The etiology of endometriosis

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THE ETIOLOGY OF ENDOMETRIOSIS

Presented to the Faculty of the University of Nebraska College of Medicine as Partial Fulfillment of Requirements for the Degree of Doctor of Medicine

by

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TABLE OF CONTENTS

1. Introduction .................................. 1
2. Historical Sketch .............................. 2
3. Etiology ........................................ 8
   A. Embryonal Theories of Origin .............. 9
      1. Wolffian Theory .......................... 9
      2. Muellerian Theory ....................... 13
   B. Post-Embryonal Theories of Origin .......... 20
      1. Direct Uterine and Tubal Wall Invasion .... 20
      2. Implantation Theory ..................... 23
      3. Serosal or Coelomic Theory .............. 100
      4. Serosal or Coelomic Theory .............. 130
      5. Hormonal Theory of Origin .............. 142
      6. Metastatic Theory ....................... 164
         a. Lymphatic. ............................
         b. Venous. ..............................
4. Summary ...................................... 177
CHAPTER I
INTRODUCTION

Endometriosis is a disease process, occurring in women during the period of greatest sexual activity, of frequent incidence, characterized pathologically by wide distribution in peritoneal structures, particularly the ovary, uterus and recto-vaginal septum, with the formation of endometrial-like tissue in these situations, appearing morphologically and functionally identical. Glands lined with a columnar epithelium in a richly cellular stroma are the histological criteria, but there may be present a variable quantity of effused blood, cystic spaces lined by columnar or flattened epithelium and containing tarry blood. Physiologically these endometrial-like structures pass through various phases of the menstrual cycle, including that of menstrual hemorrhage, and by undergoing decidual change during pregnancy, though the latter, of course, is not specific to endometrium, but found constantly in the ovaries and frequently in the peritoneal covering, of the pelvic organs.

Synonyms are, Muellerian Endometriosis, Muellerianosis, Endometrioma, Endometriomyoma, Muellerianoma, Endometriosis, and Adenomyoma.

The purpose of this paper is to present the present knowledge concerning the etiology of this most intriguing subject. The various theories will be present with the evidence for and against their plausibility. It will be noted at once that there is no definite agreement on this matter and a wide diversity of opinion exists. It is hoped that some light and organization will be thrown on this confusing subject.
CHAPTER II

HISTORY

Adenomyomata of the uterus have been known for a long time. Our earliest knowledge of endometriosis dates back to 1860 when von Rokitansky first described an adenomyoma as a pathological entity. Babes in 1882 according to Kahn (34) reported a case of intramural myoma containing cysts which were lined by epithelium. He, in common with the subsequent supporters of his theory, attributed the presence of glandular tissue in these tumors to inclusions of Muellerian rests. Little attention was paid to the subject until von Recklinghausen roused new interest in it by a series of publications from 1893 to 1896 in which he ascribed the origin of the tumors to the development of rests of the Wolffian ducts. Almost simultaneously, there appeared the work of Cullen (9), in 1896, describing adenomyoma of the round ligament. He has since made voluminous contributions covering the whole field of the so-called adenomyomata. He is credited with having been the first to demonstrate that the glandular inclusions in adenomyomas of the uterus are of endometrial origin. In 1898, after removing a similar tumor from the round ligament on the opposite side of the same patient he had reported two years before, Cullen (10) suggested that the glands might be due to an abnormal embryonic deposit of a portion of Mueller's duct. This was suggested, he said, from the striking resemblance of the glands of the adenomyoma to those of the uterine mucosa and from the fact that their stroma resembles that of the uterine mucosa. At this time he referred to a case reported by A. Martin in 1891. The patient was seventy years old and complained of a rapidly growing tumor. The growth sprang
from the left round ligament and contained twelve litres of chocolate-colored fluid. There were several small cysts in the pedicle which contained clear fluid. One of these cysts was lined with a low cylindrical ciliated epithelium. Quoting from Cullen: "Martin says that in this case the structure and contents corresponded to those of tumors arising from the parovarium."

Shortly after the first report of an adenomyoma originating outside of the uterus, according to Cullen (10), Pfannenstiel reported two vaginal adenomyomata and Blumer reported an adenomyoma in the inguinal canal.

The presence of endometrial tissue in the ovaries has been noted for many years. The first report in the English and American literature of endometrium-like tissue in the ovary was reported by Russel. Russel (53), in 1899, described under the title "Aberrant Portions of the Muellerian duct found in the Ovary", an ovary that he had removed from a woman at the menopause. He said in this description:

"On microscopic study of the ovary we were astonished to find areas which were an exact prototype of the uterine glands and interglandular tissue. The whole formed an exact reproduction of a portion of the uterine mucous membrane and muscle."

Russel believed that the tissue which he had discovered represented the displacement of a part of the Muellerian duct.

This communication did not appear until March, 1899, and meantime von Franque had published in July, 1898, a brief preliminary report of a similar case.
HISTORY

In 1898 Ivanoff claimed that the cystic spaces in the fibromyoma originated in some cases from ingrowing processes of peritoneum.

Pick, according to Graves (24), believed, in 1905, that the presence of the endometrial tissue in the ovary was due to invasions of the Wolffian ducts through the hilus of the ovary. He also believed that they might arise from adenomatous tissue that dipped down from the superficial epithelium of the ovaries. This tissue he stated was capable of developing adenomata or cystadenomata of the ovary, the structure of which corresponds in detail to the endometrium of the uterine body. His description of four cases appears minutely that of the well known endometrioma of the present day. To these tumors he gave the name "Adenoma Endometrioides Ovari." 

Adenomyomata of the umbilicus, containing uterine mucosa, were first reported by Cullen (11) in 1909. In an article on this subject, three years later, he reported a total of nine cases. The ground work of much of our present knowledge of endometriosis was laid by Cullen in his momental findings and numerous publications on adenomyomata. He was the first to show that the uterine adenomyomata are not products of Wolffian rests, but are for the most part invasive growths of the uterine mucosa. He also described the ectopic forms of adenomyomata, and attributed them tentatively to aberrant muellerian epithelium.

The first report of a case of adenomyoma of the recto-uterine or recto-vaginal septum in the English and American Literature was by Lockyer (40) in 1913.

During 1919-1920 aberrant endometrium, excluding uterine adenomyomata, began to be recognized as a clinical entity and not as just a
5.

HISTORY

pathological curiosity. In 1919 Casler (7) reported a case in which, after panhysterectomy for diffuse myomatous enlargement of the uterus, the patient continued to menstruate through the vaginal vault. Examination of the removed uterus had shown the musculature was penetrated everywhere by endometrial stroma without glands. Three and a half years later the remaining ovary began to enlarge, and when removed four years after the original operation, was found to contain, in addition to normal ovarian elements, large quantities of typical endometrial tissue. R. Meyer, during this time, also reported several cases on this subject and proposed his serosal theory of origin of endometrial tissue.

Cullen (12) in this interval reported aberrant endometrium in ten places and published papers on the distribution of these involvements.

In 1920, Mahle and MacCarty (42) reported ten cases of extra-uterine and extratubal tumors showing the typical morphology of adenomyoma. It is interesting to note the distribution of these tumors. They were found in the umbilicus, abdominal wall, sigmoid colon, groin, and recto-vaginal septum. During this period of time thousands of cases in which aberrant and omentium occurred in the ovaries evidently escaped unrecognized.

In 1921, however, the presence of endometrial tissue in the ovary was still considered a great rarity, as is made evident by the fact that Norris (46) of Philadelphia, reported a single case which he considered remarkable. He attempted to explain the finding upon an embryologic basis. The next year Janney (32) of Boston, in an article entitled, "Report of three Cases of a Rare Ovarian Anomoly", described
three cases of his own and collected from the literature the four others that have been mentioned above.

Already in September, 1921, however, Sampson (62) of Albany, had reported a series of twenty-three cases of "Perforating Hemorrhagic (Chocolate) Cysts of the Ovary" which he showed to be lined by tissue of Muellerian or Endometrial nature. He described in detail the pathologic and clinical aspects of these hemorrhagic ovarian cysts and also the associated pelvic adhesions containing endometrial tissue, which he termed endometriosis. He believed that the areas of endometrium found in the pelvic adhesions were implants from epithelium escaping from perforating endometrial cysts of the ovary, but he made no attempt, in his first communication, to explain the origin of the endometrial tissue in the ovary. Since then he has written numerous articles on this subject. In his first paper he presented an entirely new theory for the origin of aberrant endometrium. According to his theory some of the mucosa from the lining of the uterus or fallopian tube becomes detached and travels out through the fallopian tubes to be deposited on the surface of an organ in the peritoneal cavity. Here, he believes, it becomes implanted and grows, infiltrating its host. Before the birth of this theory the aberrant endometrium was believed to have arisen from remnants of either the Wolffian or Muellerian Duct, or from a metaplasia of the pelvic peritoneum. The implantation theory of Sampson became very popular from the time of its introduction and has remained so up to the present time. Since his introduction of the theory he has made some additions and new suggestions such as the possibility of transmission through the veins
and lymphatics to various sites so as to explain certain difficulties which his implantation theory presents in its careful study.

Up to the time of Sampson's first article, in 1921, fewer than twenty cases had been published in the literature. Immediately following the appearance of this work reports of similar findings were published in England by Blair Bell, Fletcher Shae, and Donald, and in this country by Janney, while observations were made before and not given out until after Sampson's paper. Lauche and Dougal in 1923 further presented material on this interesting subject as did Halban in 1924.

Since this time there have been articles too numerous to mention on this subject with contributions by many authorities. It will be seen that endometrium-like inclusions in the ovary have been noted for many years. Pick has accurately described the chocolate cysts and Cullen has exhaustively covered the field of the adenomyomata. But to Sampson belongs the credit of discovering the frequency and the significance of endometriosis and of having described a very excellent theory of origin of these tumors.
CHAPTER III
ETIOLOGY

There are numerous theories of origin and all of them will be discussed in detail but stress will be laid on the two most important theories considered the most likely at the present time. These theories, first that of Sampson, namely the Implantation theory, and second, the Serosal and Coelomic theories. These are given the greatest credence at the present time and are receiving the greatest support.

The following classification is used in the consideration of etiology:

A. Embryonal theories of origin.
   1. Wolffian theory
   2. Muellerian Theory

B. Post-Embryonal Theories.
   1. Direct Uterine and Tubal Wall invasion.
   2. Implantation theory.
   3. Serosal or Coelomic Theory.
   4. Luteal Origin of Tarry Cysts.
      a. Lymphatic.
      b. Venous.
A. EMBRYONAL ORIGIN

1. Wolffian Theory

In 1898 von Recklinghausen reviewed the literature and with a report of many new cases came to the conclusion that the adenomyomata of the uterus were derivatives of the Wolffian duct. He thought he could recognize a close similarity between the glandular part of the adenomyomata and the elements of the Wolffian duct. In many places in these tissue the glands were arranged in such a manner as to resemble the glomeruli and von Recklinghausen called these areas pseudo-glomeruli.

Accepting the dominant theory of displacement as a working hypothesis von Recklinghausen saw, in the close anatomical relationship between the ducts of the primordial kidney and the generative organs, sufficient ground for the possibilities of the transference of embryonal rests from one structure to the other. The Muellerian duct lies to the outer side of the Wolffian duct during the earliest period of embryonic development; later on it assumes an anterior and still later a mesial position to the latter, so that it may meet the opposite duct, fuse with it and thus form the fallopian tubes, the uterus and vagina. The primitive urinary and genital ducts lie in a fold of tissue known as the plica urogenitalis. These folds gradually approach each other in a mesial direction and as they extend caudally, they finally unite in front of the pelvic colon and form a common cord containing the Wolffian ducts and the fused Muellerian ducts.

The crossing points of the muellerian over the wolffian ducts, and their close relationship during the embryonic period constitute the keystone of von Recklinghausen's histogenetic theory. In addition to
1. Wolffian Theory

the embryological data, von Recklinghausen has further adduced microscopic evidences to prove the organoid formations simulate the component parts of the mesonephros by presenting the following morphological arrangements: (a) narrow straight tubules lined with ciliated epithelium analogous to the collecting tubules; (b) secreting tubules; (c) ampullae; (d) end tubules; and (e) the fusion of many tubules to form main or principal canals. The stroma in which these tubules are embedded consists of a cytogenous connective tissue. Around the cystic glands the cytogenous tissue is scant, and their epithelium rests immediately upon the muscle bundles. The glands which showed an irregularity of their lumina due to a bulging inward of part of the circumference were regarded as pseudoglomeruli.

He was the first to ascribe the origin of the glandular elements of adenomyomata to the embryonic rests. He saw in them a close resemblance to the tubules and pseudo-glomeruli of the Wolffian body, and believed that all the adenomyomata of the outer portion of the uterus arise from the uterine mucosa or from rests of the Muellerian ducts.

In summing up his observation von Recklinghausen stated: "The epithelial constituents of the adenomata and cystagenomata of the fallopian tubes, of their interstitial portions, and of the outer peripheral layers of the uterus, are derived from rests of the Wolffian body, while the centrally located adenomyomata of the uterus arise from the uterine mucosa, or its equivalent, the Muellerian ducts."

Pick in 1898 accepted the theory of a dual genesis of these tumors on the ground that the Wolffian and Muellerian systems stand in
1. Wolffian Theory

close relationship developmentally. He ascribed the extra-uterine
tumors to growths from the paraophoron and Gaertner's ducts.

Meyers at first accepted the wolffian rest theory of von
Recklinghausen but later discarded it completely in favor of his secool theory.

Pick (24), in 1905, believed the presence of endometrial tis-
sue in the ovary due to invasions of the Wolffian ducts through the
hilus of the ovary. He also believed that they might arise from ade-
nomatous tissue that dipped down from the superficial epithelium of the
ovaries. This tissue he stated was capable of developing adenomata or
cystadenomata of the ovary, the structure of which corresponds in de-
tail to the endometrium of the uterine body. His description of four
cases appears minutely that of the well known endometrioma of the
present day.

From an embryological standpoint this theory is plausible. The
female ducts follow the general course of the mesonephric ducts. At
first lateral in position, the Muellerian ducts cross the mesonephric
ducts when well caudad and enter the genital cord mesial to them. As
development continues it is possible that these closely associated
structures might become displaced and form rests in the various struc-
tures such as, for example, the round ligament which lies in close con-
tact with the Wolffian duct before its descent into the inguinal region.

Lockyer (40) in 1913, in a report of a case of a woman aged
thirty-five, with various symptoms with a mass felt in the post vaginal
fornix fixed to the supra-vaginal cervix and adhered to the pelvic
1. Wolffian Theory

floor and some bowel involvement, gives a microscopic description of the growth which was an adenomyoma—composed of the usual structure of an adenomyoma, concludes "It should suggest that this growth arose in some vestigial remains of the wolffian duct, such remains generally resulting in cysts, if they take on activity at all, and a fact which I have not hitherto published about these cysts is that they have been observed by me to burrow into the posterior wall of the cervix uteri." He has continued to adhere to these teachings.

Cullen and Meyer have done much to disprove this theory of origin as will be discussed subsequently under the Muellerian theory and the Seriosal theory of origin.
2. Muellerian Theory

This theory assumes that the basis of endometriosis is certain aberrant portions or rests of the Muellerian duct. The embryology of this structure in brief is that the Muellerian ducts cross the mesonephric ducts when well caudad and enter the genital cord mesial to them. In embryos of two months their caudal ends lie dorsal to the urogenital sinus and extend as far as the Muellerian tubercle, a projection into the median dorsal wall of the primitive sinus and extend as far as the Muellerian tubercle, a projection into the median dorsal wall of the primitive sinus formed by the earliest entrance of the mesonephric ducts. Here they end blindly and it is not until the middle of the third month that the Muellerian ducts break through the wall of the urogenital sinus and open into its cavity. Even before this takes place, their caudal ends, which were pressed close together between the mesonephric ducts in the genital cord, combine into the single primordium of the uterus and vagina. The paired cranial portions of the Muellerian ducts become the uterine tubes whose ostial ends undergo later an actual bodily descent from the third thoracic to the fourth lumbar vertebra.

Cullen (9) in 1896, presented the Muellerian theory of origin and has followed this quite closely. In an article entitled "Adenomyoma of the Round Ligament" in this same year
2. Muellerian Theory

he describes a case of this and states several conclusions in regard to the etiology of this structure. In a gross and microscopic description he finds that the glands present in the tumor are similar to those of the endometrium of the uterus. He found a nodule in the round ligament and gives a microscopic description of it. The nodule is to a large extent composed of muscle tissue but contains glands running in all directions. These glands are surrounded by a stroma similar to the stroma of the uterus. The glands in places are impossible to distinguish from the uterine glands. In many places the glands present a peculiar arrangement and correspond to the pseudo-glomeruli of von Recklinghausen. These consist of stroma resembling that of the uterine mucosa. In conclusion he says the glandular elements in this case correspond very closely to that found by von Recklinghausen, in adenomyomata of the uterus. In this case he was able to trace a marked resemblance between the tumor glands and remains of the Wolffian body and came to the conclusion that the glands were derived from that source. While admitting the probability of the glands in the case being due to the remains of the Wolffian body, he could not, from their striking resemblance to those of the uterine mucosa and from the fact that their stroma resembles that of the mucosa, refrain from suggesting the possibility that they may be due
2. Muellerian Theory

to an abnormal embryonic deposit of a portion of Mueller's duct.

