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ENDOMETRIOSIS

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INTRODUCTION

Endometriosis is the occurrence of endometrium-like tissue in such locations as the ovary, recto-vaginal septum, uterine wall, and various other extrauterine sites. Endometriomata are tumors, usually cystic in character, which are lined with endometrium or tissue resembling endometrium both physiologically and morphologically. The term endometrioma is synonymous with such terms as endometrial adenoma, mullerianoma, "chocolate" cyst, hemorrhagic perforating cyst of the ovary, Sampson's tumor, and adenomyoma. Such tumors have been recognized since 1893 with a few scattered cases previously reported but most of the investigation and classification of such tumors has been accomplished since 1921. A great deal of experimental and clinical material with varying and often confusing contents has been published but such work has at least led to a critical and thorough analysis of the subject. Authorities and case analyses agree to a great extent on the clinical evidences and treatment of such a pathologic state but there is considerable controversy as to the pathology and especially the etiology of this disease. In this discussion I shall endeavor to present a composite picture of the various types of endometriosis derived from reference to writings of a number of leading authorities with special emphasis on the etiology which will be taken
up last, as there are many factors of the pathology, symptomatology and treatment which have a bearing on the probable cause.

HISTORY

Rokitansky is given the honor of being the first to describe an adenomyoma as a clinical entity in his report in 1860 describing a case of a uterine fibroid containing epithelium. In 1884 the next report of such a nature was made by Gresskoff, Shroeder, and Herr on a series of 200 cases of adenomyomata of the uterus collected from case reports throughout western Europe. This was followed by a report of a series of such cases of uterine adenomyomata by Von Recklinghausen in 1893, and in 1896 he published his report along with his theory that such tumors were derived from embryonal tissue and were of mesonephric origin. He was the first to demonstrate the similarity between the tissue of this type of tumor and the tissue lining the uterine cavity. In 1896 Cullen also reported a series of cases and brought forward his theory that such tumors in the uterus and tubes were the result of direct invasion by the endometrium. In this same year he also reported a case (5) of his in which an adenomyoma was removed from the round ligament, and thus he was the first to definitely identify endometrial tissue springing from some point outside of the uterus. Two years later he published a further
report of this case and stated his theory that the glands might be due to an abnormal embryonic deposit of Muller's duct. At about this time Robert Myer of Berlin published reports agreeing with Cullen's theory for derivation of uterine adenomyomata by direct invasion of endometrium but suggesting that Von Recklinghausen's work gave a plausible etiological factor for formation of adenomyomata other than in the uterine and tubal walls. In 1897 S. Iwanoff brought forward the suggestion that such uterine tumors might arise from the pelvic peritoneum, a theory which was known as the serosal theory. In 1898 Fraenkel contributed much to the pathological and histological study of these tumors. Russell (31) of this country published his work in April, 1898, the first in American and English literature, referring to a case reported by Burkhard in 1896 and describing the finding of "aberrant portions of the Mullerian duct in the ovary". This was the first report of such a tumor in the ovary. He stated his theory at this time that such cysts of the ovary arose from the ingrowth of germinal epithelium into the ruptured graffian follicles with subsequent epithelial and connective tissue changes. In July, 1898, Von Franque reported a similar case of removal of such a tumor from the ovary. A few scattered cases were reported during the next 20 years. Cullen in 1909 (5) was the first to describe a case of endometriosis of the umbilicus and in 1917 (7) gave an
excellent description of endometriomata of the recto-vaginal septum. Lockyer (23) gave the first report in American and English literature of such tumors of the recto-vaginal septum in 1913. In 1919 Casler (3) described a case in which a patient after removal of the uterus and one ovary continued to menstruate from the vaginal vault. Four years after the first operation the remaining ovary began to enlarge and was removed showing presence of an endometrial cyst which had given rise to the vaginal hemorrhage at the menstrual periods. It is interesting to note that most reports at this time showed the finding of extra-uterine endometrial tumors to be rare, and in description of the distribution of such tumors the ovary was seldom mentioned. Presumably the thousands of cases in which aberrant endometrium occurring in the ovary escaped recognition since later studies show the ovaries to be a common site for such "implants".

In 1921 J. A. Sampson revived Russell's work and gave his revolutionary theory of the transplantation of endometrium during menstruation thru the fallopian tubes to the ovary and from the ovary to the pelvic peritoneum. He correlated much of the previous works and showed the relationship or similarity of the adenomyomata of the uterus and the endometrial adenomata outside of the uterus with emphasis on the "chocolate" cysts of the ovary. His work
again revived interest in the subject which has brought much of the present knowledge of the subject. Mestitz and Halaban in 1924 stated their theory of migration of endometrium from the uterus to the ovaries and peritoneum by way of the lymphatics much like the spread of a malignant growth. Schiller's later view was that these cystic tumors arise by metaplasia of the lymphatic endothelium at the site of the tumor.

Each of these theories prospered for a time as they were presented but were soon subjected to criticism and ridicule resulting in much confusion and difference in opinion. At present only two or three of these theories are widely accepted as possible causes of the disease but this wide interest and extensive clinical and experimental research has at least made the profession conscious of endometriosis as an entity. The tumors are more widely recognized and their greater incidence is appreciated by most gynecologists but few cases have been reported by the general surgeons.

PATHOLOGY

Uterine Wall and Fallopian Tube:

The tumors in the walls of the uterus are found most commonly in the fundus and in the cornua, and in the case of the tubes are most common in the distal third. Grossly they are typical adenomatous tumors presenting many cryptic
spaces surrounded by connective tissue and smooth muscle tissue, and usually containing a brownish thick substance resembling old blood. These tumors do not usually cause much change in the size nor shape of the uterus but may appear as oval masses protruding into the uterine or tubal cavity or appearing on the outer surface especially in the thinner walled tube. On section these adenomyomata appear to contain a number of small cavities which give off many smaller glandular processes. Microscopically the cavities are lined with a single layer of columnar epithelium, occasionally ciliated and containing many small granules in the case of the tubal tumors. Beneath the epithelium is a vascular and loosely cellular connective tissue of varying depth closely resembling the connective tissue of the stroma of uterine lining. The stroma of the tumor is surrounded and divided by a thin layer of more dense connective tissue. The entire structure is contained in a mass of smooth muscle which according to Dougal (9) differs from the structure of a uterine fibroid only in the fact that the muscle tumor is not encapsulated. Cullen in his report in 1896 which was later confirmed by the work of Robert Myer and others showed that in many cases these endometrium-like growths in the muscular uterine wall were directly connected to the endometrium lining the uterine cavity, the endometrium apparently having penetrated its
underlying membrane giving rise to the glandular epithelial ingrowths.

Ovarian:

The ovarian endometriomata are most commonly found on the lateral and inferior surfaces of the ovary and appear as small minute to much larger bluish or purplish cystic ovoid masses. The average size is 2 to 4 centimeters in diameter. They usually lie very near the surface but may be deeper in the tissue. On section these tumors are found to be composed of thin walled cysts containing a brownish thick fluid. Microscopically the cavity is found to be lined with cuboidal to columnar epithelium ranging from a single layer to pseudo-stratified epithelium, and may present a ciliated appearance. The epithelium is surrounded by a layer of vascular, cellular, and loose connective tissue which in turn is surrounded by a denser layer of connective tissue. The epithelial lining in most cases is invaginated giving a number of small tortuous glands resembling uterine glands. Sampson (33) gives a thorough description of these tumors in his report entitled "The Life History of Ovarian Tumors of Endometrial Type". He states that "during menstruation there is a hemorrhage into the tissue surrounding the endometrium lining the cyst. Blood partly escapes into the cyst by perforation of the epithelial lining leaving a denuded area. Later there may also be an invasion of the cystic cavity and stroma by endothelial leucocytes. This gives rise to a pigmented
lining of a hematoma without an epithelial lining which might be confused with a hemorrhagic corpus luteum cyst, the leucocytes being mistaken for luteal cells. The repair process now takes place by growth of hyalin fibrous tissue arising in the stroma of the denuded lining of the hematoma and growth of epithelium over the denuded area from the remaining endothelium. The contents of the hematoma consists for the most part of red blood cells, cast off epithelium, parts of the stroma, and leucocytes. This picture varies with the relation of the time of observation to the date of menstruation. With enlargement of these cystic tumors with hemorrhage during menstrual periods there is an associated increase in tension causing rupture and the ovarian surface then takes on a drawn, irregular, scar-like surface, or adhesions may form to adjacent structures.

