensive sympathectomy. Dailey and Tafel make a similar recommendation based upon 30 cases in which they performed superior hypogastric sympathectomy. Schmitz feels that it is of value only in adenomyosis. Counseller feels that it may actually be a factor in causing extension of the lesion in pelvic endometriosis, and he seldom uses it now in these cases.

4. Radical surgery is indicated in women near the menopause or in those somewhat younger who have had their family or in whom the extent of the lesion makes the chance of relief with ovarian conservation very slight. Bilateral oophorectomy with removal of the uterus, if possible, is the preferred procedure. Bowel resection is indicated only with complete obstruction, since with the removal of the ovarian function the bowel lesions will atrophy. The same applies to cases with bladder involvement.

Irradiation Treatment.—Irradiation by radium or x-ray stops ovarian function and thus checks the recurring menstrual exacerbation and progress of

the endometriosis. It does not remove the ovarian cyst or other mass, which in itself may keep up discomfort and disability. However, irradiation may be useful in the following two classes of cases:

Poor Operative Risk.—In a person seriously handicapped from the operative standpoint, irradiation may be used to check the increasing pain and disability from endometriosis. This applies especially of course, to patients approaching the menopause, in whom the continuation of ovarian activity is not so important as in earlier life.

The preferable form of irradiation to employ depends on the particular conditions present. When the endometriosis is principally in the uterine wall (adenomyoma), a radium application within the uterus is the best plan, because concentrated irradiation is given at the seat of the process and without the extensive intestinal irradiation occasioned by x-ray. Also, radium application in the uterus works in well with diagnostic curettage which is needed to exclude malignancy and which may be carried out at the same time. On the other hand, if the endometriosis is scattered widely in the pelvis and unaccompanied by uterine bleeding indicating curettage, deep x-ray therapy is the preferable form of irradiation. One of our cases had almost complete obstruction of the rectum due to infiltration of the rectovaginal septum; she obtained permanent relief with x-ray therapy. In another case radon seeds in a painful nodule in the septum gave relief for ten years in a thirty-year-old patient; when the pain recurred at forty, x-ray sterilization gave permanent relief.

Irradiation treatment is employed on a tentative basis. It may give sufficient relief in a case of endometriosis, and it may not. Also, the possibility of an error in diagnosis is to be kept in mind, and if satisfactory result is not secured by irradiation in a reasonable time, operation is again to be considered.

Postoperative Activity.—When activity persists in an area of endometriosis after operation, irradiation treatment is to be employed. In some cases where it was thought best to leave an ovary, there may be new development of endometriosis or renewed activity in some small area left. Occasionally there is persistent activity even when both ovaries have been removed along with the endometrial cysts. In either case irradiation treatment is to be employed.

In a case of ours a woman in her early thirties continued to have pain after removal of a large endometrial cyst of the left ovary. The infiltration along the lower rectum which could not be removed was thought to be the cause. We decided to screen the right side where the remaining ovary was located and radiate the left side. After this procedure the patient was relieved and has now been menstruating regularly for ten years without further treatment. Hays and Portmann reported 34 cases of endometriosis treated by radiation, with control of symptoms in 97 per cent of the cases.

Special Dangers.—Experience has shown that operation for pelvic endometriosis carries certain special dangers. These dangers are due to the extensive dense adhesions caused by the unusual process. These adhesions are not simple agglutination of surfaces, as in inflammation, but real tissue ingrowths into the walls of adjacent structures, such as small intestine, sigmoid, and rectum. The two special dangers are, first, a tear into the bowel and, second, postoperative intestinal paralysis and peritonitis.

Injury to Bowel.—In endometriosis the adherent walls are fused by tissue growth and cannot be separated easily, as can inflammatory adhesions. Any attempt to separate them carries danger of a tear into the intestinal tract. This fact must be kept in mind in trying to enucleate the mass to be removed. Rough or hurried separation by palpation only is to be avoided, as the line of cleavage may extend into the bowel lumen. Dense adhesions should be carefully separated under sight as well as touch, and the line of separation should not be allowed to encroach on the intestinal wall.

It is important also to limit the separation as much as possible, breaking adhesions only where necessary to allow safe removal of the abnormal mass. The cyst wall should be re-

moved as far as practicable, especially the endometrial lining. It is permissible to leave some of the outer layer of the cyst wall, if necessary for the safety of the intestine or other attached organ.

In cases requiring removal of the uterus, the adherent rectum can usually be separated down far enough to permit supravaginal hysterectomy. An attempt to separate dense adhesions in the cul-de-sac sufficiently low to allow complete hysterectomy may cause a tear into the rectum. It is safer as a rule to leave the cul-de-sac adhesions and the cervix. If there should be a complicating cervicitis that persists, the cervix may be coned later from below.

Postoperative Peritonitis.—Another serious problem presented by these cases of endometriosis is to get the patient through the postoperative stage without intestinal paralysis and peritonitis. Just what factor it is that makes these patients so prone to postoperative intestinal paralysis and peritonitis is not altogether clear, for there is no primary infection. A plausible theory is that the extensive damage to the intestinal walls first interferes with peristalsis, causing postoperative intestinal paralysis, and second, favors escape of colon bacilli into the damaged area, causing peritonitis. Whatever the cause, the tendency to fatal postoperative peritonitis is painfully evident to those engaged in treating these patients. Several trying experiences in the handling of these cases convinced us that this disease constitutes one of the most serious pelvic conditions for which operation is required in the child-bearing period.