It can, thus, be seen that Cullen did not agree with von Recklinghausen and subsequently gave evidence to the fact that the theory of von Recklinghausen was not very tenable. Consequently at present the theory of Wolffian body origin of these tumors is not given much credence. Russel (53) in his article in 1899 entitled "Aberrant Portions of the Muellerian duct found in the Ovary" believed the epithelium he found in the ovary was due to "an anomalous point of development of portions of the Muellerian duct in the germinal epithelium." At that time there was a question as to the derivation of the gland like spaces as well as the papillary and adenomatous tumors of the ovary. Whether they take origin from germinal epithelium, the remains of Wolffian body, or the Graffian follicle. His conception like those of other men was based on the anatomical and embryological interpretation of the material that was presented to them. He describes a portion of ovarian tissue in the case he presents in which there were areas of tissue which were an exact prototype of the uterine glands and interglandular tissue. Some of these groups were surrounded by groups of muscle tissue, non-striped in character. On the posterior surface at a considerable distance from the hilus, was a shallow groove partly filled with glands of the uterine type, opening on the abdominal side. The epithelium covering
2. Muellerian Theory

this group gradually merged into a single layer of low columnar cells and at the edges of the groove spread out over the surface for a short distance as the germinal epithelium.

According to Russel (53) on the basis of Nagel's work and Waldeyer's observations, the epithelium of Muellerian duct is exclusively derived from true germinal epithelium. He states: "If we accept this view of Nagel it is not difficult to conceive that a portion of germinal epithelium which forms the ovary should at times, attempt to produce structure which its function elsewhere calls upon it to do. Such an accident may be represented by simple tubes or spaces lined with ciliated columnar epithelium of the tube, or villous and papillary outgrowth analogous to the mucous membrane of the tube or even the more complicated structure of the uterus. Glands, interglandular connective tissue, and muscle."

In the specimen he describes in this article there is a collection of glands in a groove on the surface of the ovary. The epithelium covering them is continuous with a single layer of columnar cells at the margin of the groove and extends a short distance over the surrounding surface. He takes this as direct proof that the germinal epithelium is capable of producing glands analogous to those of the uterine mucosa.

Kossman (53) insists that all intraligamentary cysts reaching considerable size spring from rudimentary tubes.
2. Muellerian Theory

lying in the broad ligament, which he has found to exist in about 10 per cent of women. His arguments which appear plausible are as follows:

"The secreting portion of the primitive kidney, the glomeruli, disappears completely during untra-uterine life and may, therefore, be left out of consideration. The par-ovarium, paroophoron and Gartner's ducts are simply conducting channels during fetal life, and their epithelium has at no time in their history secretory power. If it had, they would sooner or later all become cystic, as they have no external openings. On the other hand, the mucous membrane of the tube has undoubtedly the power of secretion, and by occlusion of its openings always forms a cystic tumor, hydro-salpinx. He draws a sharp distinction between the embryological germinal epithelium during the formative stage and that of a later period. After the differentiation of the epithelium into its various parts, these specialized parts are entirely distinct in their character and without power of further reproduction. The germinal epithelium after the developmental stage remains functionally inactive and exists only as a single layer of epithelial cells covering the surface of the ovary. All tissues of the body are subject to the rule that after differentiation has taken place in fetal life, it can never be transformed into another. Further papillary growth covered with ciliated cylindrical epithelium has, in this region, its only anlage in the tube.
2. **Muellerian Theory.**

This holds good for the tube, ovary and broad ligament. Those arising in the ovary are from isolated plaques of epithelium of the fimbriated end of the tube which have become differentiated from the germinal epithelium at an abnormal point."

Norris (46) agrees with Russel in that the portion of the germinal epithelium which forms the ovary may at times form these structures. This, of course, will be dependent on the theory of origin of the Graffian follicle that the particular author accepts. Nagel pointed out that the germinal epithelium at the point of the groove in the germinal epithelium contained the sexual cells which are the progenitors of the ovules in the female. He has also demonstrated that in the further development of the Muellerian duct the primitive duct closes at its distal extremity, forming a blunt tube which sinks into the Wolffian body and pushes backwards besides the Wolffian duct. The primitive duct remains entirely independent of the Wolffian duct.

The conclusion drawn is that the epithelium of the Muellerian duct is from the germinal epithelium. Waldeyer believed that the graffian follicle originated from rests of cells forming the germinal epithelium, these becoming isolated from their fellows by connective tissue penetrating the area from below and surrounding them. Waldeyer was the first to focus
2. Muellerian Theory

attention to the groove in the germinal epithelium.

This theory is based on certain embryological and morphological characteristics of these tumors the value of which will be discussed later. The theory is presented as part of an attempt to completely present the various theories of origin.
B. POST-EMBRYONAL THEORIES OF ORIGIN

1. Direct Uterine and Tubal Wall Invasion

This form of origin assumes that the endometrium lining the uterus and the mucosa of the tube directly invades the wall with the formation of endometriomas in the muscular substance of the uterus and the tubes.

The direct uterine wall invasion by the endometrium was clearly recognized by Cullen (9) as early as 1896. He began to study these tumors at the same time as von Recklinghausen. From the first he has maintained they are of endometrial or Muellerian origin. In most of the uterine adenomyomata studied by Cullen he was able to trace by serial sections a communication between the glandular tubules of the tumor with those of the endometrium. From this he concluded that the uterine adenomyomata are for the most part invasive growths of the endometrium. He was unable to explain some of the superficial subperitoneal adenomyomata, however. Meyer agreed with the origin of the uterine adenomas as explained by Cullen.

Sampson has developed Cullen's theory of the endometrial origin of the uterine adenomyomata and has shown that the tissue of the uterine wall may be invaded in several ways by living endometrial tissue that is capable of nidation and growth. Sampson (55) states that adenomyoma of the uterus and tube may be primary or secondary. The primary type is by direct invasion of uterine or tubal wall by the mucosa lining their cavities. The secondary type, which is more
1. Direct Uterine and Tubal Wall Invasion

frequent, is where the wall is supposedly invaded by epi-
theleim implanted on its peritoneal surface, which is de-
ived from the perforation of an ovarian hematoma of the
endometrial type or from or through the frimbriated extrem-
ity of the tube. We are concerned with the former in this
discussion. The adenomyoma may be the result of the direct
invasion from the uterine mucosa as in the cases minutely
described by Cullen. Sampson also believes that an ectopic
endometrium, e.g., of the ovary, may adhere to the surface
of the uterine serosa and invade the wall, from without by
direct extension. Endometrial tissue may also be implanted on
the peritoneal surface of the uterus and invade the uterine
wall. This accounts for the superficial adenomyomata of which
source cannot be traced to the mucosa.

Sampson (66) has been able to demonstrate that venous
capillaries and large venous sinuses in the mucosa empty di-
rectly into similar sinuses of the uterine wall. He has also
shown that during menstruation lining fragments of them mucosa
may escape into the venous circulation of the uterus. Thus
he has practically proved that metastatic endometriomaata may
be established in the uterine wall.

There is also the possibility that embolic or metastatic
endometriomata may be disseminated in the uterine wall by the
lymph channels. This has also received some support by Sampson.

The endometriomata of the uterine horns may develop,
according to Sampson, from ingrowths either of the uterine or
tubal mucosa, the histologic source being difficult to deter-
1. Direct Uterine and Tubal Wall Invasion

mine. These glandular proliferations are frequently found in association with gonorrheal or tuberculous infections and are accountable chiefly for the inflammation theory in the etiology of endometriosis.

Sampson (55) states that primary adenomyoma of the tube generally arises in the isthmus of the tube, where the epithelium more closely resembles that of the endometrium than does the epithelium situated in the ampulla, but even in these adenomyomas we frequently find that the dilated tubules attempt to reproduce the structure of the mucosa of the tube, so that sometimes a careful microscopic study of a stained section may be required to distinguish the lumen of the tube from some of the dilated tubules in the wall.

This theory of origin has received general support and acceptance as far as endometrioma of uterus and tubes of the primary type are concerned.
2. Implantation Theory of Sampson

In 1921 Sampson (54) published his first paper on "Perforating Hemorrhagic (Chocolate) Cysts of the Ovary" in which he attempted to show that they were hematomata of endometrial origin, though it is to be remembered that Pick recognized their endometrial character in 1905. Sampson reviewed twenty-three cases in his paper. He used as a standard, in the determination of presence of endometrial tissue, ectopic endometrium in which there is cyst (Hematoma) formation due to retention of "menstrual blood" similar to conditions in ovarian hematomas and not normal endometrial tissue. He uses the endometrial cysts found in uterine adenomyomas in which there is a columnar, cuboidal, or low epithelium. The epithelium may even be absent in portions of the structure. Also, in these cysts, the characteristic "endometrial stroma" may be very thin or even entirely lacking, the epithelium resting directly in the tissue of the uterine wall or myoma. In the cases he reported the histological picture was identical with these cysts of the uterus, except where there is a modification due to tissue peculiar to the ovary. Sampson maintains that uterine or tubal endometrium or epithelium at times during menstruation escapes into the peritoneal cavity through the tubes. This regurgitated menstrual secretion finds lodgement on the ovary.
2. Implantation Theory of Sampson

or the adjacent tissue, such as the intestine and the
and the pelvic peritoneum, particularly the culdesac.
Runge and Wolff (51) have demonstrated the "epitheliali-
ization" of ovarian hematomas by the invasions of the
"surface epithelium of the ovary" through the opening
caused by the rupture of one of these. Runge (51) by
serial sections to the place of rupture, demonstrated that
the epithelium lining the cysts was continuous with that
covering the surface of the ovary. Wolff's work (51)
confirms that of Runge, and he states that the epithelium
invading and relining the cavity of the cyst may be low,
cuboidal, or columnar; when columnar it is due to lateral
compression. He believes that glandlike structures in the
underlying stroma arise from a pushing downward of the
overlying epithelium. If these cysts are of the endometrial
type and if their epithelial lining arises from invasion
of the surface epithelium of the ovary through the place of
rupture, we must conclude that a metaplasia of the epithelium
occurs, in which it may not only assume the morphology but
also the function of these structures. It may be possible
that following the rupture of the hematoma or whatever
structure preceded the secondary epithelial invasion, mis-
placed epithelium of endometrial type was present in the
periphery of the ovary at this site and this epithelium was
2. Implantation Theory of Sampson

stimulated to become invasive and reline the cavity of the hematoma. We often find glandlike structures in the ovary, especially (54) in its periphery, which are usually known as "cell inclusions". Sampson (54) states: "I believe that some of these glandlike structures are due to misplaced epithelium of endometrial type which under "proper" stimulation might become invasive and actually reline the cavity of the hematoma through the opening caused by the intitial rupture, or by hemorrhage into the lumen of the gland, they may develop into "endometrial" hematomas".

Implantation, according to Sampson (54) may occur only on the ovary, or on both the ovary and pelvic peritoneum, or on visceral or parietal peritoneum alone. Adenomata, so formed, react to menstruation and, especially in the ovary, may develop into hematomata by retention of menstrual blood. Such hematomata may remain superficial in which case they are recognized as minute red or purple elevations on the surface of the ovary, the color depending on the age and the period of the menstrual cycle. There may be, however, a deep invasion of the ovary with the formation of cysts of varying size which contain the typical chocolate fluid. Sooner or later the increased tension of the contained blood causes rupture of the cysts wall with dissemination of its contents and a portion of endometrial
2. Implantation Theory of Sampson

lining to adjacent structures. Thereby fresh implantations arise which are found in the culdesac, the recto-vaginal septum, the sigmoid, the appendix, the cecum, the ileum, the uterus, tubes, and parietal peritoneum. Dense adhesions then form about the site of perforation. These in brief are the essentials of the theory that Sampson has propounded.

Sampson (54) in describing the microscopic findings of the cysts in this series of cases states that he "is inclined to believe that most of the apparently different kinds of cysts represent various stages in the development and retrogression of one type of cyst and the various phases in its "menstrual cycle". The initial perforation may have been the rupture of an "endometrial" graffian follicle or atretic follicle hematoma; or following ovulation, an abnormal corpus luteum may have developed due to the invasion of "endometrial tissue present at the site of rupture". He divides the cysts into three groups:

1. Shows a portion of the hematoma, usually the deeper, is lined by a luteal membrane the exact origin of which in some specimens is difficult to state. The rest of the cysts usually toward the perforation, is apparently being relined by invasion of the epithelium, through the perforation, from epithelium situated in the periphery of the ovary at the site of rupture. This epithelial relining or regeneration is of the endometrial type,
2. Implantation Theory of Sampson

both in structure and function. With the advance of the epithelial invasion, the "luteal" membrane retrogresses, and eventually the entire cyst may be relined by this epithelial tissue. This group represents either the development of an endometrial cyst from the invasion of a follicular hematoma by misplaced endometrial epithelium or else it represents the regeneration of an "endometrial" cyst after a menstrual hemorrhage.

2. Apparently represents either an earlier or a later stage of the former. The cysts are entirely lined with epithelium, low cuboidal, and columnar; all three types of epithelium are often present in the same cyst. The picture suggests periodic hemorrhages in the recent hematomas in the subepithelial stroma and in the pigmented cells in the same situation.

3. These are smaller cysts and more difficult to recognize as an ovarian hematoma of endometrial type. The cyst wall is composed of ovarian tissue which lacks a vascular stroma and in places may also lack a definite epithelial lining. When the latter is present, it is usually low to cuboidal and rest directly in the ovarian tissue. However, tissue of endometrial type is present in pockets in the periphery of the ovary about the perforations. The exact counterpart of the lining of this
2. Implantation Theory of Sampson

Ovarian hematoma may be found in some of the uterine hematomas occurring in adenomyoma of the uterus. These are apparently due to the retention of menstrual blood. Tissue of the endometrial type is also present in pockets in the periphery of the ovary about the site of perforation and the tissue in these pockets may resemble normal endometrium more closely than that lining the hematoma in the same ovary. Microscopic study of these hematomas shows that periodic hemorrhage similar to that of menstruation occurs. He has come to the conclusion that these ovarian hematomas are of the endometrial type just as are the uterine hematomas found in the adenomyoma of the uterus. As there is continued hemorrhage in these pockets sometime or possibly many times in the life of these hematomas, material, including epithelial tissue and menstrual blood, may escape into the peritoneal cavity from the hemorrhagic cysts or from the endometrial pockets in the ovary about the site of perforation and lodging in the natural pockets and peritoneal folds of the pelvis, they may cause adhesions. Adenomas of the endometrial type often develop between the folds of peritoneum thus resulting. These adhesions may be small and quiescent, or they may be invasive; if they are invasive they may cause adenomyoma of the uterus by invasion of the uterine wall from without or adenomyoma of the uterosacral
2. Implantation Theory of Sampson

ligament, round ligament, rectovaginal septum, rectum, sigmoid, etc., namely whatever structure or organ is invaded by the adenoma arising from the "infective" contents of the cyst or ovary lodging in its surface.

The question arises: In what way do the contents of the cyst or ovary cause the development of these adenomas? Is it due to some specific irritant present in the cyst contents which stimulates the peritoneal endothelium, thus causing a metaplastic and the development of endometrial tissue typical both in structure and function? Sampson (54) believes that the condition found in many of these specimens is analogous to the implantation of the ovarian papilloma or carcinoma on the peritoneal surface of the pelvis from rupture of an ovarian tumor containing these growths.

In a review of 13 cases in which histological examinations of the secondarily involved tissues were made, Sampson (54) believes that they are as a result of the dissemination of the contents of the ovarian cysts or possibly the tubes in which the tissue is spilled into the natural folds of the peritoneum where secondary growth occurs with invasion of the exposed tissues.

Sampson (54) offers the following evidence that perforating hemorrhagic cysts of the ovary are hematomas of endometrial type.
2. Implantation Theory of Sampson

1. These hematomas, as the uterine mucosa, manifest their "activity" during the menstrual life of the patient. In two patients operated on at the time of the menstrual period, one the day that menstruation was due and the other the last day of menstruation, the histologic changes in the ovarian "endometrial" tissue corresponded to the phase of the menstrual cycle indicated by menstrual history of the patient.

2. Microscopically the epithelial lining of the hematomas is similar to that of the uterine hematomas, due to retention of "menstrual" blood, often present in "adenomyomas" of the uterus.

3. Periodic hemorrhage occurs in the ovarian hematomas which are similar in gross and microscopic appearance to that of menstruating endometrium.

4. The "chocolate" contents of ovarian hematoma resemble old menstrual blood.

5. In two patients operated on at the time of menstrual period, on the day it was due and the other the last day of menstrual flow, the microscopic changes in the ovarian "endometrial" tissue corresponded to the phase of the menstrual cycle indicated by menstrual history of the patient.

6. The fact that material escaping from the ovarian hematomas may give rise to development of adenoma of endometrial type in the tissue thus soiled is further proof that
2. Implantation Theory of Sampson

these hematomas contain "endometrial" tissue.

Sampson (54) states that the origin of "adenomyoma" of the uterus may be divided into two groups. First, where the growth has apparently arisen by direct invasion of the uterine wall. This will be considered in more detail under another heading. Second, arising from the invasion of the serous surface of the uterus by adenoma of the ovary, i.e., invasion from without. Histologically the two tumors are identical. It may also be possible that the adenoma from without may invade the entire wall and thus reach the mucosa lining the uterine cavity.

Sampson (55), in 1922, describes the "Life History of Ovarian Hematomas (Hemorrhagic Cysts) of Endometrial (Muellerian) Type". He reviews a series of twenty cases. He decides that the epithelium primarily giving rise to these implantations is derived through, or from, the fimbriated ends of the fallopian tubes. It lodges either on the surface of the ovaries or on the peritoneal surfaces of other pelvic structures, especially in the culdesac, or on both the ovaries and pelvic peritoneum and develops into glands or tubules (adenomas) or endometrial (Muellerian) type. The primary peritoneal implantation adenomas are usually small and insignificant, but may spread and become invasive. The implantations on the ovary invade the tissues of that organ and as a result of their reaction to menstruation
2. Implantation Theory of Sampson

Implantation Theory of Sampson develop into superficial or deep hematomas of endometrial type, which usually perforate into the peritoneal cavity. Perforation occurs in the superficial ovarian hematomas while they are still small, a few mm. in diameter. On the other hand, the hematomas developing in the deeper tissues of the ovary may attain a much larger size, from 1 to 9 cm. before perforation of the ovarian hematoma, whether the latter is smaller or larger, may carry with it epithelium which is cast off from its lining by menstruation. This may give rise to secondary implantation which is often apparently more invasive and has a wider distribution than the primary implant. The ovary may be looked upon as an intermediary host in the development of implantation adenoma of the Muellerian type but not as an essential one. The implantation adenomas of uterine and tubal (muellerian) type in the ovary may also do likewise and spread to form cysts and possibly carcinoma.