Recto-Vaginal Septum:

The tumors at this site appear as bluish or purplish firm nodules in the septum between the anterior rectal wall and posterior vaginal wall. They vary in size from minute bodies to large masses obliterating Douglas' cul-de-sac, and the overlying peritoneum may be irregular and present or may be absent. Many of the larger tumors of this classification involve the rectal or vaginal wall or cervix of the uterus, but characteristically the overlying mucousa of these organs is not involved. The tumors are often asso-
associated with ovarian endometriosis and give rise to dense fibrous adhesions causing displacement of organs and even obstruction of rectum and ureters. On section and microscopical examination the growths appear much the same as those previously described.

**Broad Ligament:**

In this location the bluish nodule appears between the two peritoneal folds of the ligament usually near the uterus and resembles those previously described in structure. They are found to be closely associated with the veins and lymphatics although authorities differ as to the exact relationship. However this point has not been worked out clearly and is thought to be doubtful by many men.

**Round Ligament and Vulva:**

A rather superficial soft swelling is found in this location. The swelling may extend into the groin or vulva and appear as firm nodules. There is a gradual enlargement of the mass and the overlying area appears purplish. Due to rupture and extravasation of the cystic contents, fluid may pass into the vulva or up onto the lower abdomen. On section and microscopic examination the adenomata appear to be similar to those previously described.

**Umbilical:**

At this site there is a soft protruding bluish brown mass which lies just below the skin. The overlying skin is intact but may be irregular, rough and pigmented. On sec-
tion and close examination these tumors are much like those previously described and in several cases even a few smooth muscle fibers have been found. The growth extends through to the peritoneum which in two cases appeared to be dimpled immediately beneath the adenoma and was found to be made up of cells ranging from low cuboidal to columnar. This abnormal peritoneum extended towards the glandular tumor as an elongated process or cone.

**Cecum, Sigmoid, and Vermiform Appendix:**

In a number of cases endometrial adenomata have been found in the walls of the cecum, sigmoid, ileum, and vermiform appendix which resemble closely endometriomata found in the ovary and pelvic peritoneum. They appear as firm, protruding growths of varying size in the wall of the viscous causing a moderate constriction of the lumen. On section a number of small cystic cavities and glandular processes are found in the muscular wall, causing a thickening of the wall at this point. With closer observation the spaces are found to be lined with a single layer of columnar epithelium which is surrounded by a very vascular and highly cellular loose connective tissue. The spaces are usually filled with cellular debris and red blood corpuscles.

**Laparotomy Scar:**

A reddish or bluish tumor at the site of a previous abdominal incision is characteristic of an endometriomata
of the abdominal wall. It is a firm mass lying just beneath the true dermis and not adherent to any abdominal organs. On section this adenoma appears to be similar to those previously described. It is usually attached to the deep fascia but may extend through the entire thickness of the abdominal wall.

Generally speaking, in order to classify a new growth as an endometrioma, the necessary characteristics are: the arrangement of the tissue in a number of cystic cavities of varying size with many small cryptic or glandular branches; the observation of a single layered and sometimes ciliated columnar epithelium lining the cavities; and a loosely cellular and vascular connective tissue stroma. There is usually a pigmentation of the stroma, and the cavity contains cellular debris and old blood. This tissue varies in appearance with the time of observation in relation to the time of menstruation. The tissue may demonstrate other changes similar to that of the uterine mucousa as decidual changes during pregnancy and atrophy with cessation of ovarian function. Theodore Doderlein has recorded a remarkable instance of a pregnancy within the cavity of an adenomyoma which chanced to be connected with the uterine cavity by a narrow isthmus. These tumors tend to increase in size slowly and if in more elastic tissue will rupture and produce adhesions binding it to adjacent organs or peritoneum.
CLASSIFICATION

The classification of endometriomata has been a difficult task due to the great number of synonymous terms in use and because of the lack of clarity as to the origin of the growths in their various sites. This classification is offered in which the endometriomata are arranged according to anatomical site and also according to the probable etiological relationship.

A. Intrauterine and tubal:—strictly speaking, this class includes only the adenomyomata obviously arising from ingrowths of normal endometrium and surrounded by a muscle tumor.

1. Uterine.
   (a) Fundal.
   (b) Cornual; most common.

2. Tubal.

B. Extrauterine:

1. Intraperitoneal.
   (a) Ovarian.
   (b) Pelvic Peritoneum.
   (c) Anterior and posterior surfaces of uterus.
   (d) Intestinal:—ileum, cecum, vermiform appendix, sigmoid, and epiploic appendix.

2. Extraperitoneal.
   (a) Recto-vaginal septum, rectum and cervix.
   (b) Broad Ligament.
(c) Round Ligament:-groin and vulva.
(d) Umbilical.
(e) Vesicular.

3. Transplants:-direct transplantation of endometrium due to manipulation.
(a) Laparotomy scar.

INCIDENCE

The incidence of endometriomata was not formerly thought to be very great and was, in fact, considered a rare finding. In the past 15 years and especially since the stimulating writings of Dr. Sampson the occurrence has been found to be much higher, probably due alone to the fact that surgeons, diagnosticians and pathologists are aware of the symptoms and pathological picture and recognize the condition as such. Sampson (36) early pointed to a high incidence and in 1927 made the statement that he had found endometriomata in 43% of the women between the ages of 30 and 50 years who had undergone abdominal operations under his observation since 1921, and that he thought the incidence to be between 10% and 20% of women between 30 and 50 years of age. Dougal (9) a British gynecologist makes a more conservative estimate when he states that in his practice 12% of abdominal surgery in women of active sexual age was done for the presence of endometriomata. Judd and Foulds reported in 1923 that since January 1, 1911, there had been
494 patients operated on at the Mayo Clinic for the presence of endometriomata while during the same period 5970 patients were operated for fibroids. A further comparison by Hill (13) of Richmond, Virginia, for four years from 1927 to 1931 reports that an incidence of 135 cases of aberrant endometrial tissue was found in 1100 operations for pelvic diseases. In comparison with these figures the following common pelvic diseases were found in these same patients over the same period:

Total cases: 1100 patients operated.

Endometriosis--135 cases.
Uterine fibroids--497 cases.
Chronic salpingitis--280 cases.
Uterine displacements--202 cases.
Cystadenomata of ovary--40 cases.

Janney studied 4853 ovaries which had been removed for conditions not specifically ovarian and found 3 cases of endometriosis. It is thus seen that although it is not as commonly found as some of the pathological conditions yet it is not a rarity.

Recently more exact records have been compiled as to relative incidence of endometrial adenomata in the various common sites of occurrence. Keene and Kimbrough (17) of Philadelphia offer a study of 118 cases operated in the past two years with the following location:
Ovary: 110 cases.
  Unilateral--63 cases.
  Bilateral--47 cases.
Recto-vaginal: 6 cases.
Umbilicus: 2 cases; 1 also ovarian.
Laparotomy scar: 1 case.

Dougal (9) of London offers the following record of his cases:
  Diffuse: 6 cases.
  Cornual: 6 cases.
  Ovarian: 44 cases.
  Recto-vaginal: 44 cases.

He further states that 34 of the cases showed both ovarian and recto-vaginal endometriomata at the same time.

Sampson (34) previously made a similar observation in 1922 when he stated that in 37 cases of ovarian endometriosis with evidence of perforation, pelvic peritoneal endometriosis was found in all but one case and in the 3 ovarian cysts without evidence of perforation no peritoneal "implants" were found. He further points out that the pathology of the pelvic peritoneum varies with the size of ovarian cysts and extent of perforation.

W. W. King (21) of Sheffield, England, writes that classification of endometriomata as to anatomical position is difficult because they are often multiple and in his series classifies them according to the organ most involved:
Recto-vaginal: 52 cases.
Pelvic peritoneum: 26 cases.
Ovaries: 23 cases.
Uterus: 17 cases.
Tubes: 4 cases.