The first of these experiences is recalled vividly because of the many days of anxiety before the patient was past the acute danger, and also because of the difficulty encountered later in closing the intestinal opening which had been made for drainage during the intestinal paralysis. At the primary operation typical endometriosis was found, with dense adhesions and the "chocolate" contents leaking from the cyst. There was no pus and no evidence of infection, consequently no drainage was employed, the abdominal wound being closed entirely as in all noninfected cases. In the next few days the patient developed intestinal paralysis with persistent reverse peristalsis and fecal vomiting. This was finally overcome by opening the distended intestine and draining away the contents. This maneuver permitted use of the stomach and upper intestine for purposes of nourishment. The postoperative course constituted a long, hard seige, but the patient survived the acute symptoms and the intestinal tract finally resumed its normal function. Then came the problem of closing the large artificial fistula remaining from the intestinal drainage. This proved difficult but was finally accomplished, and the patient eventually made a complete recovery.

In the second experience a young married woman, in good general health, had a painful pelvic mass requiring operation. The operation revealed bilateral ovarian cysts with extensive adhesions and "chocolate" contents. There was no pus and no evidence of infection. The cysts were enucleated, and the abdomen was closed as usual. After operation intestinal paralysis and a low-grade peritonitis developed. The peritonitis increased, an acute nephritis developed, the patient went from bad to worse, and finally died in spite of peritoneal drainage and intestinal drainage and everything else that was done.

In studying over these two experiences the decision was reached to drain all cases of extensive endometriosis or of extensive adhesions suspicious of endometriosis, and this plan has been followed since with satisfaction. The results have been so uniformly good that since adopting drainage these cases are not dreaded, as they formerly were.

Not long after adopting the drainage rule in these cases, Dr. H. S. Crossen was called hurriedly one night to a hospital to see in consultation a patient who was then dying of peritonitis. A young married woman of prominent family had been subjected to operation for a troublesome pelvic mass. No pus was found and after the intra-abdominal work was finished the abdomen was closed with expectation of prompt recovery. The development of fatal peritonitis was a great surprise and shock to all concerned. Inquiry revealed that extensive dense adhesions were encountered in the operation and also some cysts having typical "chocolate" contents.

In another instance a colleague inquired abruptly, "Do you drain in all cases of endometriosis?" On receiving the reply, "In all cases of any extent," he stated, "I wish I had," and then related the details of a case of endometriosis in which the patient had just died of postoperative peritonitis.

Since the advent of the antibiotics our ability to counteract the peritonitis is enhanced, but in extensive cases drainage for the first few postoperative days is still advisable.

Dean reports six cases in which rupture of an endometrial cyst resulted in an acute abdominal emergency, and O'Loughlin and Sheehan report a death in a twenty-six-year-old patient from spontaneous rupture of an endometrial cyst.

McGuff et al. reported three cases from the Mayo Clinic and reviewed thirteen from the literature in which endometriosis was the cause of ileal obstruction.

Sampson was the first to point out that carcinoma of the ovary may originate in an endometriosis of the ovary, and Teilum was able to demonstrate the actual transition from benign endometriosis to adenocarcinoma. Recently Corner et al. collected three cases from the records of the Boston Free Hospital, and they were able to collect only eight undoubted cases from the literature.

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Chapter 12
MALFORMATIONS

The growth of an organ may be arrested, or it may develop normally and then degenerate, or it may develop in an abnormal way. In any case there results a malformation. Most genital deformities are due to partial arrest of development, and to understand them it is necessary to have clearly in mind the way in which the organs develop.

POINTS IN DEVELOPMENT

The first structures indicative of the genitourinary organs are the **wolffian ducts,** which appear in the embryo about the fifteenth day, and the **wolffian bodies,** which appear on the eighteenth day. These structures represent the future kidneys and genital apparatus. They lie on each side of the median line.

During the fourth week another duct appears near the wolffian body on each side. These are the **müllerian ducts.** The wolffian ducts go to form the excretory ducts of the genital apparatus in the male. The müllerian ducts go to form the excretory ducts of the genital apparatus in the female. A part of the wolffian body of each side finally forms the genital gland of that side, i.e., the ovary in the female and the testicle in the male.

At the end of the first month the middle part of each wolffian body shows thickening and proliferation, resulting in the formation of elevated bands called "genital ridges." These are the earliest traces of the genital glands. For a few days they remain indifferent. Very soon, however, a difference in the two sexes is noticed. The primitive female gland "possesses a large number of the primitive sexual cells and evidences a tendency of its elements to arrange themselves into groups, in which the large primitive ova become central figures." The primitive male gland, on the other hand, shows a tendency to the formation of a network of cell cords—the forerunners of the seminiferous tubules. "Microscopic examination of the sexual primitive glands even at the end of the fifth week is capable of distinguishing the future sex of the being." In a short time there is a difference in the gross appearance of the gland, with a difference in the arrangement of the ducts.

The parts played by the wolffian ducts and müllerian ducts differ in the two sexes. In the **female** the müllerian ducts are the most important. The lower portions of the ducts of Müller become fused and form the vagina and uterus, and the upper portions remain separated and form the fallopian tubes (Figs. 921 to 923). The lower end of the vagina is formed from the