Sampson further describes this process. Should the epithelium escaping from the tube fall on suitable "soil" it develops into glands or tubules of endometrial type which generally react to menstruation. These adenomas are usually found on the structures which are most frequently in close contact with the fimbriated end of the tubes, such as the lateral and under surfaces of the ovaries and the peritoneal surface of the structures in the culdesac. Implantation
2. Implantation Theory of Sampson

adenoma may also occur only on the surface of the ovary or ovaries, or on both the ovaries and on the pelvic peritoneum, or on the pelvic peritoneum alone. As the implantations on the ovary invade the tissues of that organ, and, as a result of their reaction to menstruation, develop into superficial or deep hematomas of endometrial type. The casting off of all of their epithelial lining by menstruation may cause the death of the hemorrhagic cyst before perforations occur; but most often they rupture, or perforate into the peritoneal cavity. Perforation occurs in the superficial ovarian hematomas while they are still small, a few mm. in diameter, and as the result of menstruation and perforation of the entire epithelial lining may be cast off and the hemorrhagic cyst may disappear.

The hematomas developing in the deeper tissues of the ovary may attain a large size, several cm. in diameter, before perforation occurs. As the menstrual blood is retained in the cavity of the hemorrhagic cyst and in the stroma of its lining for a long time, many interesting histologic changes occur in the wall of the cyst in the attempt to absorb the menstrual blood, and to reline the denuded surface by epithelium from that which had not been removed by menstruation. The development and activities of the endothelial leukocytes which act as scavengers, play an important part in the absorption of the menstrual blood
2. Implantation Theory of Sampson

and the deposit of the pigment derived from the blood, in the walls of the hematoma. Perforation permits the contents of the hematomas to escape into the peritoneal cavity, and may temporarily relieve the embarrassment caused by its retention. The perforation is sealed by the ovary or cyst becoming adherent to adjacent structures at the site of perforation. The hematoma again fills up with blood at its next reaction to menstruation and repeated perforations may occur. As the reaction to menstruation is destructive, and as the repair and regeneration of the epithelial lining is accomplished under great difficulties (due to retention of the menstrual blood), the ultimate tendency of the hemorrhagic cyst is one of regression.

In its reaction to menstruation, portions of the epithelial lining are cast off into the cavity of the hematoma, and may be found lying free on the surface of the ovary about the perforation, and in the tissue of the structures adherent and adjacent to it, as well as in situations where the material escaping through the perforation would be apt to lodge. This indicates that these adenomas may be derived from the implantation of epithelium cast off by menstruation into the cavity of the hematoma and escaping through the perforation. Implantations may arise from small as well as large ovarian hematomas; generally the larger the hematoma and apparently the larger the perforation, the greater the distribution of the implantations from this source. These secondary implantations often resemble normal endometrium
2. Implantation Theory of Sampson

more closely than the epithelial lining of the original ovarian hematoma, and are often invasive, and more closely resemble normal endometrium than the implantations found in the pelvis without evidence of an ovarian hematoma with perforation, i.e., those resulting from a primary implantation from or through the tube. For these reason, Sampson (55) considers the ovary as an incubator, hot bed, or intermediary host in the origin of all implantation adenomas of endometrial type. He believes that the tubules of endometrial type in the ovary from which hematomas of endometrial type arise are from epithelium escaping from or through the tube. This is based on the following data:

1. Epithelium is found on the surface of the ovaries in these specimens, invading the underlying tissue as tubules. Epithelium lining the tubules is often ciliated; sometimes tubules suggest tubal origin and sometimes uterine. The ovarian tissue about the epithelium on the surface of the ovary as well as that about the tubules in the deeper portions sometimes react to menstruation.

2. In some cases minute adenomas of apparently the same age are found only on the surface of the ovary, in others, both on the surface of ovary and on pelvic peritoneum, and in still others only on the latter. These are all most frequently present in places where material escaping from the tube would be most apt to lodge and suggests a common
2. Implantation Theory of Sampson

origin from the latter.

3. These hematomas are unusual in women under
and if they were of developmental and not acquired origin
we would expect them to occur in younger soon after puberty.

4. They develop during the menstrual life of
the patient, when tubal and uterine epithelium would be more
likely to escape from or through the fimbrated end of the
tube than before puberty and after the menopause. It is
possible that the implantation on the ovary of epithelium
derived from or through the tube may occur before puberty and
after menopause, and may develop into ovarian cysts or even
carcinoma.

5. The uterus in these cases is often retroflexed,
contains leiomyomas and polyps, conditions which might favor
a back flow of menstrual blood through the tube.

6. In 56 cases of ovarian hematoma of this type
which he has studied, the tubes were apparently patent in all,
suggesting this source of implantation was open in all of
these cases. The presence of occluded tubes would not
exclude the origin of ovarian implantations from this source
as they might have occurred before the tubes had become
closed. In the 15 cases of pelvic implantation apparently
not derived from a perforated ovarian hematoma the tubes
were patent in all but one instance. In that case bilateral
hematosalpinx was present with adenomyoma of the fimbrated
2. Implantation Theory of Sampson

ends of both tubes. The implantation adenoma of the posterior surface of the uterus resembled histologically the adenoma in the tube and was found at the operation in close proximity to the end of one of the tubes, from which he believes it arose.

7. Implantation of endometrial type on the peritoneal surface of the pelvic structures apparently arise from the escape of contents of an ovarian hematoma of this type and furthermore similar implantations occur on the posterior surface of the ovary about the perforation, and possibly also on the opposite ovary. The implantations involving the ovaries from this source simulated the original ovarian implantations but were apparently often more virulent and more closely resembled typical endometrium in these specimens studied. As implantations arise from the perforation of the ovarian hematomas so may ovarian hematomas arise from implantations. The most obvious source of the latter in the absence of an ovarian hematoma with evidence of perforation is from the fallopian tubes or through them.

8. These ovarian hematomas are often bilateral and usually develop and perforate on the lateral or under surface of the ovaries, the portions of the ovaries which are anatomically most frequently contacting the fimbriated ends of the tubes.

9. The escape of the ovum from the ovary into the fallopian tube during ovulation is an evidence of the close contact of the opening of the tube and its fimbriae with
2. Implantation Theory of Sampson

the surface of the ovary. This same close contact would favor the implantation of epithelium on the surface of the ovary from the fimbriae of the tube or from the epithelium escaping from its lumen.

10. We have abundant proof that apparently normal uterine and tubal epithelium may be invasive, as demonstrated in the development of "adenomyoma" from the invasion of the uterine and tubal wall by the epithelium lining their cavities.

11. In studying the situation of the fimbriated end of the normal fallopian tube, as found at operation, he found that there were two situations that were most frequently related to the free end of the tube. First, it may be behind the ovary dependent on the length of the tube and the position of the ovary and below. The distal pole of the ovary frequently extends beyond the attachment of its suspensory ligament in such a way as to form a groove between it and the suspensory ligament. This distal portion of the fallopian tube easily slips into this groove, and the fimbriated end of the tube lies between the ovary and the side of the pelvis, or beneath the ovary, often with the opening directed towards the ovary, due to the tetherlike action of the distal portion of the mesosalpinx. If this groove is shallow or absent the distal portion of the tube usually
2. Implantation Theory of Sampson

hangs down in the pelvis (over) mesial to the ovary in such a way that the tubal fimbriae are in close contact with the structures in the bottom of the culdesac. Even in this latter group, the fimbriated end of the tube is often found tucked beneath the ovary. These are the two most frequent situations of the tube but occasionally it is found in others. Material (including epithelium) escaping from the fimbriae of the tube or through its lumen, would be apt to lodge on the structures in close contact with the fimbriae of the tube. If implantation of epithelium should arise from this source we would expect to find them on the lateral and the under surface of the ovary and in the culdesac, especially about the uterosacral ligament. It is in these situations that the early (primary) implantation adenomas are most frequently found. The implantation adenomas seem to thrive in ovarian tissue and smooth muscle. As women spend the greater part of the day with the body in the upright position the tendency for the fimbriated end of the tube to be tucked beneath, or lateral to, the ovary would be increased, and sediment escaping from the tube would naturally settle on the lateral and under surface of the ovary and in the bottom of the culdesac, especially on its anterior surface.

14. Implantation adenoma may occur on the ovary alone, especially on its lateral or its under surface, or on the
2. Implantation Theory of Sampson.

Surface of the ovary adjacent to the pelvis, especially the culdesac, or in the pelvis alone. The pelvic implantations are usually small but may spread and become invasive. The ovarian implantations usually develop into adenomas of endometrial type which sometimes attain large size. Perforation of adenomas usually occurs with implantation adenomas resulting in the pelvis, which in their distribution correspond to implantations of carcinoma from a malignant ovarian cyst.

He believes that when there is evidence of an ovarian hematoma with perforation the hematoma is usually the principal and sometimes the only source of the implant. All specimens of extensive implantation adenomas which he has seen have been associated with an ovarian hematoma of endometrial type with evidence of perforation. However in a study of a group of fifteen cases it appeared that the implantations were in these particular cases, from the tubes or through the tubes rather than of ovarian origin although the latter can not positively be excluded. In these cases the lesions were smaller, less invasive and not as widely distributed as the secondary type. Many of these had a different microscopic appearance. They usually did not resemble typical endometrium as closely as did the implantations which were associated with an ovarian hematoma with perforation. Believes that some of the implantations arose
2. The Implantation Theory of Sampson

from the tubal mucosa and others from the uterine mucosa.

Sampson (55) concludes, on the basis of this data, that the observations suggest that the ovarian implantations from which the hematomas arose may have been derived from both tubal and uterine epithelium; but even if of tubal origin, by its growth in the ovarian hematoma, it was converted into structures of the uterine type.

In all he has studied 65 specimens of ovarian hematomas in various stages of development and retrogression. Some of the hematomas had not perforated and these arise from glands and tubules of endometrial type which penetrate the ovary from the surface. The development of these hematomas has been discussed above. There is then a reaction to menstruation at the menstrual period.

The reaction to menstruation manifests itself by hemorrhage into the ovarian tissues beneath the epithelial lining; and by rupture through the overlying epithelium into the cavity of the hematoma, carrying with it some of the epithelial lining. There is then an attempt to repair. First, the blood goes through several physiological changes which manifest themselves by the bluish discoloration of the cysts and microscopically there is evidence of disintegration of the tissues. Endothelial leukocytes, as phagocytes, appear and devour the red cells. They then break down and set free the blood pigment. Hyaline fibrous tissue arises in the
2. Implantation Theory of Sampson

stroma of the denuded lining of the hematoma. This process gives rise to a thickened pigmented lining of the hematoma without an epithelial covering which in certain stages of its development might be confused with the lining of the corpus luteum hematoma, the endothelial leukocytes being mistaken for luteal cells. Next there is an attempt to reline the cavity that has been formed due to the denudation of the epithelial lining in at least a part of the wall. The picture is, of course, viable as far as the reaction to menstruation is concerned and many of the cysts react differently to menstruation.

Sampson states that the mechanism of perforation can be readily explained by the menstrual hemorrhage in a thin portion of the wall of the cyst which has reached the surface of the ovary. The hemorrhage ruptures first either into the peritoneal cavity or into the cavity of the cyst; perforation occurs and some of the contents of the cyst escape and become implanted. The soil apparently must be suitable for the reception of the material. The cyst then may become sealed and repeat its previous performance unless there is a complete loss of the epithelial lining. The perforated area may become adherent to another structure that is in the vicinity, such as the pelvic tissues including the side of pelvis, posterior layer of broad ligament, or uterine wall; and these assist in sealing the perforation. In freeing the ovary or hematoma
2. The Implantation Theory of Sampson

At operation the perforation is usually reopened or the healed thin wall is torn at the area of weakness. The above cycle will continue until there is no more stimulation by ovarian hormone producing menstruation and thus at menopause these structures cease growing and reacting. The perforations, in all cases which he has seen, have been situated on the lateral surface or free border of the ovary and never on its mesial surface. This would indicate that the hematoma arose from tubules which had invaded the ovarian tissues from these surfaces, the portions of the ovary which are normally most frequently in contact with the fimbriated ends of the tube. The contents of hematomas vary, consisting of blood (menstrual), blood pigment, cast of epithelium, endothelial leukocytes, cholesterin, and stroma cells, in various stages of activity and disintegration, and in various proportions, depending on the age of the hematoma and upon the menstrual cycle it was removed.

Sampson in operating on a case found a pregnancy in the uterus with various involvement of other tissues by endometrial lesions. The typical decidual reaction of pregnancy was found in three different situations, the cavity of the uterus, the ovarian hematoma and those of the implantation adenoma of the posterior ovarian wall. The lining of all
2. The Implantation Theory of Sampson

three was apparently similar. The lining of the lesion in the left ovary of the patient was that of typical decidual tissue, with the surface epithelium still present in the depressions. It was identical with that of compact layer in decidua vera of the pregnant uterus. There was likewise a decidual reaction in the implantation adenoma in the posterior uterine wall. One of the dilated tubules resembles a miniature uterine cavity, a portion of whose mucosa showed a definite compact and spongy layer. The reaction in the compact layer was not quite as striking as that on the wall of the ovarian hematoma, but the glands of the spongy layer had a microscopic picture identical with that of the glands in the spongy layer of the decidua vera of uterine cavity. Sampson(65) studied two cases with ovarian hematomas of endometrial type in women past the menopause and found that there was no evidence of a recent menstrual reaction. Apparently as soon as the influence of hormonal stimulation disappears these lesions subside since there is no more menstrual reaction.

He summarizes the evidence that these hematomas or hemorrhagic cysts are of endometrial type.

1. They develop from glands or tubules in the ovary which are lined by cuboidal or columnar epithelium (often ciliated) resembling tubal and uterine epithelium. Hemorrhage occurs in the ovarian tissue about the glands or tubules at time of menstruation.
2. Implantation Theory of Sampson

2. The glands of tubules, from which these hematomas develop, are derived from epithelium which has escaped from the fimbriae, or through the lumen of the fallopian tube, becoming implanted in the surface of the ovary, has invaded its tissues.

3. The microscopic of the epithelium, lining these ovarian hematomas is similar to that of the hematomas and dilated cavities found in the primary adenomyomas of the uterus and tube.

4. Every variation in structure of the lining of ovarian hematomas (often seen in different portions of the same hematomas) is due to different phases in its reaction to menstruation such as: The inactive stage without evidence of hemorrhage, the subepithelial hemorrhage, the escape of blood through the overlying epithelium carrying some of the latter with it into the cavity of hematoma in the attempt to absorb the extravasated blood, and especially the development and activities of the endothelial leukocytes as scavengers, and finally the regeneration of epithelium lining over denuded portions from epithelium which as not been removed by menstruation. The perforation of hematoma is the result of the reaction to menstruation.

5. The reaction to menstruation, pregnancy and old age is similar to that of the mucosa of the uterus.
2. Implantation Theory of Sampson

6. The microscopic study of these hematomas shows that portions of epithelial lining are cast off by the menstrual hemorrhage and this epithelium may be found free in the hemorrhagic contents of the hematoma where perforation has occurred. Adenoma of the endometrial type may be found on surface of ovary about the site of perforation and in other tissues adherent or adjacent to it, as well as in situations where material escaping from the perforation of ovarian hematoma and in structures are of endometrial type; often resembling normal endometrium more closely than the lining of the ovarian hematoma. If adenoma of endometrial type develops from implantations of epithelium cast off by menstruation from the lining of the hematomas and escaping through the perforation, then the epithelial lining of hemorrhage must also be of endometrial type.

Sampson (55) concludes that the primary origin of ovarian and peritoneal implantations (those developing from epithelium escaping from fallopian tube) may arise from both tubal and uterine epithelium. He found three groups histologically.

1. Those consisting of glands or tubules and dilated tubules, often lined by ciliated epithelium and without the characteristic stroma of normal endometrium, or with stroma poorly developed. The structure resembles that of the mucosa of a primary adenomyoma of tube, and strongly suggests that the implantations might have been derived from epithelium of
2. Implantation Theory of Sampson

of the fallopian tube.

2. Adenomas consisting of stroma and glands similar to those of normal endometrium. Microscopically the picture strongly suggests that these adenomas were derived from uterine epithelium escaping through the lumen of fallopian tube, namely, from menstruation with a back flow into the peritoneal cavity, or from portions of tubal mucosa which have reacted to menstruation.

3. Suggest a mixture or represents transitional stages from one to another.

It is difficult to determine the factors which favor implantation and growth of tubal and uterine epithelium on surface of ovary and on the peritoneum. He suggests that the menstrual blood is favored in retrodisplacement of the uterus.

Sampson (56) in 1922, in a discussion of "Intestinal Adenomas of Endometrial Type" believes that an important and probably the principle source of these implantations is the epithelium escaping from an ovarian hematoma of endometrial type which has perforated. He considers 12 cases in these series and in majority of these cases the implantations apparently arose from such a source. He considers the ovary as an intermediary host, hotbed, or incubator, which may impart an increased vigor and virulence to this epithelium, so that when it escapes from the ovary it may be more virulent
2. Implantation Theory of Sampson

and invasive than before the hematoma developed and the perforation occurred. It may, however, not be an essential host (intermediary), for it is possible that pelvic implantations may arise from tubal and uterine epithelium escaping from the tube; and so important implantations from both sources may be present in the same specimen. The few cases he has interpreted as possibly arising from epithelium escaping from the tubes have lacked the vigor, invasiveness, and wideness of distribution of the implantations usually found in those cases associated with an ovarian hematoma with evidence of perforation and also usually a slightly different histologic picture from the latter. The larger the perforation the wider the distribution of the implantations and apparently the greater their virulence.