Hill (13) reported on 135 cases operated in Richmond, Virginia, in the past four years with the following distribution:

Ovary: 99 cases.
Tubes: 20 cases.
Adenomyomata of uterus: 21 cases.
Anterior and Posterior surfaces of Uterus: 8 cases.
Rectum and Sigmoid: 7 cases.
Cul-de-sac: 5 cases.
Appendix: 4 cases.
Cecum: 2 cases.

From observation of these statistics the ovary is found to be the most frequent site of "implantation", which may be bilateral or unilateral. The second most common site appears to be the recto-vaginal septum with the peritoneal endometriosis coming next in frequency. The adenomyomata of the uterus and tubes are next most frequent sites of occurrence with the more distant sites, as broad and round ligament and umbilicus, being fairly rare. Least commonly, the more invasive extension of
the growths of the individual organs as in the rectum, sigmoid, appendix, vagina, laparotomy scar and cervix are rarely found. Naturally this disease due to its symptomatology and sites of occurrence would be more commonly detected by gynecologists but the very few cases reported by general surgeons during abdominal operations leads to the conclusion that the disease is often overlooked and may exist in many cases with no great discomfort to the patient at the time.

SYMPTOMATOLOGY

The symptoms caused by the presence and invasive growth of endometriomata vary greatly due to the difference in site, size and extent in each case. The pathology may be present without any symptoms and again may give rise to a very complicated and complex series of symptoms. There are a number of factors common to endometriomata in all sites of occurrence which may be applied to these tumors generally.

1. Age Incidence:

It is generally stated that endometriosis occurs usually during the period of ovarian activity. There have been no cases reported of the presence of endometriomata found in the embryo or in girls before the onset of menstruation, and few cases have been reported after menopause. In the series of 110 cases reported by Keene
and Kimbrough (17) the youngest was 22 years and the oldest 60 years of age. The incidence by decades showed the following facts:

- 20 to 30 years -- 18.6%
- 30 to 40 years -- 49.1%
- 40 to 50 years -- 24.4%
- 50 to 60 years -- 6.8%

2. Sterility:

The extensive alterations resulting from the lesion itself as well as the complicating abnormalities render sterility a prominent factor. Keene and Kimbrough report that 70% of the women operated on for endometriosis were married and in the active ovarian period of life. Of this 70%, 40.9% were sterile. Of those who had borne children, the average period of time since the birth of the last child was 9.5 years. Smith (39) reports sterility in 20.6% of his patients with endometriosis and Shirer an association of 84.2%. In Donald's (8) series 50% were sterile and only one patient had given birth to more than four children.

3. Menstrual Abnormalities:

According to Keene and Kimbrough, (17) ovarian dysfunction per se is not the cause of menstrual abnormalities. In their series of cases they report no disturbance in 41.5%; menorrhagia in 44.1%; metrorrhagia in 8.4%; scanty flow in 2.5%; amenorrhea in 1.7%; and post-meno-
pausal amenorrhea in 1.7%. In their report the cases showing menorrhagia consisted of 48 patients of which number 32 showed presence of uterine fibroids, so that in only 16 of these could the symptom be ascribed to an ovarian dysfunction. Donald, Smith, and Shirer were also reluctant to attribute menstrual irregularities to the ovarian involvement, but rather classified it as a symptom of a complicating finding and not the endometriosis. King (21) states that menorrhagia was present in over half of the cases of uterine adenomyomata without other apparent cause and 25% of extrauterine endometriomata showed similar excessive loss of blood without other apparent complicating lesions. Thus in one fourth of his cases menorrhagia was present with no other cause than an extrauterine endometriomata showing that some ovarian factor may be present.

Dysmenorrhea is a common symptom of endometriosis and Keene and Kimbrough report this symptom present in 49.1%. This was a history of acquired of increasing dysmenorrhea, the pain being premenstrual in type and persisting thru the first day or two of menstruation. W. W. King states that dysmenorrhea was present in over half of his cases, generally spasmodic in type, sudden in onset, and in a patient who has been previously free from pain. This pain during menstruation might also be due to complicating pathology, as a retroversion or pelvic adhesions are commonly found, but the characteristic finding is the fact that it is an acquired symptom usually with a
definite onset.

4. Abdominal Pain:

This is a very indefinite symptom and there is nothing characteristic about it in this disease. However there is a lower abdominal pain in over half the cases, and is of a shooting or aching type, usually worse during menstruation. The onset of the pain may be acute and accompanied by nausea and vomiting. The pain varies according to the structures involved and the degree of extension of the tumor. The intermenstrual pain may be entirely absent or amount only to a lumbo-sacral backache or discomfort.

5. Dyspareunia:

This symptom is especially present in the cases of endometriomata of the recto-vaginal space, cervix, and vagina. However it was present in 57% of Donald's cases and in 8% of King's cases.

6. Associated Pathological Manifestations:

The presence of a complicating disease is a striking feature in endometriosis. Keene and Kimbrough (17) found uterine myomata in 55.4%; chronic salpingitis in 20%; and adherent retroflexion in 14.5% of their cases. W. W. King (21) reported myomata in 22%; adherent retroversion in 21%; and evidence of previous inflammation in 39.7%. G. V. Smith (39) reported myomata in 41.6% and adherent retroversion in 25.8%. Most authorities agree on
this interesting finding and J. A. Sampson lays special stress on this factor as favoring his theory of transplantation of sloughed endometrium at menstruation, as this pathology favors back flow.

**Predisposing Factors:**

As seen above, inflammation and obstruction to menstrual flow may be a factor, or as indicated by the presence of fibroids in a large number of cases, there may be some factor causing abnormal growth of tissue. Dougal (9) reports that in his cases 10% had undergone curettage of uterine mucousa for various reasons. In cases of endometriosis in a laparotomy scar there is usually a history of a cesarian section, uterine suspension, or other operations involving the uterus.

For convenience, the symptomatology will be taken up separately for the various sites of "implantation". It will be seen that the symptoms vary greatly but that a constant valuable aid is usually obtained in the fact that the symptoms are intermittent and directly associated with the menstrual cycle.

I Intrauterine and Tubal:

These are the true adenomyomata containing endometrial tissue and present symptoms very similar to uterine fibroids. The patients complain of menorrhagia, dysmenorrhea, and occasionally metrorrhagia. On examination the tumor mass may be felt causing an irregularity
in the surface and enlargement of the uterus or tube. Unless the cystic cavity be entirely cut off from the uterine cavity, the enlargement is slow and few symptoms are presented. However if the contents of the cyst is retained the growth may be rapid.

II Extrauterine:

A. Intrapерitoneal:

(1) Ovarian:

The endometriomata of the ovary in many cases are minute, slow growing, and often are symptomless being discovered only during an abdominal operation for another disturbance. However with increase in the size of such tumors there may be a menorrhagia, slight lower abdominal pain or low backache, and dysmenorrhea especially during menstruation. Due to the frequency of associated pathology the symptoms of uterine retroversion or myomata may be the predominating complaints. The ovarian cysts tend to rupture and initiate formation of extensive pelvic adhesions. Thus on vaginal examination a small adherent ovarian cyst may be detected or a slightly tender and densely adherent ovary palpated.

(2) Pelvic Peritoneum:

The symptoms here also vary greatly with the
size and extent of the growth. In the case of a few small scattered nodules there may be no symptoms. They are commonly found in association with ovarian endometriosis and usually are associated with uterine retroversion and myomata. They may present the general symptoms of endometriosis and on vaginal examination a tender, adherent adenexial mass may be felt on one or both sides of and blending into the partially fixed uterus. Typical of the lesions are nodules palpated in the cul-de-sac.

(3) **Anterior and posterior surfaces of the uterus:** Endometriosis of the anterior and posterior surfaces of the uterus present much the same picture as the similar tumors of the pelvic peritoneum, and on palpation firm, tender nodules may be felt at these sites. They may be confused with subserous fibromyomata but are usually less firm and smaller.