Sampson (58) draws an analogy between carcinoma and endometriosis. It would appear that the spread of the carcinoma and the endometrial tissue are similar in that upon rupture of an ovarian tumor, for example, there is dissemination of the tissue and implantation of the tumor material on peritoneal structures. He believes that menstrual blood is the most frequent source of the endometrial lesions, mainly as a backflow from the uterine cavity through the tubes, carrying with it fragments of the uterine mucosa and at times tubal epithelium, and less frequently, from the tubal mucosa which occasionally reacts to menstruation. Apparently menstrual blood may also
2. Implantation Theory of Sampson

escape into the peritoneal cavity from menstruating endometrial tissue on the surface of the pelvic organs and from the perforation of an endometrial hematoma of the ovary or any other organ. Menstrual blood differs from normal blood both in its chemical and in its cellular constituents. It is undoubtedly more irritating and as a result of this irritation and the reaction following it, gland-like inclusions of the peritoneal mesothelium and of the surface of the ovary may occur, just as they may occur in peritonitis of bacterial origin and in the serosal reactions against malignant implantations. Blood pigment (from the menstrual blood) and lymphocytes may be present in the tissue about these gland-like inclusions, thus suggesting endometrial tissue which has menstruated. These reactions cause confusion in the diagnosis of endometrial lesions and this is increased because both endometrial tissue and the reaction of the serosa may be present in the same section and endometrial tissue wherever situated does not always possess a characteristic structure. The development of the hematomas is fundamentally the same wherever the site of involvement. There may be accumulation of menstrual blood in the lumen of a gland or cavity in endometrial tissue which had invaded that organ and also possibly from the endometrial invasion of a cystic or ruptured graffian follicle with subsequent relining of its cavity with subsequent relining of its cavity with endometrial epithelial
2. Implantation Theory of Sampson

tissue. The former mode of origin occurs in the ovary and in other pelvic structures. There is then an increase in the size of the cavity due to the accumulation of fluid in the cyst contents and growth of the epithelial lining attempting to adapt itself. Should the endometrial tissue on the surface of the host involve an area, relatively large, it gradually sinks into the host and at the same time the tissue of the latter, about the edges of the implant, attempts to envelop it. If successful, an endometrial cavity is found, surrounded entirely by the tissue of the host. (Uterus, sigmoid, or ovary, as the case may be.) In other instances a portion of the wall of this cavity is completed by some other structure which became adherent to the host, as has been well illustrated. In other instances the endometrial tissue simultaneously invades two adjacent pelvic structures which become adherent to each other. There may then be perforation in the pelvis as is evidenced by finding contents in the pelvis at operation, with hematomas partially collapsed and on squeezing the ovaries, more of their contents escaped through the perforation. These contents then give rise to implantations.

Sampson (56) also suggests the possibility of direct uterine wall invasion with subsequent spread from the serosa of the uterus by perforation of the resulting hematomas which have invaded the surface of the uterus.
2. Implantation Theory of Sampson

Novak (48) is one of the chief opponents of the implantation theory of endometriosis. In a histologic study of many hundreds of Fallopian tubes with particular reference to their contents, Novak found only seven which contained particles of maternal mucosa lying free in the lumen. None of the women from whom these seven tubes were removed were menstruating, most of them being many days from this period, and in no instance did the endometrium in the tubes have the appearance of endometrium thrown off at menstruation. In five of the seven cases the particles of the free endometrium were so large that it would seem almost impossible for them ever to have entered the tiny uterine orifice of the tube. Novak believes that the tissue was moving towards the uterus rather than away from it, endometrial tissue being found in the ovary in two of these patients. In several other cases only a very small amount of ovarian tissue was removed and subjected to examination.

Novak does not believe that the blood regurgitates through the tubes during menstruation. In thirteen patients operated upon by himself during menstruation, he has not seen regurgitation in one. He says that histologic examinations of tubes removed during menstruation characteristically show no blood in their lumen. He calls attention to the fact that no blood was found in the pelvis of thousands of women operated upon by thousands of surgeons immediately
2. Implantation Theory of Sampson

after menstruation, although it would hardly have had a chance to be absorbed during this time. He also calls attention to the absence of any frequent peritoneal reaction, as after a ruptured tubal pregnancy, that we would expect to get with the hemorrhage into the cavity from the rupture of a chocolate cyst or spilling of blood regurgitated through the tube.

Novak also questions the retrograde transportation of endometrial tissue into the tube. He thinks the ciliary current to be more important than muscular peristalsis in the passage of the ovum from above downwards. He believes antiperistalsis rare and present only in conditions of over-distension of the tube as proved by recent investigation. He calls attention to the fact that the uterine portion of the tube measured only 0.5 to 1 mm. in diameter so that it would really seem almost incredible that this opening could admit such large pieces of endometrial tissues as are seen in his specimen. He says that if a piece of endometrial tissue made its way through the uterine os of the tube it would still have an almost impassable passage through the very fine lumen of the interstitial portion of the tube; the latter passing in a gently curved or sinuous fashion through the thick musculature of the uterus.

In this connection Sampson (58) says: "I am convinced that the manipulation of the uterus and tubes, incident to
2. Implantation Theory of Sampson

Pelvic operations, may at times detach uterine and tubal epithelium and cause it to be transferred not only to the abdominal wall, but also to the tissues of the pelvis. This is particularly true for endometrial tissue where the abdominal operation has been preceded by a curettage. In such cases I have frequently observed blood escaping through the fimbriated ends of the Fallopian tubes in patients operated upon during the normal menstrual periods by Danforth (13) and others. Blood has been reported at the fimbriated ends of the tubes following curettage by Heaney (27) and others.

Novak (48) questions the ability of the endometrium cast off at menstruation to grow on the ovary or peritoneum. He says that the tissue thrown off is degenerating and doubts that it will have sufficient vitality after traversing the tube, to grow where it falls. Since it takes the smaller ovum a number of days, at least, to pass down the tube, even with the current at its back, it would probably take much longer for tissue to pass upward against the stream, assuming that this were possible. He insists that histologic studies show that the tissue thrown off at menstruation is dead or dying. He questions that such degenerative tissue can thread itself into the tubal orifice, make its way upward against the obstacles which have been described, and, after probably many days, and still have sufficient vitality to grow where
2. Implantation Theory of Sampson

It falls. He states that this would be impossible, especially as autolytic and degenerative changes are very rapid in the cast-off tissue of menstruation. There is no evidence that the ovary, except at the time of ovulation offers any special portal of entry for "implantations" and ovulation is almost as far removed from menstruation in point of time relations as it can be. At other times the ovary is commonly smooth, with a dense fibrous albugena covered by the cuboidal germinal epithelium.

Novak further objects to the theory because, "1. The endometrium is not infrequently found chiefly, and perhaps exclusively, in parts of the pelvis, or elsewhere, where implantation from the tube would not be easy; 2. It is often present in extremely small amount, in spite of the supposed monthly regurgitation and the proliferative tendency of the tissue; 3. it is characteristically confined to the pelvis, even when extensive endometriosis is present, unlike cancer, which can implant itself over the entire abdominal cavity. All in all, the evidence indicates that if implantation plays a part in the dissemination of the endometrium, as it well may, it is the ovary from which the seed is primarily dropped rather than the tube. All the reasons urged by Sampson in favor of the tubal origin of implants speak just as forcibly and indeed much more so, for the ovary as the primary source. Endometrial
2. Implantation Theory of Sampson

tissue from the ovary would theoretically possess much greater vitality than that from the menstruating uterus, for it could readily break off from the surface or be cast out in the rupture of hematomata, without the influence of menstruation."

He contends that no evidence which has yet advanced would seem to demonstrate that retrograde transportation of cancer particles from the uterus, is a factor of any great importance in the explanation of the ovarian metastasis in adenocarcinoma of the fundus. The complication is very infrequent. The two cases in which Sampson found cancer particles in the tubal lumen have no significance and he insists that this does not prove that there is a retrograde passage of tissue, and the burden of proof lies on those who insist that it does.

Novak supports the coelomic theory which will be considered in detail in a later section.

Sampson (59) in 1926 discussing "Endometriosis of Sac of Inguinal Hernia", concludes "The clinical and pathologic study of pelvic peritoneal endometriosis convinces me that it is usually due to the escape of menstrual blood into the peritoneal cavity with subsequent local reaction. Menstrual blood at times passes into the peritoneal cavity as a back flow from the uterus through the tubes, from the tubal mucosa itself, from the perforation
2. Implantation Theory of Sampson

of an endometrial hematoma of the ovary and possibly from endometrial tissue on peritoneal surfaces. Menstrual blood, like other irritants, causes granulation and scar tissue, adhesions and peritoneal inclusions. In addition endometrial tissue is often found on the surface of, or imbedded in, these peritoneal lesions and must arise either from the implantation of fragments of uterine mucosa, which we know are often present in menstrual blood, or else in some way the peritoneum is converted into endometrial tissue by the specific stimulation of some ingredient of this blood." He believes that the experimental work of Jacobsen (30, 31) demonstrates that similar peritoneal lesions may be produced in rabbits and monkeys by scattering bits of their uterine mucosa in the peritoneal cavity of these animals. "Clinical observations indicate or at least suggest that endometrial tissue may be successfully transplanted in human beings. The local peritoneal reaction towards the menstrual blood creates conditions favoring the retention and engrafting of any living tissue in this blood, just as similar reactions make possible the implantation of fragments of cancer escaping into the peritoneal cavity. These implantation-like lesions occur in a hernia sac just as tuberculosis and carcinosis. A case is reported of pelvic peritoneal endometriosis asso-
2. Implantation Theory of Sampson

associated with an endometrial cyst of the ovary and inguinal hernia. Peritoneal lesions containing endometrial tissue were present in both the anterior and posterior culdesac and also in the walls of the hernia sac including its neck, the lumen of the latter having been occluded (or nearly so) by the endometriosis in this situation. Observations made at the operation and the laboratory study of the specimens removed indicate that the pelvic peritoneal lesions and those of the hernia sac had a common origin and from some material escaping into these cavities and the local reaction to the same, I believe that this material was menstrual blood. The endometrial cyst of the ovary is evidence that a perforation may have occurred and the patent tubes are two avenues by which menstrual blood may have reached the peritoneal cavity and the hernia sac."

Jacobsen (30,31) has performed various experiments and has demonstrated that endometrium of the rabbit and monkey can be transplanted to the animals' pelvic structures and these transplants give rise to cystic adenoma of the endometrial type. The endometriosis that results is similar to that found in human beings. However, it must be remembered that this does not necessarily apply to human beings for the conditions in the two may be different. Jacobsen (30) in 1922, performed a series of experiments using five rabbits. Certain facts were demonstrated:
2. Implantation Theory of Sampson

1. Endometrium alone from a non-pregnant animal will grow when transplanted into the fat of the mesosalpinx or on the pelvic peritoneum of the same animal and is found actively growing from 56 to 70 days after implantation.

2. Endometrium from a non-pregnant animal will grow when transplanted into the ovary of the same animal, and is found growing 64 days after transplantation.

3. Endometrium from a pregnant rabbit after transplantation into pelvic fat or onto pelvic peritoneum will grow and show more active proliferative changes than endometrium from non-pregnant rabbits.

4. An incision through a cornual segment containing a fetus may result in dissemination of endometrial cells in the surrounding tissues; transplantation endonomas thus arising.

A cyst was produced in all rabbits which was usually multilocular. Since the transplanted tissue acts for a time as a foreign body, the fibrous tissue formation about it, along with smooth muscle fibers, constitutes the capsule into which the epithelial sprouts may grow. The cysts were lined with epithelium which was either actually or potentially ciliated. Stroma in these may simulate closely that of the cornua of the uterus from which the transplant was made. There is a smooth muscle reaction about the endome-
2. Implantation Theory of Sampson.

trial tissue.

Jacobsen (30) feels that the whole question of adenomyoma seems to hang on this special influence of endometrial tissue over smooth muscle in its vicinity. As a result of the implantations, adenoma-like growths and multilocular cysts, which, histologically, show much similarity to "ovarian" cysts-adenomas of women, are produced. Under the influence of pregnancy, a more rapid epithelial growth occurs with the production of a papillary cyst-adenoma which has some of the characteristics of a malignant growth.

All these observation are in agreement with Sampson's explanation of adenomas of endometrial type. It would appear, from this experiment, that the early work of Sampson was confirmed on an experimental basis. Jacobsen states "the menstrual blood possibly contains a substance which is capable of altering the peritoneum so that the epithelial cells from the cyst may become implanted where the peritoneum is injured and develop, producing adenoma-like growths; these cells may invade, from the outside, such structures as the oviduct, uterus, appendix and intestine and cause a proliferative smooth muscle reaction, thus simulating very closely the so-called adenomyoma."
2. Implantation Theory of Sampson

Sampson (61) in 1927, published an article on "Peritoneal Endometriosis due to the Menstrual Dissemination of Endometrial Tissue into the Peritoneal Cavity", which summarizes his beliefs. Menstrual blood escapes into the peritoneal cavity from: (1) Menstruating endometrial tissue growing on the surface of the ovary and other pelvic structures; (2) The rupture or perforation of endometrial cysts or cavities of the ovary or possibly from other pelvic structures; (3) The uterine cavity as a back flow from the tubes; and (4) Menstruating tubal mucosa. Menstrual blood irrespective of its source, at times, contains bits of endometrial tissue set free by menstruation. Endometrial tissue disseminated by menstruation is sometimes alive and will grow if transferred to situations suited to its growth. The peritoneum and surface of the ovary are suited to its growth. The lesions of peritoneal endometriosis often occur in situations and under conditions indicating (or at least suggesting) their origin from menstrual blood escaping from the above mentioned sources. The local reaction of the peritoneum to the endometrial tissue is peritoneal endometriosis is similar to the local reaction of the peritoneum to car-
2. Implantation Theory of Sampson

cinosis of implantation origin. He concludes, "These studies indicate that peritoneal endometriosis sometimes arises from the implantation of endometrial tissue disseminated by menstrual blood escaping into the peritoneal cavity."

Sampson (61) in a histologic study of uteri removed at various stages of menstrual cycle in which the veins have been injected, demonstrates the mechanism by which endometrial tissue may be disseminated from that organ. The uterine mucosa contains venous capillaries which are sometimes dilated to form sinuses. These sinuses empty into similar sinuses (endothelial lined spaces without definite walls) of the myometrium and the latter empty into the arcuate veins which convey the venous blood from the uterine tissue into the venous circulation outside of that organ. During menstruation the venous capillaries of the mucosa rupture and blood escapes into the tissues and bits of the latter are set free into extravasated blood. This blood breaks through the surface of the mucosa into the uterine cavity, often carrying with it bits of endometrial tissue suspended in that blood. Incidentally this might suggest that there may be venous dissemination as will be discussed in a later section.
2. Implantation Theory of Sampson

He considers three possible sources of menstrual blood that may affect the peritoneal cavity. (1) the menstrual rupture or perforation of the wall of an endometrial cavity, most frequently seen in the ovary; (2) the menstrual reaction of endometrial tissue growing on the peritoneal surface of the ovary or any pelvic organ or structure; (3) a back flow through the tubes from the uterus and also possibly from the menstrual reaction of the tubal mucosa. He has found rupture of these various cysts at operation or has at least seen evidence of this dissemination. Ovarian and peritoneal lesions may both be secondary or the latter secondary to that of the first. If secondary, they may be due either to the stimulation of the peritoneum by some specific element of the cyst contents or else to the implantation of bits of endometrial tissue carried by the contents of the cyst escaping into the peritoneal cavity. Clinical observations have demonstrated to him that these cysts sometimes rupture or perforate during menstruation and some of their contents escape into the pelvic cavity. There is also evidence microscopically of reaction to menstruation. As the cysts rupture there is dissemination of the epithelial structures into the peritoneal cavity. There will then be growth of the
2. Implantation Theory of Sampson

endometrial tissue. He, however, believes that there is little dissemination from the secondary lesions.

Some of the objections that have been made to the work of Sampson are:

1. Menstrual blood rarely, if ever, escapes from the uterine cavities into the tubes.

2. The lumen of the interstitial portion of the tube is too small for the bits of endometrial tissue to pass through.

3. Endometrial tissue, set free by menstruation, is dead or dying and therefore incapable of implantation.

4. Several days must be required for endometrial tissue to be carried from the uterine cavity through the tubes and therefore, there is little chance for such degenerative tissue after, probably, many days of continuing degeneration and autolysis, should grow where it falls. Novak (48) states that his theory could be greatly strengthened if he could demonstrate two things. First, the capacity of degenerated endometrium given off at menstruation to grow in tissue culture, and, second, the capacity of such endometrium to grow in the peritoneum or ovary of human beings or perhaps even one of the lower animals.
2. Implantation Theory of Sampson

Sampson attempts to refute these arguments and present evidence in favor of his theory. He has found endometrial tissue which frequently presented a normal appearance menstrual blood of vagina and from the cavities of the uterus at operation. He has also given evidence to show that endometrial tissue disseminated by menstruation into the venous circulation. He has also presented evidence to show that endometrial cavities of the ovaries, at times, discharge their contents containing endometrial tissue cast off by menstruation, into the pelvis and that peritoneal implantations of this tissue arise from this source. It has also been demonstrated by this and other observations that the visceral and parietal peritoneum is suited to the growth of endometrial tissue. If bits of endometrial tissue could be carried through the interstitial portions of the tubes by menstrual blood escaping from the uterine cavity into these ducts and not spend too long a time in their transit, one would expect the peritoneal implantations of this tissue might occur from this source. By injecting opaque media (suspension of bismuth sub-carbonate or barium sulphate in melted gelatin, 15 per cent) he obtained an outline of the uterine cavity and tubes (when patent, especially the interstitial portion)
2. Implantation Theory of Sampson

by X-Ray. He suggested twelve years ago that menstrual blood may escape through patent tubes and when operating on many patients during the menstrual period has found the regurgitation of blood into the tubes in eight cases. He has also found endometrial tissue in the lumina of tubes removed during menstruation. The above x-rays also suggest that the interstitial portion of some tubes is large enough for the menstrual material to easily pass through. He has seen curetted material escape from the abdominal ostia and thus the escape can easily occur. Also the time required for menstrual blood to go through from the uterine cavity into the tubes might be very short, not several days but a few moments, and possibly no longer than that taken by uterine bleeding from a curettage. He concludes; "These observations demonstrate that blood escaping from the uterine cavity into the tubes, at times, can carry with it bits of endometrial tissue and that the time required for this may be very short." Novak, as will later be seen, believes that the primary source is the ovary or peritoneum with secondary involvement of the tubes. Sampson agrees that this might occur. During a period of five years Sampson studied material from 293 patients with peritoneal lesions containing
endometrial-like tissue. The tubes were usually patent, 284 cases out of this series. In many there was blood in the tubes and in some there was a discharge of blood from the ostium especially on compression and in some there was blood in the culdesac apparently indicating that there had been leakage. He believes that the usual source of this menstrual material is the uterus, primarily. Also the lesions of the peritoneal endometriosis often occur in situations and under conditions indicating their origin from material escaping into the peritoneal cavity. The peritoneal endometriosis occurs most frequently in situations in the pelvis most easily soiled by material escaping from the tubes and ovaries. It would seem that the tubes and ovaries are the chief distributing agents for the cause of pelvic peritoneal endometriosis. It is not peculiar to the pelvic peritoneum, as the appendix, cecum, small intestine and their mesenteries may be involved. There is a marked similarity between the distribution of the peritoneal endometriosis and peritoneal carcinosis. He believes that the peritoneal reaction is the same in both and that they may grow on the surface of the peritoneum or be disseminated and become imbedded by peritoneal tissues growing over
2. Implantation Theory of Sampson

the material. He, however, recognizes that all the lesions of the ovary and the peritoneum of an endometrial nature may not come from only one source and that there may be other means of origin of such tissue and that at times it is difficult to clearly determine the exact origin of a given tissue.