(4) **Cecum, appendix, ileum, and sigmoid:** As will be noticed these sites of intestinal endometrioses are located in the lower abdomen and might easily be extensions of peritoneal implants to involve these deeper structures, and for this reason are taken up at this time. They are usually found in association with
ovarian or peritoneal endometriosis and most of them give rise to symptoms. The intestinal symptoms may be preceded by those caused by the accompanying peritoneal or ovarian symptoms or may set in as an acute intestinal picture. These intestinal attacks are usually just premenstrual in time or during menstruation, but in a few cases the attacks have been irregular and intermenstrual in type. These attacks are usually relieved spontaneously in one or two days but tend to recur, each succeeding attack being more severe and lasting longer. The patient may show a slight degree of toxicity and low grade fever from intestinal absorption of toxic products. The clinical picture presented is similar to a partial intestinal obstruction or an acute appendicitis with constipation, severe and colicky pain in the abdomen with an acute onset. On observation during operation there is a firm usually band-like area of tissue found in the muscular wall of the intestine causing constriction of the lumen at this point. The intestinal mucousa and submucousa is not involved. Adherent ovarian are usually found during examination of these patients.
B. Extraperitoneal:

(1) Recto-vaginal septum, Cervix, and Rectum:
The endometriomata at these sites may exist as independent entities but they are usually associated with similar lesions of the ovary and peritoneum. They give rise to no symptoms at first but with growth and invasion they usually cause a feeling of pressure or fullness of the rectum, painful defecation, and tenesmus, and bleeding from the vagina or rectum coincident with menstruation, and relieved during the intermenstrual period. Menorrhagia is usually present. With further growth the tumor may completely block off the rectum or ureters. There may be accompanying general symptoms of endometriosis as previously described. On vaginal examination small, firm, tender nodules are easily detected and may involve the posterior vaginal wall, cervical or rectal wall but the mucousa of these structures are not adherent, and appear normal. The growth may extend laterally giving densely adherent masses in the adenexia.

(2) Broad Ligament:
This type of endometriosis is not found very frequently and like the previous types may be symptomless. With growth and invasion, however,
tumors in this location may give rise to the general symptoms of endometriosis. There are no characteristic findings of an endometrial tumor at this site. On vaginal examination an adherent firm, tender mass is felt in the adenexia.

(3) Round Ligament:
At this site the growth may be a small, firm, bluish nodule which is visible in the groin which may extend down into the labia. Occasionally the tumor mass may be located in the round ligament higher up. It is usually symptomless but is noticed to increase in size and tenderness during menstruation. Rupture of this cystic tumor gives rise to an extravasation of a dark brownish thick fluid which pushes up beneath the skin, giving a bluish discoloration to the skin over the lower abdomen, groin or labia.

(4) Umbilical:
An umbilical endometriosis is not a common finding and usually presents typical symptoms. It appears as an irregular, nodular swelling just beneath the dermis in the umbilicus. This mass is slow in growth and reaches full size in from six months to a year. It usually becomes swollen
and painful during menstruation and may dis-charge a brownish fluid resembling old blood. The overlying skin is irregular and often pig-mented, and the growth extends entirely through the abdominal wall.

(5) Vesicular:
Involvement of the bladder by endometrial tu-
mor is very rare and probably arises from in-
vasive growths of peritoneal implants. They present few symptoms unless accompanied by ovarian or peritoneal endometriosis. There may be blood in the urine and tenesmus during men-
struation and on cystoscopic examination a bluish to reddish nodule, resembling a blue dome cyst of the breast, is seen on the poster-
ior or superior bladder wall with normal overly-
ing mucousa.

C. Transplants to Abdominal Wall:
(1) Laparotomy scar:
The endometrial tumors in laparotomy scars are becoming more frequent and are usually a defi-
nite entity and easily diagnosed. In this case a definite etiological factor is found in the fact that such tumors appear within six months to two years following an abdominal incision and usually following some operation involving
the uterus as a suspension or salpingectomy. This type of tumor is most commonly found following cesarian section and with the increase in frequency of such operations the incidence of endometrial transplants to the abdominal wall might be expected. These tumors also may be accompanied by similar endometrioses in the ovary and pelvic peritoneum. They appear as flat masses attached to the deep fascia or extending through the entire thickness of the abdominal wall causing pain, swelling and bloody discharge during the menstrual period. During their earlier stage they appear as tender fixed masses and on palpation are often confused with an incarcerated omental herniation.

Diagnosis:

Endometrial tumors show a wide variation in symptoms which are dependent on several factors chief among which are the extent of the lesions, particularly the invasion of adjacent structures plus the complicating pathology. The clinical picture as a whole rather than isolated symptoms leads to a correct diagnosis. Such a symptom complex of subjective findings as the following may be presented:

1. Age--between 22 years and menopause.
2. Sterility--relative or absolute.
3. Abnormal menstruation, usually menorrhagia.
4. Acquired dysmenorrhea.
5. Dyspareunia.
7. Intermenstrual lower abdominal pain with increased discomfort during menstruation.
8. Pain in the rectum or bladder with direct relationship to menstruation.

Objective findings likewise vary with the extent and nature of the lesion but in the presence of ovarian endometriosis, well developed peritoneal implants, or a combination of the two, observations are fairly uniform. The common findings are adherent, tender, firm masses in the adenexia, adherent cystic ovaries, and nodular masses in the cul-de-sac which may involve the rectal or cervical walls but the overlying mucousa is not involved. Tumors of the umbilicus, laparotomy scars, round ligament, etc., give characteristic findings and symptoms.

COMPLICATIONS

Due to invasion and growth of endometrial tumors obstruction of the rectum and ureters may be caused with the usual results. Upon rupture of large endometrial cysts, the cyst contents are very irritating to surrounding tissue causing formation of dense adhesions with resulting adherent retroversion of the uterus.

Sterility is a common finding in these patients but whether it is a result of the pathology presented or whether they are both due to the same etiological factor as endocrine disturbance is not known. Grunbaum made a
comparison of statistics of sterility in patients with uterine myomata and patients with endometriosis and found that in the case of myomata 20% to 25% showed sterility while in cases of endometriosis 68% were married and 48% of these were relatively or absolutely sterile.

The relationship of endometriomata and malignant growths is of little importance. In only one or two of the vast number of cases and microscopic reports has there been any definite evidence of malignancy of such endometrial tumors. They may be confused with malignancies in diagnosis but in the opinion of such authorities as Sampson, Novak, Lockyer, Myer and others there are few of these tumors which become malignant. Robert Myer states that the fact that the endometrium breaks through the basement membrane in the case of direct invasive growths into the uterine wall is not an indication of malignant growths but that this infiltrative behavior of the mucousa is due to a lack of true submucousa in the tubal and uterine wall.

The relation of endometriosis to pregnancy is of interest but of minor importance. During pregnancy endometrial tumors usually increase in size rapidly due to decidua formation within the tissue of the growth. Micholitsch of Vienna contends that adenomyomata of the fallopian tubes resulting from direct invasion of the wall by tubal mucousa leaving an open isthmus would increase the frequency of tubal pregnancies and demonstrated an early example of
such a case in one of his patients. Theodore Doderlein showed a similar case in an adenomyomata of the uterus which contained an embryo and placenta.

TREATMENT

Ovarian function is necessary to the activity and proliferation of all lesions included under endometriosis. Conversely, cessation of activity and progressive atrophy follow ablation of this function. The treatment of this condition should be in this line therefore for permanent arrest, whether surgical or by irradiation, but since this is a disease usually found in younger women the treatment is often perplexing.

Keene and Kimbrough (17) give the results of their treatment of 48 patients in which one or both ovaries were conserved and only two cases have had subsequent pelvic disease, one a retention cyst of the conserved ovary and the other a transplant in the vaginal vault. In 21 patients whose menstrual function was preserved, irregularities in bleeding occurred but once. Of 14 married women in whom the child-bearing function was preserved and who were operated on a year or more ago, 28% have had a normal pregnancy. Ovarian lesions showed a 95.8% cure in the cases of excision of the tumor mass only leaving the remainder of the ovary. Such treatment is preferable as such a sudden removal of ovarian function is very distressing to a young patient.
The more conservative treatment should be practiced when possible. This consists of removal of the endometrioma itself either by cauterization or incision. This method should be used in cases of small ovarian adenomas that can easily be excised, and minute superficial peritoneal implants that are easily destroyed by cauterization or incision. Small peritoneal implants increase in size very slowly and therefore may be allowed to go untreated, if necessary. In the case of endometriosis of the rectovaginal septum, in which the nodules are small and not invasive, surgical removal is indicated. Radiation with radium or X-ray or both is of value in these cases previous to operation to prevent the formation of a rectovaginal fistula. In the case of endometriosis of uterus, umbilicus, round or broad-ligament, vesicular, or laparotomy scar wide surgical excision is indicated.