The incidence of endometrium-like tissue in the abdominal scar after cesarean section was utilized by Sampson (62) to support the theory that peritoneal endometriosis, at times, might arise from the implantation of bits of uterine mucosa escaping into the peritoneal cavity. Cullen (X) reported three cases of postoperative endometriosis of the abdominal scar and he expressed the belief that they arose from the endometrial tissue transplanted by the surgeon.

In more recent years several cases of endometrium-like tissue in abdominal scars have been reported and many of these followed operations where the uterine cavity had not been incised. These cases have influenced the supporters of the serosal theory of endometriosis of the peritoneum to claim that the endometrium-like tissue of laparotomy scars arises from the inclusion of bits of the peritoneal serosa in the wall and its subsequent trans-
2. Implantation Theory of Sampson

formation into muellerian mucosa rather than from the growth of bits of muellerian mucosa transplanted by the surgeon.

Novak (48) questions the origin of the endometrial tissue in abdominal scars by transplantation. He mentions a case reported by Pankow where such a condition developed in the abdominal scar of a woman at the age of thirty, following the removal of an appendix when she was a child. He reports a case of his own containing typical endometrium following the removal of one tube and ovary. He does not believe that there is sufficient evidence for assuming that these cicatrix endometriomas are due to the actual transplantation of endometrial tissue, especially in cases where the uterus is not entered at operation. On the other hand, he states that this possibility can not be denied. He believes that the arguments which he has set forth in his paper speak for the possibility of the origin of such growths from the coelom derived peritoneum, as with the similar growths elsewhere in the peritoneum.

Sampson (62) has been interested in endometriosis of laparotomy scars for several years, but had not had an opportunity to study a case of his own until Sept. 1926, when he encountered one following ventrofixation of the
2. Implantation Theory of Sampson

uterus after cutting and ligating both tubes.

If tubal sterilization of salpingectomy is ever in any way responsible for the presence of muellerian mucosa in the abdominal scar, we would expect frequently to find endometriosis of the tubal stump and also of adjacent or adherent structures following operations in which the tubes have been removed or cut and the uterus retained. If it is true that the muellerian mucosa in abdominal scars, following salpingectomy arises from a transformation or differentiation of bits of peritoneal serosa included in the abdominal wound, as claimed by the supporters of the serosal theory for peritoneal endometriosis, the endometriosis of the tubal stump and the neighboring pelvic structures should have a similar origin. If it can be shown that the endometriosis in the latter structures, at times, arises from tubal and uterine mucosa by direct extension and transplantation, a similar origin, at times, might account for the muellerian mucosa in laparotomy scars following salpingectomy.

After considering certain phases of the subject of endometriosis, Sampson (63) summarizes the evidence indicating that peritoneal endometriosis, at times, arises from the implantation of muellerian epithelium escaping
2. Implantation Theory of Sampson
derived through or from the tubes as follows:

1. It occurs in women and not men.

2. It is an acquired lesion and usually (possibly always) developed during the menstrual life of women and most frequently in the latter half of life.

3. Experiments in the autotransplantation of bits of muellerian mucosa in the lower animals by Jacobson and others show that it may be successfully transplanted to the peritoneum of these animals.

4. The study of postoperative endometriosis in women shows (or at least suggests) that tubal and uterine epithelium may be successfully transplanted by the surgeon.

5. The study of endometrial tissue in the ovaries suggests that this tissue may spread to the peritoneum by the implantation of epithelium which escapes from the ovary both through the perforation (menstrual) of endometrial cysts and also the menstrual reaction of endometrial tissue on the surface of the ovary. This evidence is purely circumstantial, but to him it is most convincing.

6. Peritoneal endometriosis often occurs without any discernible endometrial tissue in the ovaries, the latter, therefore, not being essential to the development of the peritoneal lesion.
2. Implantation Theory of Sampson

7. One of the outstanding features of patients with peritoneal endometriosis is that the tubes are usually patent. In 342 patients with peritoneal lesions containing endometrial-like tissue (other than post operative) encountered by him in the last six years, both tubes appeared to be patent in 330. A unilateral hematosalpinx was present in 3 and bilaterally in 4. Patent tubes apparently increase the incidence of peritoneal endometriosis and the relatively large number of patients with a hematosalpinx must be of some significance. In the cases with occlusion of both tubes, the peritoneal lesions might have been present prior to the closure of the fimbriated ends of the tubes.

8. The peritoneal lesions often occur in situations and under conditions indicating their origin from material escaping from or through the patent tubes.

9. The present study shows that the traumatized mucosa of the tubal stump (after salpingectomy) may not only invade the stump but also any structure adjacent or adherent to it and give rise to the lesions of the peritoneal endometriosis, including typical endometrial cysts or hematomas of the ovary.

9. The present study shows that the traumatized mucosa of the tubal stump (after salpingectomy) may not
2. Implantation Theory of Sampson

only invade the stump but also any structure adjacent or adherent to it and give rise to the lesions of the peritoneal endometriosis, including typical endometrial cysts or hematomas of the ovary.

10. These same studies show that this misplaced tubal mucosa may assume the structure of the uterine mucosa. Therefore, many of the endometrial-like lesions of peritoneal endometriosis could be of tubal and not of uterine origin.

11. It has been shown that bits of the uterine mucosa, set free by curettage, may be carried by blood escaping from the uterine cavity into the tubes.

12. It has also been shown that, during menstruation, blood may escape from the uterine cavity into the tubes and that this blood may contain bits of the uterine mucosa.

13. We have evidence indicating that bits of uterine mucosa may escape into the venous circulation of the uterus during menstruation and become implanted in the venous sinuses of the uterine wall.

14. Since peritoneal endometriosis develops during the menstrual life of women as the menstrual reaction is one which often causes a dissemination of bits of uterine mucosa and possibly also of the tubal mucosa, it is natural
2. Implantation Theory of Sampson

to look upon it as an important factor in the dissemination of muellerian epithelium into the peritoneal cavity.

15. Tubal epithelium might readily escape from the tubal fimbriae independent of menstruation.

16. The evidence, thus far obtained, shows that peritoneal endometriosis might arise from the implantation of both tubal and uterine epithelium.

17. The present studies support this theory and emphasize the origin of peritoneal endometriosis from the implantation of tubal epithelium, but do not exclude its origin from other sources.

In considering the bearing of the present studies on the etiology of endometrium-like tissue in the ovaries other than postoperative, Sampson states:

"These studies demonstrate that the traumatised mucosa of the tubal stump may, by direct extension, invade the adjacent ovary and give rise to typical endometrial cysts or hematomas of that organ (three cases) and in one instance endometrial tissue on the surface of the ovary apparently arose from the implantation of tubal mucosa from the tubal stump. As has been emphasized, the tubes are usually patent in patients with endometrial tissue in the ovaries and the endometrial lesions on the surfaces of that organ in situations readily contaminated
2. Implantation Theory of Sampson

by material escaping from the patent tubes and where that material would be protected and held in place, thus favoring taking of the graft. Circumstantial evidence indicated that, at times, endometrial tissue in the ovaries arises from the implantation of epithelium escaping from and through the tubes. Because a variety of epithelial structures arises in the ovaries, it is natural to assume that the endometrium-like tissue in that organ, at times, might arise from other sources than the implantation of epithelium escaping from and through the tubes."

These studies support the theory that endometrium-like lesions in the ovaries may arise from the implantation of muellerian epithelium escaping through or from the tubes. It emphasizes the part played by tubal epithelium, but it does not exclude its origin from other sources.

Sampson (62) summarizes his findings:

1. Endometriosis was found in and about the tubal stumps in 30 of 36 patients who had had a previous salpingectomy or tubal sterilization.

2. Post-salpingectomy endometriosis usually arises from sprouts growing out from the traumatized mucosa or the tubal stump. These sprouts may invade not only the
2. Implantation Theory of Sampson

wall of the tube but also the uterine cornu and any structure adjacent or adherent to the stump, such as the tissues of the broad ligament, the ovaries (three cases) and even the abdominal wall in two cases.

3. The misplaced tubal mucosa in these lesions, at times, retains its original structure and at other times assumes both the structure and function of the uterine mucosa including its reaction to menstruation and pregnancy. It presents the histologic picture of endometriosis of nonoperative origin including typical endometrial cysts of hematomas of the ovary.

4. In the various operative procedures, incident to salpingectomy, bits of tubal and uterine mucosa may be transplanted by the surgeon both in the immediate field and also in remote ones. Endometriosis, with the same histologic structures as that present in sprouts, spring up as seedlings in situations where tubal and uterine epithelium might have been shown. It is natural to assume that some of these seedlings sprang from epithelium transplanted by the surgeon.

5. If tubal epithelium transplanted during salpingectomy grows it should also grow if transplanted during other operations than salpingectomy and by other means than operations."
2. Implantation Theory of Sampson

Sampson (63) in considering "Pelvic Endometriosis and Tubal Fimbriae" summarizes his findings:

Primary fimbrial endometriosis develops from the activation and differentiation of the tubal mucosa of the fimbriae into a structure resembling endometrium. A like condition may arise in the mucosa of the ampulla of the tube. These are distinct pathologic entities which may be grouped with primary uterine endometriosis, primary endosalpingiosis, and endometriosis arising from the mucosa of the proximal ends of the tube, postoperative endometriosis continuous with the uterine mucosa also postsalpingectomy endosalpingiosis continuous with the tubal mucosa. They should not be grouped with the various forms of misplaced müllerian mucosa not in continuity with the mucosa lining the tubes and uterus.

He realized that all misplaced müllerian tissue derived from the tubal mucosa etiologically should be designated as endosalpingeal, but when it becomes differentiated into a structure resembling endometrium, he is tempted to call it endometrial.

Primary fimbrial endometriosis may invade or spread over the surfaces of the wall of the tube and mesosalpinx. When it arises in ovarian fimbriae it may likewise involve
2. Implantation Theory of Sampson

the ovary and even cause endometrial cysts of that organ. This differentiated mucosa reacts to menstruation and since it is exposed to the peritoneal cavity, menstrual blood, carrying with it bits of muellerian tissue, readily escapes into the pelvis. This disseminated tissue should possess the same potentialities of implantation as similar tissue escaping from ovarian endometriosis. Primary fimbrial endometriosis in other situations may arise by extension and dissemination. The frequency and importance of this variety in the life history of pelvic endometriosis has not been determined.

Primary endometriosis probably arises in any part of the fimbrial mucosa. In his experience it has developed in the terminal portion of this mucosa, at or near the mucosal junction, in all instances in which he has been able to determine the exact site of origin. The abrupt termination of the tubal mucosa at this point, often with a definite gap between its epithelium and the mesothelium of the serosa, constitutes vulnerable and unstable area. This is manifested by evidence of injury or stimulation with loss of epithelium and reactions indicating repair of an injury, even in normal appearing tubes. The conditions found in this situation may resemble those encountered
2. Implantation Theory of Sampson

in the repair of the mucosa in the severed ends of salpingectomy stumps. He believes that trauma and repair of injured tubal mucosa constitute important factors in the etiology of endometriosis at the mucoserosal junction of tubal fimbriae and about salpingectomy stumps.

A study of conditions often present at the mucoserosal junction, other than endometriosis, indicates that epithelium is sometimes disseminated through the terminal portion of the fimbrial mucosa by reactions, the cause of which is difficult to comprehend. Could this extruded epithelium possibly cause endometriosis by implantation? This is only one of the many unsolved problems relating to pelvic endometriosis.

Many data have been collected which should be considered in determining the etiology of muellerian mucosa on the surfaces of the ovaries and peritoneum. He enumerates a few of these:

1. The frequency of tubal patency and the incidence of hematosalpinx when one or both tubes are occluded.

2. The distribution of the early lesions in situations accessible to the material escaping from the tubes and in sites where this material might be retained.

3. Their character, often indicating a local infec-
2. Implantation Theory of Sampson

tion to an injury caused by some foreign body and the repair of that injury.

4. The significance of menstrual blood both in the etiology and dissemination of pelvic endometriosis.

5. The structure of the epithelial growths in these lesions is the same as that of the tubal and uterine mucosa from which the material causing the lesions was derived.

6. The lesions of pelvic endometriosis, including ovarian, and endometrial cysts not in continuity with the tubal mucosa, are similar to those arising from the invasion of these structures by the activated mucosa of tubal stumps and of primary fimbrial endometriosis, the only difference being a break in the continuity between the muellerian mucosa in the primary and secondary situation. By what phenomena can the spanning of this break be explained?

7. The various stages in the development of peritoneal and endometriosis correspond with similar stages in the development of peritoneal carcinomatosis of accepted implantation origin.

Both uterine and tubal epithelium at times escape through the patent tubes from muellerian mucosa, a tissue
2. Implantation Theory of Sampson

frequently possessing the invasive traits of carcinoma. Tubal and uterine epithelium sometimes becomes activated as the result of trauma and repair causing endometriosis under these circumstances (tubal stumps, mucoserosal junction of fimbriae and incised wound of the uterus.) Therefore it is possible that a similar repair of injury arising from the traumatized (and therefore sometimes activated) epithelium escaping from or through patent tubes, may result in endometriosis on the surface of the various pelvic structures on which this activated epithelium lodges. Occasionally similar lesions apparently arise from muellerian epithelium transplanted during operations on the tubes and uterus.

On the other hand the supporters of the metaplasia theory for the origin of pelvic endometriosis other than that in continuity with the mucosa ling the tubes and uterus, may claim that this is excellent ammunition with which to shatter the implantic theory. Since tubal mucosa may become differentiated into endometrium-like tissue, it is their privilege to assert that mesothelium and the surface epithelium of the ovary, also derivatives of the coelomic epithelium, could become differentiated into either uterine or tubal mucosa if activated by the proper stimulant and that such a stimulant may be present
3. Serosal and Coelomic Theory

to well defined and invariable natural laws. The clinical
and microscopical evidence furnished by the study of ade-no-
myomatous tumors bear undeniable testimony to the scientific
claims embodied in the above biological axioms. Lauche (5)
has correlated these scientific truths to the clinical facts
in his latest monumental contribution, the basic principles
of which are the following: (1) Adenomyoma is a neoplasm
peculiar to the female. (2) The epithelium lining the glands
responds formatively and functionally to the various hormones
in the same manner as does the endometrium. (3) This
reaction occurs in the tumor and in the uterine mucosa
simultaneously. (4) The hormonic response is greatest during
the height of sexual activity.

Robinson (5) then in a group of photomicrographs of an
ovarian adenomyoma demonstrates these facts.

Of the other morphological changes which take place in
the heterotopic endometrial structures is a decidual reaction.
Williams and others have observed it in gravid adenomyomatous
uteri; he has observed decidual reactions in the tubal
mucosa in cases of intra-uterine and extra-uterine gestation,
as well as decidual reactions of the serosa of the appendix.
The pertinent facts aduced from this demonstration prove that
there is a structural and a functional identity between heter-
otopic endometrial proliferations in the ovary and the uterine
2. Implantation Theory of Sampson

in material escaping from or through the tubes. Sometimes endometriosis in the surface of the various pelvic structures is not encapsulated and closely resembles the differentiated mucosa of a primary fimbrial endometriosis, hence why not a primary mesothelial endometriosis in such cases? Sampson (63) would expect that this might occur in patches of tubal mucosa should the latter be present in these situations. He has demonstrated this phenomenon in tubal epithelium which had spread over the surface of the tubes, mesosalpinx and ovary from the fimbriae. We must not lose sight of the fact that a similar type of lesion also occurs in peritoneal carcinomatosis and that the surface of the skin grafts, even very small ones, is uncovered.

The general laws governing the healing of wounds of various structures and organs are the same whether caused by the surgeon or by the disease. A comparative study of peritoneal endometriosis and peritoneal carcinomatosis demonstrates that in each one is the histologic structure of the parent tissue (Muellerian mucosa in one and carcinoma in the other) from which they have arisen as the result of something escaping into the peritoneal cavity.
2. Implantation Theory of Sampson

The same study convinces one that not only are the microscopic pictures of the various stages in the development of the peritoneal lesions in the two conditions similar, but also their end results. Therefore, one is tempted to believe that the fundamental method is the same in the secondary growth in both instances.

If endometriosis arises from a differentiation of the mesothelium due to some stimulant escaping through the tubes we might well infer that peritoneal carcinomatosis might arise from a differentiation of the mesothelium caused by some substances escaping from the parent cancer. Even if this be true, as is possible in some instances, it does not prove that all of the lesions of peritoneal endometriosis and carcinomatosis arise in this manner and that implantation is not the chief method of their origin. Our present conception of metastatic cancer is based on the transplant of carcinoma cells escaping from the primary tumor.

Everett (17) studied the tissue from the isthmic portions of the tubes of uterine cornua of 122 cases, in which no operative procedures had been done in the tubes. Thirty-seven of these cases showed invasion similar to that reported after salpingectomy, but less extensive and the author thinks trauma might cause further
2. Implantation Theory of Sampson

invasion of the process present before operation. He summarizes his work as follows: It has been pointed out that an adenomatous formation composed of either tubal epithelium or endometrium, or in a few cases of both simultaneously, occurs rather frequently in the region of the uterine cornu and tubal isthmus. A previous operative trauma of this region is not essential for the production of such an adenomatous formation. Nor is it necessarily associated with any previous inflammatory process. It may be considered then as a truly neoplastic formation or primary adenomyoma.

"From the types of epithelium described in these adenomyomas it is evident that they may arise from tubal epithelium as well as endometrium. The presence in a few cases of spaces lined by tubal epithelium as well as islands of a metaplasia of one of these types of mucosa into the other. The finding of ten cases in which the interstitial or isthmic portion of the tube, is lined by endometrium rather than tubal mucosa, is further evidence of the histologic variability of this region, and suggests again the possibility of a metaplasia of one of these types of mucosa into the other.

"Evidence gathered from the literature, particularly
2. Implantation Theory of Sampson

from the work of Sampson, tends to show that a number of cases reported as endometriosis are really cases of aberrant tubal epithelium. It is noted, however, that Sampson has called attention to this fact from time to time and in more recent work on "Endometriosis Following Salpingectomy" has stressed the probability of a metaplasia of tubal mucosa into endometrium.

"In a review of 24 cases diagnosed as endometriosis in our own laboratory it has been found that in a third of them there was in addition to the tubal epithelium an endometrial-like stroma. In a few instances cysts lined by tubal epithelium and others with real endometrium occurred in some cases. In one very striking case the same hemorrhagic cyst of an ovary was lined in part by tubal epithelium, while another area of the cyst wall showed real endometrium with stroma and glands. Such cases lend additional evidence to the hypothesis that tubal epithelium may, by metaphasia, be transformed into endometrium.

He concludes: "From the evidence presented above we may derive the following conclusions:

1. An operative trauma is not necessary for the production of an adenomatous process in the uterine cornu
2. Implantation Theory of Sampson or tubal isthmus.

2. Such adenomatous processes do not necessarily result from an inflammatory process.

3. The tissues involved in such an adenomatous process may be either tubal mucosa or endometrium, or both in one and the same case.

4. There is evidence to suggest that in some cases in which endometrium is present it may arise from tubal epithelium by metaplasia.

5. Many cases diagnosed as endometriosis are really collections of cystic spaces lined by tubal epithelium.

6. In some cases of ovarian and pelvic endometriosis real endometrium and spaces line by tubal epithelium occur simultaneously, again suggesting the possibility of metaplasia."

In the consideration of experimental and clinical evidence there has been much produced in the support of the implantation theory. Allen et Al (3) in 1928, found that the sensitiveness to ovarian and pregnant stimuli is maintained as long as the hormone is produced. They are of the opinion that heterotopic endometrium in the human female displays the same predisposition to shed
2. Implantation Theory of Sampson

blood at the menstrual time and produce a decidual reaction during pregnancy as does the uterine mucosa.
Graves (25) presents four cases to prove that the growth of endometrial tissue (aberrant) responds functionally to ovarian activity with regression and growth similar to that of endometrium and shows a structural identity.
Graves in considering "Adenomas of Endometrial Origin in the laparotomy Scars following Incision of the Pregnant Uterus" reviews nine cases, two of which are his own, describing the lesions found in these structures.
He is of the opinion that there was a transplantation of the uterine mucosa, during the operation to the abdominal wall. Heim (41) in a series of experiments on apes, divided them into three groups: in the first group, implants were made into the peritoneum of pieces of the animals own decidua menstrualis; in the second, a fistulous opening was made between the uterus and peritoneal cavity during menstruation; in the third group, fresh human menstrual fragments were implanted into the peritoneum and ovarian epithelium, with simultaneous injection of human ovarian extract. These animals were all killed from four to six days following these experiments and no growths were obtained, only inflammatory
2. Implantation Theory of Sampson

foi remained as evidence of the implantations. Here, again, is contrary evidence, the significance of which is hard to evaluate. Dossensa (41) in a series of experiments, on white rabbits and mice, removed the uterine mucosa, examined it and scattered it in the abdominal cavity obtaining cystic growths of the tissue without scarification of the peritoneum. These cystic cavities were lined with columnar epithelium and were surrounded by a vascular connective tissue stroma and non-stripped muscle fibers; this evidence he believed to give support to the theory of Sampson. Katz and Szenes (41) transplanted pieces of endometrium into the peritoneal cavity of rabbits in some before and in some after castration. The transplanted tissue grew in those not castrated but did not grow in the castrated animals. From this they concluded that endometrial implants were possible but required ovarian hormone substance for their growth. Walz and Heim (41) on the other hand, say it is only the basal cells of uterine glands which are productive of new cells and the cells shed before menstruation do not include these basal cells of the gland and therefore cannot grow and multiply. From this work with in vivo experiments it would seem that uterine tissue containing the basal layers of glands will grow and multiply
2. Implantation Theory of Sampson

with implantation in the presence of ovarian hormone, but menstrual blood which does not contain the basal layer of glands will not grow and multiply.

Allen (1) took small bits of endometrium, ovary and peritoneum and immediately slipped them into the anterior chamber of the eye, using 25 rabbits. For comparison, in a few animals, endometrium was implanted into one eye and rather large strips of peritoneum or ovary into the opposite eye. The animals were autopsied at intervals of 15 days and 13 months. The eyes were enucleated, fixed, sectioned and stained. He concludes:

"1. Uterine epithelium in rabbits possesses more marked proliferative and heteroplastic tendencies than the epithelium of the peritoneum or ovary. 2. This proliferative tendency carries with it the property to stimulate local connective tissue response. 3. Transplanted endometrial tissue does not proliferate. 4. Follicular activity is maintained in this location for a considerable length of time. 5. Metaplasia of uterine epithelium may be produced by transplantation into the anterior chamber of the eye in rabbits." He believes that the clinical evidence seems to indicate that when endometrial cells are displaced from their usual location, they con-
2. Implantation Theory of Sampson.

continue to grow and sometimes produce symptoms. Adenomas growing in laparotomy scars are ample evidence of this vicarious growth. The method of displacement in these instances is quite definite; namely, operative procedures which injure the uterine mucosa.

We do know that normal endometrium is a tissue that possesses a peculiar viability. In addition, it has a marked power of proliferation which we see so well expressed during the changes incident to pregnancy and the rehabilitation of the mucosa following the menstrual period.

The cells of the endometrium are therefore, in constant state of change, due to cyclic stimuli. Embryonal cells quickly grow to maturity and are again replaced by a group of new cells of high activity.

Cron and Gey (6) have shown that even the cells of the older endometrium cast off at menstruation can readily be grown in culture media. Epithelium from a menstruating uterus was cultured in vitro. The epithelium (decidua menstrualis) was obtained by gently removing with a dull curette a small amount of the menstrual flow during the second day of period. Specimens were put in normal salt solution, washed and concentrated with centrifuge. Part of the remaining tissue sectioned and examined. Tissues
2. Implantation Theory of Sampson

put in a plasmotic medium containing heterologous embryonic extract as the growth promoting substance. The tissue then showed cellular activity. The experiment established beyond a doubt, according to these men, that the epithelium of the decidua menstrualis, which is found in the menstrual fluid, is viable.

The stimuli which produce the rhythmic changes in these structures of the female pelvis are the result of the action of the female sex hormone or hormones, which is being so actively investigated.

Numerous investigators including O'Keefe and Gorssen (50) and Jacobson (30, 31) have shown that when endometrial tissue is transplanted in the experimental animal it retains its power of growth.

E. S. King (36, 37, 38) opposes the implantation theory of Sampson. He states (37):

"The striking feature of the evidence in favor of the implantation hypothesis is the large number of circumstantial observations (Singly of little importance) and the complete absence of anything in nature of direct proof."

He believes that there are certain general laws which must be kept ever to the fore in pathological investigation. First certain principles have for their support
2. Implantation Theory of Sampson

a large mass of evidence accumulated during many generations and these should be applied to observations before the introduction of new or conjectural variations of these principles. Second, pathological structures should be interpreted in terms of physiological reactions and embryological character of the tissue in which or from which they arise. He says that for the explanation of endometrial implantation certain unusual if not unique pathological processes have been invoked. The implantation of presumably normal adult tissue into other organs of the body, where these implants assume an irritative character is a departure without precedent from accepted pathological teaching. The necessity for introduction of idea of "hot bed" or "incubator" suggest immediately that some ordinary feature has been overlooked. The passage of abnormal tissue along natural passages with subsequent implantation on a surface has been described on several occasions though in but few examples can this explanation be satisfactory. Usually other mechanisms are used as more probable explanations.

King (37) insists that passage of tissue through the vessels from the uterus to the ovary is difficult of comprehension in the absence of emboli of the lungs, in the case of veins; or in the lymph nodes in case of
2. Implantation Theory of Sampson

the lymphatics. Sampson on the other hand, believes this is so. In addition King continues, a retrograde spread from the uterine vessels into the ovarian veins or lymphatics must be postulated to explain the position of the cysts.

Pathological teaching with regard to the relationships of certain enoplasms to their parent tissues has been emphasized, of recent years, by the use of terms as chorioma, folliculoma, thymoma, among many others. When tissues which will respond in a certain manner to abnormal stimuli are present, it seems unnecessary and indeed, undesirable to postulate extraneous material until that of the involved organ has been explored thoroughly.

King (37) believes that morphological and even physiological similarity does not constitute identity ("Endometrial"). Too readily has it been accepted that the endometrial character of the epithelium of the perforating chocolate cysts can be concluded with safety from morphological similarity, the presence of subepithelial stroma, the occurrence of hemorrhage into and around the cysts, and the presence of decidua changes in epithelium and stroma during pregnancy. This conclusion can be attacked from two different points of view: (1)
2. Implantation Theory of Sampson

The development of tissues apparently identical with a given type, may take place at a distance from the usual site of occurrence of the site of tissue without there being any question of transplantation. Examples of this are the development of squamous epithelium in a bronchus or of "gastric" glands in a gall bladder.

(2) Other tissues, obviously not endometrial, may show the characteristics mentioned. Examples of this are columnar epithelium indistinguishable by the methods in use from uterine epithelioma occurs in ovarian cysts and tumors. A subepithelial stroma is common to many glandular neoplasms, not only in the ovary but in other parts of the body. Hemorrhages occur in cysts other than the "endometrial", e.g., the luteal cysts. Decidual changes may be found in subepithelial tissue near the surface of the ovary and decidual cells have been described in sub-peritoneal tissue of most of the lower abdominal organs. The writer has observed "glands" derived from an epithelial down growth which showed columnar epithelium and stroma containing decidual cells. The occurrence of this change can be of little importance in the determination of the endometrial origin of the perforating blood cysts.

King (37) attempts to show that the implantation
2. Implantation Theory of Sampson

hypothesis, at least as far as the ovary is concerned, is not on certain foundation. He believes in the luteal origin of the tarry cysts of the ovary. Contends that if a section through one of these cysts is taken in a certain manner the luteal cells will not show, and then the examiner will conclude that these cysts are endometrial in character. In the discussion of the luteal origin of the tarry cysts this will be considered in more detail. He believes that these structures arise by metaplasia from cells which are present in the ovary, and not from cells of another organ by a peculiar process of transplantation.

In further discussing the implantation theory of endometriosis, he says: "Consider the condition of the multiple blood cysts of the ovary from the view of the protagonists of the transplantation hypotheses. The condition found in the ovary consists of numerous blood cysts and blood is found both in the cavities and in the walls. They are lined by an epithelium which in a typical case is columnar but may be cuboidal or flattened (stated to be due to the pressure of the cyst contents). Beneath the epithelium, there is a stroma of spheroidal cells which resemble the immediately subepithelial tissue in the wall of the uterus. In some circumstances this
2. Implantation Theory of Sampson

may be scanty or absent. Most reports and descriptions recognize some follicles or luteal bodies in the organ, but they are regarded as incidental. The presence of hyaline tissue in the wall of some of the cysts has been mentioned. The difficulties in the acceptance of the Implantation Theory are several:

(a) The absence of epithelium (or the extreme flattening of epithelium) and the absence of "stroma" which may occur over large areas of the cyst walls, renders necessary the further hypothesis of destruction or distortion of these tissues. Their original presence on these areas in which it is not found is pure assumption.

(b) The hypothesis ignores the hyaline tissue which is present in the walls of some of the cysts.

(c) It overlooks the associated small cysts of the ovary which are of follicular or luteal origin and therefore overlooks completely the normal processes of the organ involved.

(d) It takes no cognizance of the pathological changes in tarry luteal cysts.

Physiological changes play an important part in the implantation hypothesis. Hemorrhage occurs in these cysts in association with the menstrual period. It is known, however, that hemorrhage into luteal cysts occur
2. Implantation Theory of Sampson

at these periods also. I have observed at operation bleeding from a tarry luteal cyst (proved by subsequent section) during a menstrual period. Both tarry material and fresh blood were present. The occurrence of hemorrhage does not necessarily support an endometrial origin."

King (37) using the ovary as the starting point agrees with Sampson as to the further spread of endometriosis in the peritoneal cavity. Rupture of cysts with formation of secondary growth on the peritoneum is accepted by Sampson. He considers that the ovary provides a "suitable soil" for the early growth of these cysts. The objection is that endometrial growths do not occur in the peritoneum more frequently without the involvement of the ovary. In this respect it should be noted that sometimes microscopic examination of the ovaries which appear to be normal and which are associated with peritoneal cysts show also the epithelium lined cysts. He states that "if we grant that the ovary is the starting point for abdominal blood cysts, then both the implantation hypothesis and the tarry cyst suggestion are on common ground, because the transperitoneal spread of tissue in the peritoneal cavity, after the rupture of the cysts is a well recognized phenomenon. The ability of the
2. Implantation Theory of Sampson

glands arising in the tarry cysts to invade tissue as shown by their development beyond the confines of the wall, of the original cyst. That they should develop further when split into the peritoneum is therefore not surprising." He also does not agree with the analogy of Sampson concerning peritoneal carcinosis. He does not believe that these are cases of transplantation.

In summary it may be said that the only point of difference is that King doesn't agree with the trans-tubal regurgitation of endometrial tissue but rather begins the life history with the tarry cyst, which in reality, is a luteal cyst in the ovary and then continues similarly to Sampson's theory. The luteal cyst theory of King will be discussed in more detail in a later section.

King (36) also contends that the fact that implanted endometrium will produce blood cysts can not be taken as evidence that cysts in the ovary which are superficially similar are of that origin. He cites a case, where an apparently normal ovary that was not previously the seat of any endometrial characteristics, was transplanted into the anterior abdominal wall where it subsequently developed blood cysts. He is certain that these cysts are of ovarian origin. This will be again referred to
2. Implantation Theory of Sampson

later. He states that "one of the most important arguments raised is that transplantation of endometrial tissue, either accidentally found during operations on human beings or experimentally on animals, results in the formation of blood ruptured ovarian epithelium lined blood cysts. From the similarity of these two implants, it is argued that they are identical and therefore that the ovarian cysts are endometrial in origin." Contends that this is a fallacy. The experiments with uterine mucosa are merely an example of growth of transplanted tissue such as occurs in many other cases, e.g., the bladder wall, stomach, bone and many other tissues. If the original tissues are similar, and this is generally recognized, then one would expect the implants of both to be similar. It does not necessarily indicate their identity.

Dougal (15) believes that there is retrograde menstruation as is evidence when performing abdominal operations during the menstrual period where occasionally blood is seen dripping from the fimbriated ends of the tubes or lying in the posterior culdesac.

Many observers as Enser (16) are of the opinion that although this theory of implantation may explain certain
2. Implantation Theory of Sampson

sites that do not fit in at all and one of these is the endometrioma of the umbilicus.

In the foregoing there has been an attempt to present the chief evidence in favor of the theory of implantation as well as some of the more important objections with some refutation of the objections. It may be stated that at the present time this is one of the most important theories used in the explanation of the phenomena of endometriosis and has a widespread support among various authorities.
3. Serosal Or Coelomic Theory

This theory is based on the fact that the epithelia of the female genital system are derived from the coelomic epithelium of the urogenital folds, which in turn is a modification of the primitive peritoneum. These epithelia comprise not only the germinal epithelium of the surface of the ovary, the lining of the follicles, and possibly the ova, but also those invaginations of the Muellerian duct represented by the endosalpinx, endometrium, endocervix, and vagina. In other words, the entire epithelial apparatus has a common ancestor in the peritoneum. Now it has been shown by Fischel (51) that the coelomic epithelium does not "use up" its developmental potentialities, and that in later life it may awaken to new activity and produce differentiated structures identical with those which it produced when in the embryonic stage. Thus, it is supposed, that the germinal epithelium of the surface of the ovary may invade the ovarian substance and create endometrium, and result in the so-called hemorrhagic or chocolate cysts. It is also believed that the pelvic peritoneum may at any point develop this innate tendency and produce the so-called ectopic endometriomata.