Radical treatment is indicated in many cases where large ovarian or peritoneal endometriomata have invaded the surrounding organs and have become densely adherent. A bilateral oophorectomy is advisable but incision of the diseased area is rarely necessary. Incident to the cessation of ovarian function a gradual regression occurs, a process which may take months. If the intestine is obstructed the operators may take advantage of the atrophic process by doing a temporary colostomy, which may have to be done before the oophorectomy. Surgery is the procedure
of choice in the treatment of symptomatic intraperitoneal lesions and irradiation with X-ray or radium should be resorted to only in rare instances. Few cases of improvement have been reported in the treatment by the use of irradiation.

In cases of extensive adhesions and large ovarian cysts with gross lesions of the uterus, a bilateral oophorectomy and hysterectomy is the operation of choice. Adenomyomata of the uterus should be treated by hysterectomy with conservation of the ovaries.

Associated pathological findings as uterine retroversion or fibroids should be searched for and corrected at the time of operation.

ETIOLOGY

As in the case of most neoplasms, the etiological factors of endometriosis are not fully understood. Many theories have been presented but no one theory seems to apply to these tumors in all cases. An endometrioma is a benigend tumor with the power of invasive growth and apparently transplantation. It contains an epithelium which resembles endometrium both morphologically and physiologically. This similarity has led those studying the condition to attempt to account for this presence of misplaced endometrium in many ways. The most prominent and reasonable theories will be discussed at this time with the opinions of other authorities concerning them. These hypotheses may
be classified according to the period of life during which they are thought to arise:

1. Developed from embryonal tissue: - dystopic.
   (a) From Wolffian duct or body.
   (b) From Mullerian duct.

2. Postembryonal development: - heterotopic.
   (a) From the serosa--serosal theory.
   (b) From lymphatic endothelium.
   (c) From atretic Graffian follicles and corpora lutea.

   (a) By way of the Fallopian tubes.
   (b) By way of the veins.
   (c) By way of the lymphatics.
   (d) By direct invasion from uterine mucousa--primary.

**Dystopic theories.**

The Wolffian theory was one of the earliest proposed, being stated by Von Recklinghausen in 1896. It proposes that endometrial adenomata arise from embryonal rests or inclusions of the Wolffian duct or body. Von Recklinghausen first presented this theory concerning the origin of the adenomyomata of the uterus from the mesonephros and mesonephric ducts and went so far as to describe the glandular structure of the tumors as similar to the arrangement of the mesonephric duct, the collecting tubules, and the
glomeruli. He maintained that these tumors were abnormal embryonal inclusions of the Wolffian duct and body in the wall of the uterus and other previous sites of formation. The mesonephros and mesonephric duct arise embryologically from the previously formed pronephros and pronephric duct in the urogenital fold. This tissue is retroperitoneal, located in the posterior portion of the body and bulging into the coelomic cavity. It extends from the seventh segment caudally but the cephalic portion of the pronephros soon disappears and the caudal portion persists and develops. Certain structures are normally formed from this body many of which are only vestigial in nature in the adult female. Among these structures are the epoophoron, the paroophoron and Gartner's duct. The inguinal fold is a thin fold of tissue which connects the inguinal crest (inguinal ligament) and the caudal portion of the urogenital fold in the embryo and it later becomes the round ligament of the uterus.

This theory might therefore serve to account for the occurrence of tumors at certain sites such as the round ligament, broad ligament, and uterus but this theory fails to account for the similarity of the tissue to endometrium. On further close examination of these tumors and with serial sections, the arrangement of these cystic and glandular cavities are not found to be regular nor to resemble the mesonephros. This theory has therefore been generally disregarded since 1900.
The Mullerian theory was first offered by Cullen as an explanation for the origin of the extrauterine endometrioses. This is also a dystopic theory or one of embryonal origin by inclusion or arrest of the tissue of parts of the Mullerian duct. This duct arises by an infolding of the coelomic endothelial lining on the lateral surface of the urogenital fold and forms the fallopian tubes, uterus, and vagina. In this case little or no part of the duct undergoes retrogression in the female and the opportunity for embryological displacement or rest would be decreased. It would not account for endometriomata in many of the sites of occurrence but presents a favorable hypothesis for the presence of endometrium-like tissue as this duct gives rise to such tissue normally. Embryological inclusions or rests have never been found in younger children or the embryo but this does not mean that the potential tissue is not present and the stimulating factor has not as yet caused growth which calls attention to the presence of such tissue. However this theory as an exact cause of such tumors has not been accepted for all cases.

**Heterotopic theories.**

The postembryonal development of endometriosis has been more seriously considered and offers many possibilities in regard to the etiology of these tumors. These theories present more the aspect of metaplasia of one type of tissue
to another. The first theory of this nature, known as the serosal theory, was presented by Iwanoff in his attempt to account for the presence of adenomyomata of the uterus which apparently arose from the peritoneal surface. He stated that such tumors were directly connected with the low cuboidal cells of the peritoneum and that they arose by metaplasia of these peritoneal cells. More recent study has led to the belief that Iwanoff was observing pelvic peritoneal implants which had invaded the posterior uterine wall giving rise to adenomyomata. Russell had somewhat the same idea in his theory in 1898 (31) in accounting for ovarian endometriosis when he stated that this tumor was due to the invagination of germinal epithelium into the ovarian tissue. He suggested that this tissue became pinched off from the parent tissues with subsequent metaplasia of the epithelium and surrounding stroma. Runge and Wolfe have recently showed a number of ovarian sections in which this very process is presented as well as cyst formations in various stages of their development. Professor Robert Myer later presented his theory that all endometrioses were due to metaplasia of the cells of the peritoneum under the stimulation of a chronic inflammatory process. According to his theory, the epithelium is derived metaplasia of the overlying peritoneal endothelium and the connective tissue derived from normal stroma made cellular and hyperplastic by chronic inflammation. Jacobson (14) in 1928 reported
similar experience in his observations that the low cuboidal cells of the peritoneum became cuboidal and even columnar under the effect of chronic inflammation. A number of cases of umbilical endometriosis have been reported (25) in which there seemed to be an extension of the underlying columnar celled peritoneum into the tumor mass suggesting serosal origin in these cases. Elizabeth Weishaupt suggested that endometriomata of the round ligament, groin, and vulva arose by metaplasia of the cells of the peritoneum of the diverticulum of Nuck (processus vaginalis), a vestigial structure in females which is a small diverticulum of peritoneum accompanying the round ligament thru the inguinal canal. This process, however, is found persistent in only a few cases. Walz and Heim later described a coelomic basal cell which is bi-potent, that is to say it is capable of forming two types of cells, serous and endometrial. Under the proper stimulation these partially undifferentiated cells might further differentiate into endometrium. This stimulation might be due to ovarian hormones or other endocrine secretions but it has not been isolated. Williams (43) describes the finding of small areas of subepithelial decidua especially on the ovaries and omentum during operations on patients during pregnancy and some authorities favoring the serosal theory interpret these findings as a response of these basal cells to the change in ovarian secretion during pregnancy. Lockyer (23 and 24)
added further to the serosal theory in his writings in which he points to the embryological fact that the Mullerian duct is derived from the coelomic epithelium of the urogenital fold. Thus the lining mucous membrane of the tubes, uterus, and vagina are derived from the same parent tissue as the pelvic peritoneum and especially the germinal epithelium, namely the coelomic epithelium. Thus the partially undifferentiated basal cells of the peritoneum and germinal epithelium might well be expected to have the power to differentiate into endometrium under excessive or abnormal endocrine function. Runge and Wolfe limited their concept of the serosal theory to the germinal epithelium. In their observation of apparently normal ovaries they found evidence of unfolding of the germinal epithelium into the ruptured Graffian follicles and subsequent growth of this epithelium and development of a subepithelial stroma. They show that both the germinal epithelium and the coelomic epithelium forming the Mullerian duct arise from the coelomic epithelium covering the urogenital fold. They reason that the basal cells of the germinal epithelium should be especially able to differentiate into endometrial cells and that due to the direct effect of ovarian hormones on this tissue implanted in the ovarian tissue, every factor for the serosal theory would be stressed.