Ivanoff in 1898 believed its origin to be from a metaplasia of the peritoneal mesothelium, which view has been recently revived by R. Meyer and Lauche. Lauche (51) referring to Walz, describes the coelomic basal cell as bipotent that it is capable of forming two types of the cells, serous epithelial
3. Serosal Or Coelomic Theory

cells and endometrial cells which are unipotent and differentiated. These two types of cells have a common origin but develop along two divergent lines of differentiation according to the principles of physiological specialization and adaptation to environment and function. It is in the highest degree unlikely that a serosal cell could undergo metaplasia become converted into an endometrial cell and explain the occurrence of uterine glands in the peritoneum. It would appear that the only logical explanation is that such endometrial cells have arisen from basal coelomic epithelial cells, occurring scattered in the serous epithelium which has differentiated during post-fetal life at the primitive stage and possessing the primary function of reproduction.

Leuche (39) in 1923, discusses extragenital heterotopic epithelium in the intestines with a structure of uterine mucosa. He is of the opinion that heterotopic proliferation of epithelium in the intestines, adenomas in the scars after laparotomies, and true umbilical adenomas are relatively rare. The author has observed one case of such proliferation in the intestines, four adenomas in laparotomy scars, two cases of umbilical adenomas and two cases of proliferation in the inguinal region.

The author makes the following conclusions: All heterotopic benign proliferations with the structure of the
3. Serosal Or Coelomic Theory

uterine mucosa derive from the peritoneal epithelium. The following formations belong to this group; 1. Heterotopic proliferations of the epithelium of the intestines originating in the serosa. 2. "Adenomas" in the scars after laparotomies. 3. True umbilical adenomas. All these three groups have the same structures; all of them appear only in sexually ripe women and all of them have relation to the menstrual cycle. Histologically and clinically they have similar symptoms. They consist of glandular tissue and cysts lined with one layer of cubic or cylindrical epithelium; at least in a few places a stroma can be found which is rich in cells. The height of the epithelium depends upon the proximity of the stroma; the epithelium is cylindrical even in cysts if they are located close to the stroma. The glands have exactly the same appearance as in the uterus: the same applies to the stroma; therefore a conclusion is justified that the new formation originates in the uterine mucosa. Such tumors in the umbilical region can form from remnants of a physiological umbilical hernia; they do not originate from the omphalo-mesenteric duct. In the inguinal region such proliferations derive from the residues of the vagina process of the peritoneum. Three processes are theoretically possible: 1. Formation of real tumors, so-called blastomas. 2. The tumors may be products of transplantation of uterine mucosa. 3. In majority of cases the formations are to be regarded as proliferations formed as result of compensatory
3. Serosal Or Coelomic Theory

formation of the uterine mucosa. Real blastomas are those which derive from residues of embryonal protrusions of the coelom or from parts of Müller's ducts; some umbilical and inguinal proliferations belong to this group; they are characterized by sharp borders and are not connected with peritoneum. Usually some muscular fibers are present. The proliferations in the abdominal wall are mostly transplantations of the uterine mucosa in the laparotomy scars; they can not be regarded as result of inflammation because the stroma has no appearance of granulation tissue. However, inflammations play a role as contributing factors. Hence a nomenclature suggesting inflammation is not proper. The presence of inflammation in combination with action of ovarian hormones seems to be necessary to provoke the formation of such tumors. All proliferations which are not tumors and not the result of transplantation of the uterine mucosa should be grouped under the name of fibroadenomatosis.

Before continuing the discussion of the various ideas and contentions concerned with this theory it would be well to review several basic principles.

The method dominating every histogenetic and pathological inquiry is the descriptive, which aims at an accurate recording of the form, shape, and size of the individual cells, and of the relationship they bear to each other and to the stroma as a whole. Its postulate is; morphological similarity proves genetic identity. This idea caused the adherents of the
3. Serosal Or Coelomic Theory

mesonephric theory to adopt a primordial kidney origin, because the arrangement of the glands in the adenoma seemed similar to those in the primitive aorta; and those who by ocular observation discerned an endometrial foundation concluded that the genetic source was the uterine lining. We can not minimize the value of this method but we must bear in mind that it constitutes only one of the means by which a conclusion regarding the histogenesis may be rejected. To solve the structural origin of a tumor by morphological data only is as erroneous as to arrive at biological deductions from facts which are the result of cultural and environmental influences. In fact one of the weakest links in Darwinism is the over emphasis laid upon the purely formative side of evolution. We must also not forget that a fully formed cell such as we see in adenomyoma or in other tumors is the product of genetic potentialities plus biological forces, which came into play in the latter stages of ontogeny. Histogenesis research must therefore antefate the period of cell differentiation.

Fischel (51) stated: "When we examine a tissue or an organ we find that its chief components, the epithelium and the connective tissue, present well defined and differentiated structural characteristics. In the embryos, however, all epithelial cells, arising from all the three germinal layers appear alike; the same holds true of the embryonal connective
3. Serosal Or Coelomic Theory

tissue which consists essentially of the same cells throughout the body. Somehow, somewhere, at the proper time and moment, in the process of development, genetic forces harbored within the embryo, become liberated and distributed to the individual cell groups of the germinal layer, the latter respond to these stimuli and begin to build up the tissue and organs they are destined to construct. What the forces leading to differentiation are, we do not know as yet. Biologists call them determinants, but we do not know that for the unfolding of the genetic potentialities harbored within the cells, certain biochemical and physiochemical conditions must arise within the embryo. We may hence assume justly that normal and abnormal growth are respectively the results of a balanced or a disproportionate play, between the stimulating and the inhibitory forces. We also know that the multipotency of the epithelium of the germinal layers is only partly used in the upbuilding of the body. The rest or excess of the epithelial cells, remains permanently or temporarily quiescent, depending upon whether the genetic forces remain potential or become kinetic. Besides the growth influences furnished by the embryo, and the growth requisites supplied by the cells, there is also an intercellular factor, strikingly affects the process of differentiation; namely the structural and functional relationship between the covering
3. Serosal Or Coelomic Theory

epithelium and the underlying connective tissue.

Upon the biological phases of intercellular reciprocity, Fischer (51) expressed himself as follows: "We may postulate it as a law in organic development, that the epithelial elements play the dominant and leading role, the connective tissue the subordinate or dependent part. The former becomes differentiated in a definite manner in the early stages of development into typical types for each organ; the connective tissue portion on the other hand differentiates itself much later, and the manner of its differentiation is dependent upon the formative influences which the overlying epithelium exerts upon it. The connective-tissue dependence upon the epithelium continues throughout life; during the embryonal state the dependence is formative, and later on functional."

Another pertinent biological fact in the study of histogenesis is the constant reciprocal relationship between genetic potentialities and genetic forces. We have stated before that the primitive epithelium is multipotent so that it can form any type of epithelium, but this property is enjoyed by it only up to the time of segregation when this apparently homogeneous mass of epithelial cells subdivides itself into definite cell groups, each of which is destined to form a specific tissue or organ. The moment this division
3. Serosal Or Coelomic Theory

has taken place, then the genetic potentialities inherent in, and characteristic of, each cell group, unfold themselves, and remain invariable properties of these cells throughout their entire existence. Furthermore, these genetic potentialities respond structurally and functionally only to their own and peculiar genetic forces furnished by the embryo as a whole. Through the harmonious play between the intrinsic and the extrinsic cellular forces normal growth develops and function progresses.

Hence a conclusion regarding the histogenesis must be so comprehensive as to include not only proof of structural identities between the neoplasm and the tissue or organ of which it is claimed to be derivative, but also evidences of functional similarity.

Although unable to explain satisfactorily how the mullerian rests have reached many of the adenomyomatous sites, Cullen and his school, were nevertheless right according to Robinson (51), in their steadfast adherence to their theory, for they have always observed that the adenoid growths in the tumors bore not only a structural resemblance to the endometrium, but that they also simulated the uterine mucosa functionally. The followers of the mesonephric theory could claim at best only formative resemblances, but at no time were they able to prove functional processes in the adenomatous tumors which equalled those of the fully developed kidney. One of Robert Meyer's (51) last statements, that
3. Serosal Or Coelomic Theory

"ovarian hormones may also influence primordial kidney rests to endometrial proliferation" must be accepted very guardedly and dubiously. This supposition is most likely founded upon the multipotency and structural homogeneity of the coelomic epithelium out of which both the genital and the urinary organs are derived. This is, however, not a valid reason for the admission of promiscuity between the genetic potentialities and genetic forces.

The fact that we can not as yet distinguish by the means at our command between the very earliest analges of the apparently uniform coelomic epithelium, does not warrant the assumption that cells destined to form genital organs can and will respond to stimuli prepared for the activation of urinary rudiments, and vice versa. According to Corning, (51) "We are still unable, with the means at our disposal, to detect sex differentiations before the embryo has reached the length of 18 to 20 mm.; this does not imply, however, that no sex differences exist before this period the indifferent state. On the contrary, it is becoming more probable that sex determination develops early in the ovular period."

What is true of sex determination is and must be equally true of genetic potentialities which are present in the cell long before the microscope can reveal them, and of the genetic forces, the mutual action and reactions of which are subject
3. Serosal Or Coelomic Theory

mucosa; hence both must have a common genetic source, and must be influenced by the same hormone or hormones. The same applies to all types of adenomyoma.

He continues, What is this common genetic soil from which spring all endometrial growths? Since the coelomic epithelium is the structural source of the generative organs, any morphological phenomenon arising within the body during adult life which simulates the uterus structurally and functionally must of necessity be a derivative of the same embryological rudiment. What really takes place in the evolution of an extra-uterine endometrial growth is a topical awakening of the genetic potentialities in some of the unused coelomic rests; through a sudden increase of the stimulating or through a diminution of the inhibitory genetic forces. With this explanation in mind, the difficulties presented by the theory of displacement are at once removed; and since it is not necessary for endometrial or endosalpingeal parts to be actually transported to different regions in the body, to act so to speak as adenomyomatous seeds, the terminology of displacement must be discarded. In its stead, Robert Meyer proposed the terms, heterology, or heteroplasia of the peritoneal epithelium. The same process of reasoning is applicable to the cytogeneous tissue present in the adenomyomatous tumors, which are considered by the adherents of the theory of displacement as positive proof of endometrial transportation, since this tissue is not found anywhere else
3. Serosal Or Coelomic Theory

in the body except in the uterus; this however, is not the true condition. If we recollect the biological principle that the overlying epithelium exerts a definite formative and functional influence upon the supporting connective tissue stroma, then the finding of cytongeneous tissue around the glandular spaces is but a normal and natural sequence and just as the coelomic epithelium is capable of heterotopic endometrial proliferation without having to be displaced from the primitive (or fully developed) urinary or genital tracts, so can and does the connective tissue in the vicinity of these glands undergo cytongeneous metamorphosis identical with that of the uterus without the process of displacement.

Robinson then presents a clinical verification of the biological and embryological principles. The keystone of the histogenetic arch is the structural and functional similarity between the neoplasm and the soil of its derivation. Of all the tissues in the female organism, the coelomic epithelium is unique in possessing adenomyomatous anlagen. To complete the histogenetic equation, we must add to the already known factors, genetic potentialities and genetic forces, the anatomic proof that coelomic epithelium or its later modifications into peritoneum or mucosa is present in the locations where it usually occurs.

Uterine and tubal adenomyomata, in which the anatomic continuity between the endometrium or the endosalpinx and the
3. Serosal Or Coelomic Theory

neoplasm is traceable, present no histogenetic problem.
The adenomyomata, in occupying the outer uterine zones
or situated subperitoneally are derived from the covering
serosa; a definite adenomyomatous source.

Ovarian endometrial growths arise from the covering
germinal epithelium; and while this tissue also serves as
a genetic source for other tumors, it manifests the adeno-
myomatous proclivities under certain and propitious conditions
only. Inflammation may act as an exciting cause. At times
the adenomyoma of the ovary of the ovary may be a prolong-
ation form a similar growth in the uterine wall. Which-
ever may be the case, the coelomic epithelium basically is
the starting point.

Robinson (51) states that round ligament adenomyomata,
whether of the intra or extra-abdominal portions, take their
origin from the peritoneal reflection, which accompanies it
throughout its course, at times, even as far as the labia
majora. Umbilical adenomyomata also originate from coelomic
rests, the exocoelom, which accompanies the urachus, the allan-
toïs and the umbilical blood vessels, as they make their exit
through the abdominal ring. Laparotomy adenomyomata also
originate after operation in which the genitals did not enter
into the operative scope; this has been proved clinically.
The genetic source is the injured parietal peritoneum. All
the other organs and tissues in which adenomyomata have
3. Serosal Or Coelomic Theory

developed, according to him have as one of their anatomic constituents, either a serous covering or a lining which in the broad embryological sense is the same; hence a potential adenomyomatous source. He states, "We have proved that all adenomyomata are alike in structure and function, that they all respond to the same stimulatory or inhibitory basis for a heterotopic endometrial proliferation."

In considering Tubal adenomyomata Chiari accepted an inflammatory cause with which Robinson agreed in 1913 (51). The basis of this was the associated subacute or chronic salpingitis of a Neisserian or a tuberculous nature and the seemingly identical intratubal and intraglandular contents. Robert Meyer and V. Franque have also laid stress upon inflammation as the etiologic agent in the development of pelvic adenomyomata. Sampson also seems to be in accord with this to some extent. There were reasons which R. Meyer and also v. Franque questioned whether adenomyomata should be included in the category of tumors. They were of the opinion that these neoplasia were mixed tumors. Consisting of myomata with inclusions of hyperplastically inflamed glands, hence the term "adenomyositis." In support of this view the above authors cited the clinical observation that these tumors diminish in size and disappear at times with the subsidence of the inflammation. Robinson states "It is my contention
3. Serosal or Coelomic Theory

that while inflammation may act as the primary impulse in some cases, and sets the coelomic rests into the proliferative swing, it is not the fatal cause dominating the further development of these tumors." He believes that it is really a biological metamorphosis and not an inflammatory one. "The ultimate cause of adenomyomatous growths is an excess of the ovarian hormones which under given biological conditions exert a proliferative influence upon the dormant coelomic rests to adenoid formations; the latter respond to this hormone in a functional way as well, as expressed clinically by menorrhagias and metrorrhagias, by the formation of tarry cysts in the ovaries, and by the periodic enlargements and shrinkage of the adenomata at the beginning and the end of each menstrual period."

He concludes that histogenetic investigation must anticipate the period of cell differentiation. Morphological similarity is not synonymous with histogenetic identity. Histogenetic proof demands functional as well as structural similarity between the neoplasm and the tissue or the organ of which it is claimed to be a derivative. The theory of displacement no longer fulfills our present concept of heterotopic endometrial formations; it should be discarded. Adenomyoma is peculiar to the female and is prevalent during the period of maximum procreative function. The coelomic epithelium harbors adenomyomatous potentialities which it
3. Serosal Or Coelomic Theory

unfolds when acted upon at the proper time and moment, by specific genetic forces furnished by the body as a whole. The columnar epithelium is capable of exerting cytogenic influences upon its supporting connective tissue. The genetic source of all adenomyomata irrespective of location, is the coelomic epithelium. Inflammation may precipitate an adenomyomatous process but it can not enhance its growth and development; the later being the result of biological or biochemical processes.

Nicholson (45) in 1926 discussion "Endometrial Tumors of Laparotomy Scars" reviews the peritoneal theory. This assumes that the epithelial cells of the peritoneum, when they proliferate in response to an irritation, the nature of which is unknown, undergo differentiation in situ into uterine epithelium. Although there is not very much, or very conclusive, evidence in its favour, it is applicable to certain cases at least and, which is of great importance, compatible with biological facts. It is the best theory hitherto devised to account for endometrial tumors of the intestines and peritoneal surface of the uterus and its adnexa, and applies to these of the ovariolicus, the groin and laparotomy scars. It will be well to review the evidence in its favor.

(a) Direct evidence: It has been shown in a good many intra-abdominal tumors that they permeate the wall of the gut,
3. Serosal Or Coelomic Theory

uteros, etc., from without, and in several cases direct
histological continuity has been established between the
peritoneal epithelium and that of the tumor. This applies,
as we see, to Tobler's tumor of a laparotomy scar.

(b) Biological evidence. We must assume that an organ
is produced in its normal situation, and nowhere else, because
its cells are subjected to a long sequence of appropriate
stimuli only at this spot, the cumulative effect of which
is the assumption of the corresponding physiological structure.
Thus, endometrium is produced only at one spot, not only
because the epithelium or other parts of the coelom of the
embryo is incapable of undergoing differentiation in this
direction, but because the environment, to which it is the
response, directed this change here, and nowhere else, through-
out embryonic life. Although it is inconceivable that endome-
trium could be produced in other parts of the peritoneum in
development, it is a matter of experience that it never is,
since accessory ducts of Mueller are not found except in the
immediate vicinity of the principle ducts, and endometrial
tumors are unknown in embryos and children. Until these
things have been demonstrated in them, it is contrary to
experience to assume that the tumors in women originate
in congenital accessory uteri or congenitally predisposed
cells. To the best of our knowledge the tumor is always
3. Serosal Or Coelomic Theory

acquired. It is something new. It follows from this that there is not the slightest evidence that its cells of origin were not, at one time, perfectly healthy, normal cells.

(c) Pathological evidence. Since, as he has attempted to show, the structure ultimately assumed by the cells depends largely upon the influence of their environment, it follows that, should the latter change, the former may undergo a corresponding change. Evidence is steadily accumulating that this actually happens in many pathological states. Examples are heteroropic bone formation and metaplasia of epithelium. There is no prior reason why every differentiation undergone in development by the tissues of the embryo should not be repeated during the whole life of the individual in pathological states. Since the endometrium arises in the cells of the coelom, the peritoneal cells of the adult may well produce endometrial epithelium. Again if they be subjected to a suitable abnormal environment. He believes this conclusion to be sound and unassailable, since it is backed by good evidence. Our first and, at present, insurmountable difficulty, when we apply it to endometrial tumors, is that we have no idea of the nature of the environment changes. We know that the alteration of type of metaplasia depends upon an influence exerted by the functioning ovaries, since endometrial tumors are absent in males and sexually immature
3. Serosal Or Coelomic Theory

females. Again, we know that the alternation is associated with proliferation of the peritoneal epithelium and a mild degree of inflammatory reaction. But we do not know if the proliferation be a response to an inflammation or of the nature of a compensatory regeneration, as a possible attempt at balancing a defective uterine secretion.