Schiller's studies of these tumors have led him to be-
lieve that these endometriomata arise from the endothelium of the lymphatics by metaplasia of the tissue. In his work he states that these tumors occur in close association with the lymphatics of that area and in many cases are directly connected to the lymphatic endothelium. His observations have not been verified by any other investigators and have not been noticed widely. As will be later described, Sampson shows that the smaller venous vessels in the uterus have only a single endothelial wall and this may have confused Schiller in believing the tumors to be associated with the lymphatics.

This subject of metaplasia of one type of epithelium or connective tissue to another has been widely accepted especially in Europe, but recently has been much discussed. The tendency has been to discard the idea of actual change of tissue from one type to another but to attribute this change to the presence of some less differentiated parent tissue common to both types of tissue. This concept involves a process similar to normal differentiation in the embryo. Most embryologists hold to the concept that during embryological development a regular order of steps in differentiation takes place. At these times two or more types of tissue are derived from a common parent tissue, and in the belief of most authorities after this step is passed further similar differentiation of most tissue is not probable. However, at these critical periods of dif-
ferentiation, the more adult tissue may be produced and due to a displacement or failure in growth may remain undeveloped only to undergo rapid growth later in the life of the individual due to some stimulating factor, probably endocrine, similar to that which causes differentiation and growth in the embryo. There is also the possibility that some of the less differentiated tissue might remain in this state as in the basal cell layer only to undergo development to a more adult type of tissue. This type of theory is more acceptable than the concept that one type of adult tissue changes to another as is assumed in the idea of metaplasia. The reason that some tissue derived from a common parent tissue becomes endometrium and another part becomes serous epithelium is thought to be due to the presence of certain factors in the area as the stroma and blood supply, and also the general conditions during this set critical period for differentiation of such tissue. It is conceivable that such a set of conditions might again exist in adult life and growth of endometrium would take place from a less differentiated basal cell in the peritoneal lining. Thus a very plausible theory is set up by which these endometriomata might arise from the pelvic peritoneum by a combination of the serosal and embryological development theories.

The last theory under the classification of postembryological development was recently proposed by E. S. J.
King (19), of Australia, in 1931. He points out that these hemorrhagic tumors especially in the ovary have too readily been accepted as endometrial tumors, and he states that even morphological and physiological similarity of the tissue outside of the uterus does not imply identity. This similarity may be attacked in two ways:

(1) Presence of tissue resembling gastric glands in the gall bladder or squamous epithelium in the bronchus does not bring about the conclusion of identity nor transplantation but rather of misplacement or metaplasia. These same pathological principles should be followed in consideration of endometriomata.

(2) Other tissues obviously not endometrium may show the characteristics mentioned. Columnar epithelium undistinguishable from uterine epithelium by methods in use may occur in ovarian cysts and tumors. A subepithelial stroma is common in glandular tumors. Hemorrhage occurs in other cysts than endometrial, namely luteal cysts, and decidual cells have been found in the subepithelial stroma of most of the lower abdominal organs.

King thus claims that endometrial cysts of the ovary do not contain true endometrium but are the result of retrogressive changes of the Graffian follicles. King studied the reaction of Graffian follicles and presented a series of changes through which they pass. The follicles develop during the intermenstrual period and usually one
mature follicle ruptures during this period. With the formation of the corpus luteum the remaining follicles developing at this time retrogress due to the hormone of this corpus luteum. The retrogression takes place by degeneration of the stratum granulosum and proliferation of the theca interna giving what is known as an atretic follicle. These layers then degenerate and are replaced by hyalin and fibrous connective tissue. The atretic follicle becomes cystic and may undergo dilatation during any stage of the development. The cysts may be lined by luteal cells, fibrous connective tissue, or heterotopic epithelium arising from, first, surface epithelium of the ovary; second, endothelium of vessels lying in the connective tissue; or, third, luteal cells or their progenitors. On section of ovaries in cases of endometriosis many atretic follicle cysts and a few old corpora lutea are found. Much of this pathology is verified by observations of Russell, Fraenkel, and Runge and Wolfe. King further points out that sterility is a commonly associated symptom in endometriosis and that Ascheim has shown that a hormone from the pituitary gland plays a part in causation of multiple corpus luteum cysts and sterility. King therefore thinks the endometriomata of the ovary are derived from atretic Graffian follicles and corpora lutea cysts and are closely associated with endocrine secretions probably that of the pituitary gland. As further proof of his theory of primary ovarian origin of endometriomata he sights a case (20) of his in which he performed
a left salpingo-oophorectomy and appendectomy for the relief of a gonorrheal salpingitis. Three years later a right salpingo-oophorectomy was done and the right ovary ingrafted into the right rectus muscle. At this time the ovary was grossly examined and a corpus luteum was found but no evidence of endometriosis and the ovary was considered normal. A year later the site of the ovarian graft became swollen and painful during menstruation and continued to be so during the next three menstrual periods. The graft was removed and examined. Just below the skin and subcutaneous tissue a small amount of ovarian tissue remained surrounding two large cysts containing a chocolate colored fluid and the tissue around one cyst contained a reddish pigment. The cystic cavities were rounded and showed the structure of atretic follicles with degeneration of the stratum granulosum and a well developed theca interna in some parts of the cyst walls. In other areas these layers were degenerated and replaced by fibrous and hyalin connective tissue. One cyst showed degenerated luteal tissue in the wall. Where the walls were fibrous there was epithelium ranging from low cuboidal to columnar. There was very little subepithelial stroma and there were a few crypts and glands. The cyst contained blood. King interpreted this as evidence in favor of his theory that these tumors arise from atretic follicles in the ovary since the tumor resembling an endometrioma arose within the ovarian
tissue ingrafted in the abdominal wall. This theory is very logical even though a bit incomplete and lacking in verification. The presence of a loose, vascular, and cellular characteristic stroma is not explained and the origin of the epithelium is indefinite save for the method previously stated by Russell (31).

Orthotopic theories.

In 1922 Sampson introduced his new and radical theory of origin of endometrial tumors by direct transplantation of sloughed endometrium to the ovaries and pelvic peritoneum by way of the fallopian tubes during menstruation. The ovarian hematomas were classified by Sampson (32) as (a) follicular (graaffian and atretic), (b) corpus luteum, (c) stromal, and (d) endometrial. At this time, in 1921, he described the endometrial tumors of the ovary clearly and stated his theory that on rupture of these cysts hemorrhage might cause irritation and metaplasia of the peritoneal lining to give rise to pelvic endometriosis or, more likely, that the pelvic peritoneal tumors were due to direct implantation of endometrium cast out of the ovarian endometriomata at the time of the rupture of the cysts. He further described the "life history of an endometrial cyst" (33) in which he showed the presence of large round lymphocytes in the stroma and cystic cavity which he states "might be confused with luteal cells". In this manner he disposes of the possibility recently brought up by King. In his report outlining his transplantation theory in 1922
Sampson (34) called attention to the position of ovarian endometriomata, usually on the lateral and posterior surfaces, that is in closed association with fimbriated end of the tube. He also showed that the peritoneal implants are usually found in the cul-de-sac and the lower portion of the abdominal cavity where they would appear to be located due to the force of gravity on bits of loose tissue in the cavity. He stated that in all his cases examined carefully the tubes were found to be patent. In a number of normal cases operated by him during menstruation he observed blood to be slowly escaping from the fimbriated end of the tube and in many cases he has been able to express blood from the tube. This observation has been made by a number of gynecologists but has also been denied by many. Sampson further points out that the associated pathology found so frequently, as uterine fibroids and retroversion tend to obstruct normal menstrual flow and favor the backflow through the tubes. The ovarian endometrioses were observed to be the most common and to be present in most of the cases of pelvic endometriosis. The extent of pelvic pathology varied directly with the extent of the ovarian pathology, the pelvic endometrioses found without apparent ovarian tumors being much less extensive and invasive. In this way Sampson laid the reasoning for his theory that these tumors were due to the direct transplantation of endometrium cast out of the fallopian tube.
during menstruation. He accounted for the great frequency of ovarian endometriosis by the proximity of the ovary to the tubal outlet and also stated that "the ovary has an affinity for the endometrium and acts as a sort of intermediate host, hod-bed, or incubator for the transplanted endometrium and further peritoneal implants arise from perforation of the ovarian cysts". The transplants may, however, be direct to the pelvic peritoneum in his concept. He also theorized that intestinal endometrioses were due to the invasive growths of peritoneal implants.

This theory accounts splendidly for the ovarian, peritoneal, intestinal and recto-vaginal endometrioses and much has been done both clinical and experimental to disprove or verify this hypothesis. It departs radically from all pathological principles governing normal tissue or benign neoplasms and the theory has been viewed with reservations. Novak (29) criticizes Sampson's theory and says that "it is difficult to see that such a normal function as menstruation would cause such a pathological picture". However, it must be remembered that with partial obstruction of the menstrual flow, menstruation is no longer functionally normal. Novak further states that it has been rather definitely proven by himself (28) and Te Linde, by histological examination of tissue, that the endometrium of a menstruating uterus is obviously dying before it is cast off and rapidly undergoes autolysis after sloughing.
He shows that section of thousands of fallopian tubes revealed endometrium present in only seven of them and in these the endometrial bits were too large to pass through the lumen which is generally 1 m.m. in diameter. There was no blood found in these tubes. Novak also questions the passage of endometrial particles and blood against the ciliary and peristaltic muscular movements of the tube which is towards the uterine cavity. By experiment he has found that a body of considerable size is necessary in the tube to set up a reverse muscular peristalsis. He observes that the implants are found on the pelvic peritoneum but not usually on the small intestine in contact with the tumors, and therefore there must be some susceptibility of the pelvic peritoneum to this tissue or else the tumors must arise from the peritoneum. If transplantation is the etiological factor of such tumors, Novak asks why the condition is not more often found following rupture of tubal pregnancies, insufflations, and curettages. Further, implantation of a tissue, devitalized during the process of menstruation, which has been cast into the peritoneal cavity is difficult to comprehend. The process of menstruation has some bearing on this theory and this process is fully described by Whitehouse (42). He shows that there is a vasodialation in the stroma and a change in the contour of the glands as they become more tortuous early in menstruation. Later the stroma be-
come edematous and there is a subepithelial hemorrhage and cloudy swelling of the epithelium. This is followed by a sloughing of the degenerated epithelium and the superficial part of the stroma. The blood and tissue form a semi-solid mass in the body of the uterus which is apparently acted upon by the cells of the cervical epithelium causing liquifaction. Thus the semi-solid formation in the body of the uterus would tend to prevent dissemination of the epithelial element by way of the tubes.

Generally the clinical and experimental evidence tends to verify this theory of transplantation. Clinically the endometrial tumors of the laparotomy scars following operations involving manipulation of the uterus tends to give a practical example of the process of transplantation of living endometrium. The frequency of these tumors following cesarian section, uterine suspension and other pelvic operations are accounted for by the transfer of living adult endometrial cells by the blood flow from the uterine incision or by needles, sutures, and other surgical implements used in the operation. Concerning the viability of the tissue sloughed during menstruation, Cron and Gey (4) present their experiment in which they obtained a specimen of the menstrual discharge from a normal female during the second day of menstruation by gently passing a dull curette into the uterine cavity and withdrawing a portion of the mass present there. The specimen was
thoroughly washed in sterile normal salt solution to remove blood cells and was then centrifuged. The specimen was then divided and a part was hardened and examined microscopically. The tissue was found to consist of bits of epithelial tissue with glandular formations and a very vascular and cellular stroma containing polymorphs, red blood cells and connective tissue. The gland cells were swollen and hyperplastic and some appeared to be in an active state of growth while others showed degeneration. The remainder of this specimen was cultured in vitro using a plasmatic medium containing heterologous embryonic extract. A definite growth was obtained showing that the specimen contained living tissue. Novak objects to this experiment, pointing to the method employed in obtaining the specimen with a dull curette and says that living endometrium may have been removed from the uterine wall along with the menstrual decidua. However, Jacobson (15) in histological studies of menstrual decidua also believes it to contain living tissue.

As pointed out by E. Allen and V. C. Jacobson, normal endometrium is a tissue that possesses a peculiar viability. It of necessity undergoes rapid and extensive proliferation following each menstrual period in replacing the sloughed endometrium. Many novel and thorough experiments have been carried out to prove this ability of normal living endometrium to be transplanted.
V. C. Jacobson (15), in 1922, took strips of endometrium from the uteri of five different rabbits, two of which were pregnant, and in each case performed an autotransplantation of the tissue. In the first rabbit it was placed inside the ovarian tissue and also just beneath the germinal epithelium; and on operation a number of months later a cystic tumor was found in each site. In the other rabbits he made peritoneal implants and in all cases obtained a cystic tumor lined with large-nucleated columnar cells proving that such tissue was capable of transplantation and that the characteristic growth is cystic. In 1925, Jacobson (14) reported the results of his experiments in which intraperitoneal autotransplants of endometrium were performed on 16 rabbits during oestrus with the result that 84% showed growth of endometrium, nearly always on the pelvic peritoneum rather than on the mesentery or anterior abdominal wall. A similar experiment was attempted on six rabbits during the resting stage with only one growth being found. Autotransplants made in six rabbits during pregnancy showed only two cases that resulted in growths. These transplants were made by merely placing bits of endometrial tissue loosely in the peritoneal cavity. Jacobson draws the conclusion that endometrial transplants are possible and that there is an increased viability or "virulence" of endometrium during oestrus. His further experiments
with monkeys showed ability of endometrium to become implanted on the pelvic peritoneum in all of four cases with the characteristic hemorrhage into the cystic cavities of the tumors. Dossena used white rabbits in a similar type of experiment in which the endometrium was removed and minced and then scattered in the peritoneal cavity. He found that this gave rise to growths of a cystic nature lined with columnar epithelium and surrounded by a vascular connective tissue stroma and striated muscle. Katz and Szenes made similar transplants before and after castration and noticed that they obtained no growths in the castrated animals whereas growths were found in the others. Hasselberg, Michon, Kerwin and Loeb, and O'Keefe and Crossen have verified this work and showed that when endometrial tissue is transplanted in experimental animals it retains its power of growth and sensitiveness to ovarian and pregnant stimuli. To ascertain relative powers of implantation, E. Allen and Bauer (1) made transplants of normal endometrium, peritoneum, and ovary into the anterior chamber of the eye of a rabbit. Only the endometrium was found to have the ability to grow and showed proliferation and glandular formations but there was no typical connective tissue stroma. However, the subepithelial connective tissue present was different from that of the rest of the eye and may have been transplanted along with the rest of the growing tissue, or may be the response of the connective tissue to heterotopic epithelium. Thus
it has almost conclusively been proven that normal living endometrium can be transplanted and that menstrual decidua contains living tissue capable of growth as ascertained by histological study and culture in vitro. Heim performed further experiments using monkeys, and by scattering menstrual decidua loosely in the peritoneal cavity he found that no growths would occur. On formation of a fistula between the peritoneal and uterine cavities at the time of menstruation he found that there was no evidence of transplantation. For some reason then, menstrual decidua although apparently living is not capable of peritoneal growth probably due to the devitalizing effect of the menstrual process and time elapsing before implantation.

Sampson also introduced the hypothesis of transplantation by bits of normal adult endometrium from the uterine mucousa by way of the veins (37) with a subsequent formation of endometriomata especially in the broad and round ligaments, ovary, and uterine wall. This method of transferring living tissue is more in accordance with the usual pathological principles as shown by the dissemination of malignant tissues. Sampson happened on to the experimental evidence of the type of spread of the tissue by accident during investigation of normal uteri in attempting to determine the shape of the uterine cavity. To accomplish this end he placed the uteri removed at operation immediately into a pen of hot water and injected through the cervix a suspension of barium sulphate in a wax and then
hardened the wax by placing the uteri in cold water, and X-rayed the uterus. During the injection of one of the uteri removed during menstruation, he noticed that the wax escaped from the uterine veins. On examination he found a small vein leading from the uterine cavity at the site of the sloughed endometrium into a small venous sinus in the uterine wall. This sinus in turn communicated with a radial vein which emptied into an arcuate vein and then into the uterine vein. The sinuses and radial veins are small vessels and their walls are made up entirely of a single layer of endothelial cells closely resembling lymphatic channels. Following this, Sampson worked out the accepted circulatory plan of the uterus by injection of the uterine veins. During this work he found a few cases in which these small venous vessels or capillaries ruptured into the uterine mucousa or the uterine cavity during menstruation, and in a few cases he found bits of endometrium loose in the vessels or attached to the wall of the vessels or sinuses and obviously growing. He suggests that with a greater pressure in the uterine cavity due to obstructed menstrual flow, this process may be the origin of some of the adenomyomata of the uterine wall and possibly the manner in which endometrium passes into the broad and round ligaments and ovary. Novak objects to this theory in that the venous flow is not such as to direct the endometrial particles from the uterine mucousa to the suggested sites.
and also points to the absence of embolism in the brain and lung as would normally be expected to follow such a process. Jacobson has injected a suspension of endometrium intravenously in a rabbit's ear and found a number of small areas of infarction in the lung but he states that the emboli entirely degenerated in 24 hours and no permanent nor extensive damage was done to the lung. This process is not very probable as an etiological factor in the general run of endometrioses and it is probably not very frequent in occurrence, but it offers another plausible method by which adenomyomata of the uterus may arise.

Mestitz, Halaban, and Sampson have recently and independently offered evidence of the metastasis of endometrium from the uterus to other sites by way of the lymphatics. As Sampson pointed out in his theory of venous metastasis, the venous passages in the uterine mucousa and wall closely resemble lymphatic channels and the location at these points whether in venous or lymphatic channels can not be definitely differentiated, a factor which plays a part in discrediting Schiller's theory that such tumors arise by metaplasia of lymphatic endothelium. However, these men have reported the observation of what was thought to be endometrium in the pelvic lymph glands in a very few cases with only evidence of endometriosis and not any malignancy. They offer this theory as a possible method of origin of tumors of the round ligament and umbilicus.
especially. The theory however has not received wide recognition.

As early as March, 1895, Cullen of Johns Hopkins had observed adenomyomata of the uterus and noticed in some cases an isthmus or actual patent tubular connection of endometrium between the epithelium of the uterine cavity and the cystic tumor lining. He interpreted these findings as indicating that such adenomyomata arose from direct ingrowths of endometrium and stroma into the muscular wall between muscle bundles or along blood vessels. These ingrowths, he thought, might maintain their connection with the uterine mucousa or become pinched off and isolated within the myoma and become cystic due to the retention of menstrual flow. This sort of tumor is known as a primary or direct endometriosis. Professor Robert Myer made similar observations and agreed with Cullen as to the origin of such tumors. He stated that, "A single invasive process of epithelium could send out many branches forming the adenomyomata. All that is necessary is a tiny granulation area or track of round-cell infiltration and then the epithelium bursts its basement membrane and begins to invade the muscular wall along the inflammatory track." He then believes chronic inflammation to be a precursor of this condition.

Little attention has been given to the origin of the characteristic stroma but it is thought to be either trans-
planted along with the epithelium or to be the response of local connective tissue to the presence of heterotopic epithelium. Myer thought it to be a normal response to chronic inflammation but this does not account for the formation of decidual cells during pregnancy.

In this account of the etiological factors it is noticed that every possible method of origin of such tumors seems to have been suggested and discussed. But no one theory seems to explain the origin of endometriomata in all the various sites. It is possible then that the etiology may be a combination of several factors previously described or else due to some body function which is too complex to grasp as an etiological entity. A review of the various sites of the tumors with the most acceptable theories for each might be of aid at this time.

A. Intrauterine and tubal.

1. Direct invasion (Cullen's theory)—most likely and very probable.

2. Venous metastasis—possible.


B. Extraterine.

1. Intraperitoneal.

(1) Ovarian.

(a) Serosal theory—probable.

(b) Atretic follicles and corpora lutea—probable.

(c) Sampson's implantation theory—questionable.
(2) Peritoneal and intestinal endometrioses.

(a) Implantation and invasive growth from rupture of ovarian endometrioses—most probable.

(b) Implantation from uterine mucousa by way of fallopian tubes during menstruation—questionable.

(c) Serosal theory—questionable.

(d) Embryonal inclusions—questionable.

2. Extraperitoneal.

(1) Rectovaginal septum and vesicular—peritoneal implants plus invasive growth.

(2) Broad and round ligaments.

(a) Direct mucosal invasions—possible.

(b) Embryonic inclusions—questionable.

(c) Venous metastasis—possible.

(3) Umbilicus.

(a) Embryonic inclusions—probable.

(b) Serosal theory—probable.

(c) Lymphatic metastasis—questionable.

3. Laparotomy scars—obviously accidental transplants.

From this arrangement the etiological factor is fairly definite for two types of endometriosis, namely the uterine adenomyomata and the laparotomy scar tumors. This leaves the extra-uterine group, of which the intraperitoneal group
seem to favor the implantation theory especially from rupture of ovarian endometriomata, with most of the extra-peritoneal type favoring the direct invasion and venous metastasis with the possibility of embryonic inclusions.

The observation of most writers has been that the ovarian endometrioses are most common and that they are usually found in cases where other types of peritoneal, intestinal, recto-vaginal and vesicular lesions are found, the pathology in these locations varying directly with the extent of ovarian pathology. This would lead one to the conclusion that such tumors arose directly in the ovary. There is no reason to assume Sampson's theory that the endometrium cast into the peritoneal cavity thru the tube, if this were possible, should locate and grow on the ovary rather than the peritoneum due to any attraction or affinity to ovarian tissue. Therefore we should expect a more equal number of cases of pure ovarian and pure peritoneal implants if Sampson's tubal regurgitation theory were true. Moreover, Runge and Wolfe describe the finding of epithelialization by the germinal epithelium of ruptured Graffian follicles in many cases so that a series of sections show the gradual steps in development of a cystic cavity lined with cuboidal to columnar epithelium with a subepithelial stroma. E. S. J. King also describes his findings in atretic follicles with subsequent changes to "endometrium-like cysts". He further sights his case of origin of such
a tumor in an isolated ovary implanted in the rectus muscle. The basal cells of the germinal epithelium are known to have potentialities greater than that of the other peritoneum and it seems logical that these tumors should arise in the ovary much as Runge and Wolfe have described. Moreover the ovary is peculiar in the fact that it is the only organ in the body undergoing periodic rupture leaving an avenue of entrance of the overlying epithelium. With the hemorrhage at menstruation the ovarian cyst enlarges and in time ruptures casting out the sloughed tissue, blood, and probably bits of living epithelium and stroma lining the cystic cavity broken loose by the breaking force. Such tissue has been proven experimentally to have the ability to become implanted on the peritoneum. With invasive growth, these peritoneal implants would give rise to intestinal, recto-vaginal and vesicular tumors. Novak, Russell, King, Cullen, Runge and Wolfe have all expressed much this same opinion in their more recent writings.

Extraperitoneal tumors are more of a question of theorization as to their etiology, and they probably arise in a number of ways as by direct extension of endometrium, by venous metastasis, or by embryonic inclusions. The umbilical cord in the embryo contains besides the arteries and veins, the allantois and yolk sac. Embryonic rests or inclusions of one of these bodies might leave at the umbilicus tissue capable of further differentiation into endometrium giving rise to such growths. In the broad
ligament we find the epoophoron and paroophoron and Gartner's duct all remnants of the Wolffian duct and body while the round ligament arises as a continuation or fold of the lower pole of the urogenital fold. This tissue might also contain tissue capable of further differentiation.

CONCLUSIONS

The etiological factors in many cases of endometriosis can be definitely established and in most other cases the probable factors can be found. Other than care during operative procedures and relief of chronic inflammation, these factors cannot be prevented. Endocrine secretions may play a part in this disease, and from all evidence the majority of these tumors arise by direct invasion of uterine mucousa and by changes of germinal epithelium enclosed in ovarian tissue.

The incidence of endometriosis is much greater than it was formerly believed and many cases are probably overlooked during abdominal operations. The symptoms are fairly definite and diagnosis should be accurately made in over 50% of the cases.

The treatment should be conservative when possible but should be thorough. Removal of small implants is usually permanently effective. For more extensive pathology, removal of the lesion is advisable when possible and a bilateral oophorectomy will relieve all symptoms when the necessity is such. The use of radium and the X-ray has
not met with much success in these cases. There are few serious complications and the mortality is very low.

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