This state of uncertainty is mainly responsible for the differences of opinion as to the status of these anomalies, whether they are to be regarded as regenerations or pure tumors. For it must be admitted, that, in our ignorance of tumor formation, we are inclined to call every nodule of new tissue a tumor when we can not find a cause for its presence, and a regenerative hyperplasia when we can associate it with a causative agent. Without entering into this question in detail, Hapersonally regardsendometrial tumors, together with many, if not all neoplasms, as partaking of the nature of both. They are clearly hyperplasias or accessory uteri in the perfection of their histological structure and the performance of the physiological functions of the endometrium, e.g., menstruation and decidus formation. They are tumors in their often isolated and independent mode of growth and the assumption of irregular shapes. For him they are important links between the physiological tissues and the tumors. He has named them endometrial in this paper
3. Serosal Or Coelomic Theory

because they are structurally and functionally identical with the endometrium and tumor simply in the original connotation of the word, which means no more than a swelling or lump.

He has not discussed the typical endometrial stroma of these tumors nor the plain muscle in them since the presence of these structures is readily explained when we admit that the epithelium has become truly endometrial. It is a well known fact that the epithelia in normal development and pathological growth exert an influence on the cells of the mesenchyme with which they happen to be in contact, and make these assume a corresponding structure. He, therefore, regards the stroma and muscle of these tumors simply as local mesenchyme cells or connective tissue corpuscle, altered and metamorphosed by the endometrial epithelium into uterine mensenchymal tissues.

He concludes "Endometrial tumors are acquired accessory uteri. Of the theories which attempt to explain them the peritoneal is the most generally applicable, and its acceptance offers the fewest difficulties. It alone agrees with the biological facts."

Novak (48) speaks of the Coelomic theory as a concept rather than a theory. He describes it very clearly. He says:
3. Serosal Or Coelomic Theory

"It is possible, as some have suggested that the occurrence of ectopic endometrium at various points in the pelvis is due to the presence of coelomic rests in these regions. But it is just as possible that, aside from the rest theory, that normal germinal or other epithelium of the ovary, or the normal pelvic peritoneum, may under the proper combination of endocrines and other conditions, be quickened to various differentiation phases abnormal for the tissue.

"This is mere speculation, for embryologists, on the basis of careful observations, accept the view that there is a definite and intimate relation between all of the epithelial tissue arising from any one of the embryonic layers. Each one of the original embryonic layers possesses developmental potentialities, which for various organs, are limited at various stages as a result of certain physical or chemical factors either local or general. It thus is evident that the potency of the cells is not used up, so that if, in later life, the same conditions arise which are responsible for the original growth, e.g., a germinal epithelial cell retains considerable degree of unusual developmental potency, and with the proper activation, can develop further into an endometrial or luteal epithelial cell. The same statement may be made of the pelvic peritoneum. What the activating conditions are
3. Serosal Or Coelomic Theory

we can not say, except they are most certainly or endocrine nature. As already stated, these views are not merely speculative, for as Fischel has emphasized, they have considerable support from the embryological studies.

"Applying this contention to the subject of this discussion, one can readily understand why such an intimate relationship exists between the cells of the pelvic peritoneum, the germinal epithelium, the tubal mucosa, and the endometrium for they are all descendents of a common mother tissue, the coelomic epithelium of the urogenital folds. In this sense the endometrium and the endosalpinx are to be looked upon as merely a modified peritoneum, or a modified germinal epithelium, so that it is not so startling to think that either peritoneum, or germinal epithelium plus the necessary but as yet unknown biologic activating stimulus may give this to more or less typical Muellerian mucosa.

"A consideration of possible importance lies in the fact that the activating hormones are probably found in the ovary itself, and that the frequency of germinal epithelium metaplasia may perhaps be due to its proximity to the source of supply of the hormone that there is perhaps a greater intensiveness of endocrine action in the ovary than in more distinct tissues."

There will be a more detailed consideration of the part that hormonal epithelium plays in the production of endometriosis in the later section.
3. Serosal Or Coelomic Theory

Novak thinks he is able to identify many of the stages of differentiation from the germinal epithelium to the uterine endometrium. He has found areas of epithelium growing in the ovary which closely resemble endometrium of the fetal or infantile uterus. He believes the reason all of the aberrant endometrium does not menstruate is that some of it has not differentiated sufficiently to be excited by the hormone that causes the cycle in the uterine endometrium.

Novak has also been able to demonstrate tissues closely resembling uterine and tubal endometrium growing next to each other and being continuous with one another. This is additional evidence in support of the metaplasia theory, he believes. He presents an excellent photomicrograph of such an area in one of his articles.

Enzer (16) describes a case of endometriomyoma of the umbilicus. The tumor was composed of glands and stroma similar to endometrium and smooth muscle. Two mucus-secreting glands were found in the tumor. Glands were discovered and traced to the peritoneum. He offers evidence in favor of the local origin of tissue. Both the theory of serosal origin and that of congenital misplacement are tenable in the explanation of the origin of heterologous tissue according to Enzer. He states: "It seems unreasonable to attribute
3. Serosal Or Coelomic Theory

the tumor to transplanted bits of endometrium, carried either by the blood stream or by the lymphatics. If such transplantation occurred it is difficult to explain how the tissue arrived at the umbilicus and grew in the abdominal wall without producing evidence of implantation elsewhere. The implantation theory possibly is most applicable to the endometriosis occurring in laparotomy scars.

"It would seem that the specimen reported here offers evidence in favor of the local origin of the heterologous tissue. The direct continuity of peritoneum with one of the glands would point to a metaplasia of tissue of peritoneal origin. The finding of mucus-secreting cells might indicate an origin from the remnant of the duct or from the peritoneum is of little moment, since the origin is a common one."

One element in the tumor requires explanation and that was the presence of mucus secreting cells. Roques (52) pointed out that portions of the vitelline duct occasionally persist at the umbilicus, but the epithelium does not possess the function or menstruation, nor are these portions surrounded by endometrial stroma. Since the two glands described were the only ones of this type found in a great many sections, it seems reasonable to consider them as remnants of the ducts.

The smooth muscle forming an integral part of the tumor
3. Serosal Or Coelomic Theory

is of importance. If endometrium could have been transplanted, it is hardly likely to have carried smooth muscle fibers with it, so that the local origin of the smooth muscle is probably beyond dispute. Meyer, Renesh, Nicholson and others have expressed the opinion that the smooth muscle tissue is derived from the local tissue. In regions in which unstriped muscle is not found normally its presence has been attributed to a metaplasia of the surrounding connective tissue.

However, having once established an embryologic origin for the epithelial structures, it seems more rational to explain the presence of the smooth muscle on the same basis. It does not seem likely that one element of the tumor would have one origin and another element a different origin. Furthermore, there is no proof that implants of endometrium can stimulate smooth muscle metaplasia from connective tissue or that the stroma cells of the endometrium can give rise to smooth tissue or that the stroma cells of the endometrium can give rise to smooth muscle. Those who have implanted endometrium did not find smooth muscle cells in the implants with one exception. Michon (32) transplanted minute pieces of endometrium into the ovary of the rabbit. There was hyperplasia of the smooth muscle around the transplanted epithelium. It is possible that he introduced smooth muscle fibers along with the uterine mucosa. In experiments on tissue culture,
3. Serosal Or Coelomic Theory

with successful growth of endometrium, smooth muscle cells have not been found. Transplantation would account for the presence of smooth muscle in endometriomyomas in larparotomy scars, particularly after cesarean section, provided one considers the transplantation theory tenable, and it would have application in cases in which the tumor follows an operation during which the uterine cavity was opened.

Enzer (15) states: "Both the serosal theory and the theory of congenital misplacement seem to be applicable to the tumor reported here and likewise to the other instances reported in the literature.

"Palmen takes the stand that they probably originate from the embryonic umbilical epithelium, as yet undifferentiated, contrary to those cysts and fistulas arising from remains of the fully developed vitelline duct."

Smooth muscle in the tumors has been reported by many. Fraser (20) in 1929 reported finding an endometrioma of the umbilicus in Macacus rhesus and some twenty-three endometriomas in the peritoneal cavity of the same monkey. The umbilical tumor did not contain smooth muscle nor was it connected with umbilical tumors by Barker (4) and various foregoing authors such as Giannettasio, Mintz, Herzenberg, Waegelin and Tobler. The latter recorded a deep, funnel-shaped diverticulum of the
3. Serosal Or Coelomic Theory

peritoneum to which the tumor was attached. Rocques (52) described a peritoneal fold similar to the one found in the specimen reported by Enzer above. The great majority recorded are bleeding at menstruation, and sometimes painful swelling and bluish discoloration. The tumor is not infrequent.

Spitz (65) along with Longwood, Nicholson, and Lauche, has taken rather strong exception to the implantation theory and is an adherent of the theory of peritoneal origin of the tumors.

He states: "I certainly agree with Lauche, Nicholson, and others who take strong exception to this possibility. Considering the peritoneal fossettes described by Cullen, the presence of which is reported by Frero, Rocques, Tobler, and Enzer; the cords of which were attached to the peritoneum as reported by Vilar, Wulstein, Palmen, Kohler, Foderl and the presence of sinuses by Rocques and Holm, one must consider the greater likelihood of these growths arising from peritoneal cells.

"By means of serial sections Tobler and Enzer described the source of the endometrial-like glands in their umbilical growths as coming directly from the peritoneum. Indeed, it has been shown by Nicholson, Lauche, and others, that the peritoneum is directly connected to these growths in every situation in which they have been found, possibly excepting
3. Serosal Or Coelomic Theory

the uterine adenomyoma, and even the possibility is by no means remote.

"Lauche, Nicholson, Baltzer, Foderl, Schiffman, and Seyfert and others contend that the presence of ovarian hormones is necessary for these growths to develop. They occur only in sexually mature women and the physiological symptoms of swelling, pain and bleeding are present only during the menstrual cycle. The spontaneous disappearance of the endometrial growths from the pelvis and bladder after removal of the ovaries has been reported by Graves and Keene.

"Neuman transplanted endometrium of the rabbit into the peritoneum of the same animal and of other animals from the same little. These transplants formed cysts when ovarian hormones were present. When castration has been done a few weeks before operation, no cysts were formed and the transplants were resorbed. Transplantation into the males was unsuccessful."

From the above presentation of material it is at once evident that there is even no agreement as to the results of experimental work on this subject.

Weller (61) calls attention to the fact that, with a few exceptions, the regional distribution of endometriosis coincides with that of the ectopic decidual region. The only significant difference is the reported occurrence of decidual reaction upon the diaphragm and the splenic capsule. Appar-
3. Serosal Or Coelomic Theory

ently, endometriosis has never been noted as occurring above the level of the umbilicus. It is possible to go even further in the comparison, for there is a similarity in the relative frequency of occurrence of the two conditions in various regions. He has taken special note of the sites of ectopic decidual reaction. Polster finds in (61) a collection which includes over 1000 cases of endometriosis of the ovaries, tubes and uterine ligaments, 90 in the rectovaginal septum, 80 in the intestinal tract, 56 in scars, 34 in the inguinal regions and 30 at the umbilicus. In a general way, the incidence decreases as the distance from the ovaries increases, as is true of the ectopic decidual reaction. If the analogy from distribution of the two conditions is as significant as it appears to be, the very rare occurrence of the, as yet, unknown endometriosis of the diaphragm may be predicted.

It has also been found that glandular spaces are frequently present in the retroperitoneal nodes showing an extopic decidual reaction. Conversely, a decidual reaction has been described for the cytogenic stroma of endometriosis in almost any location. The cytogenic stroma of endometriosis is the interglandular stroma of the endometrium. They function alike in the development of the decidua. Weller (65) believes that under appropriate hormonal stimulation, exactly similar decidual cells may develop from the cellular elements which lie immediately beneath the serosal cells proper over a wide
3. Serosal Or Coelomic Theory

area.

Weller concludes: "such similarities and identities of morphology and function support the serosal theory of origin of endometriosis. The subserous stromal cells must possess pluripotentiality in differentiation. Under the influence of suitable but dissimilar stimulation either the cytogenic stroma of endometriosis of the decidual reaction may result. If the former develops, it in turn may subsequently be inducted to become decidual. In the decidual reaction the mesothelial cells likewise possess latent potentiality in differentiation and that from them, particularly when entrapped in adhesions or in scar tissue, and again under stimulus of a hormone, the epithelial elements in endometriosis are derived."

It is thus seen that this theory has many adherents who have considerable evidence to support their theory. The other theories or origin will be presented in the subsequent sections although, outside of the Hormonal theory, which is an essential part of either the Implantation theory as well as the Serosal or Peritoneal theory, they are not given much credence at the present time.
4. Luteal Origin of Tarry Cysts of the Ovary.

This theory assumes that the origin of the endometrial elements in the ovary is from the Corpus luteum. The chief adherent of this theory is E. S. J. King. King (36, 37, 38) believes that there is considerable confusion on this subject and that the tarry cysts of the ovary are in reality the results of the development of luteal cysts. He opposed the Sampson theory of implantation rather strongly.

The corpus luteum is formed by proliferation of cells of stratum granulosum which give rise to the cells of developing corpus luteum. There is then hemorrhage with state of vascularization. Having reached the acme of development fatty changes occur in the cells and retrogressive changes and alteration result in gradual replacement of luteal cells by hyaline tissue and corpus albicans.

He reviews (37) the morphology and physiology of the ovary. This important to understand the theory he supports. A number of pathological conditions arise which correspond to the various stages in the life history of the luteal body.

1. Corpus Luteum Cysts
2. Corpus Albicans.
3. Corpus Luteum Blood Cysts
4. Corpus Luteum Tarry Cysts
4. Luteal Origin of Tarry Cysts of the Ovary

Corpus luteum cysts are characterized by presence of clear fluid in the cavity of the enlarged luteal body. Possesses typical luteal tissue in the wall and this shows festooning which is observed in the normal corpus luteum. Variable amount of fluid is found present. As the luteal body ages, the changes mentioned take place and these occur whether it has a very small cavity or is a comparatively large cyst. These cysts of the corpus luteum may show many appearances according to the amount of hyaline tissue and stroma tissue present in the wall. The end result when all luteal tissue has disappeared and hyaline tissue only is present, is corpus albicans cyst.

The corpus albicans cyst contains in its wall, hyaline tissue which is developed from corpus luteum tissue. Progress of change in wall of corpus luteum cysts does not proceed uniformly in all parts and at the same rate; thus typical luteal tissue may be found in one portion and hyaline material in another part.

Luteal blood cysts are merely the occurrence of hemorrhage at the stage of vascularization of the corpus luteum.

The corpus luteum tarry cysts represent merely the changes in the composition of the blood.
4. Luteal Origin of Tarry Cysts of the Ovary

cysts with change in appearance. The tarry cyst shows
the festooning of the wall which characterizes the
original body. This is important in the differentiation
of the tissue or cyst from other cysts.

In a classification proposed by Fresekel, in 1898,
luteal cysts of three types were described:
1. Those lined by luteal cells.
2. Those lined by fibrous tissue
3. Those in which a heterotopic epithelium lined
the cyst in the inner aspect of the connective tissue.

King feels that any of the cysts mentioned above
may show the heterotopic lining. This consists of cells
of columnar, cuboidal, or flattened form, with a subad-
jacent "Stroma" of round or spindle cells which often
support a number of phagocytic cells. Beneath this
"stoma" is the tissue proper of the luteal body, either
luteal cells or hyaline tissue. Crypts may be present
in the wall of the cysts and the epithelium lining these
may, owing to the peculiarities and the direction in
which the section has been made, show "gland-like" struc-
tures. The epithelium often lines only a portion of
the cyst wall.

Another group of cysts arise from the atretic folli-
cle. At the commencement of the intermenstrual cycle, a
4. Luteal Origin of Tarry Cysts of the Ovary.

Number of graffian follicles approach maturity. Rupture of one follicle is followed immediately by the retrogression of the others, and it has been shown experimentally that this is due to a hormone derived from the developing corpus luteum. This atresia is characterized by the disintegration of the stratum granulosum and a proliferation of the theca interna cells. The typical atretic follicle shows an appearance which is the reverse of that seen in the corpus luteum: i.e., a very marked theca interna layer and a very poorly marked or almost absent stratum granulosum. The theca interna cells proliferate and swell until they resemble luteal cells. They may accumulate pigment and they are arranged in a radial fashion around the cavity of the follicle. Changes comparable with those seen in corpus luteum now appear. Fatty changes with hyalinization occur. The cysts that may arise from the atretic follicle are:

1. Follicular cysts.

2. Follicular blood cysts.

3. Follicular tarry cysts (Tarry "luteal cysts")

These may all result from a change of the structure of the atretic follicle anywhere in its retrogression (of the graffian follicle). Some of the luteal cysts,
4. Luteal Origin of Tarry Cysts of the Ovary

however, according to King, may have a follicular origin. The usual sequence of events during atresia is a retrogression of the stratum granulosum and a proliferation of the theca interna cells and a "luteal" change in these cells. In one well known condition, however, although the follicles are undergoing atresia, the stratum granulosum proliferates as well as the theca interna. This is the multiple luteal cyst associated with hydatidiform mole. A great deal of discussion has been waged around the origin of these "luteal" cells. The follicles do not rupture on the surface and the ovum dies, so that the cysts belong to the retrogressive or atretic series, and it was thought that the cells arose, as usual from the theca interna layer, Strossman showed they arise from cells of the stratum granulosum.

Thus there are two varieties of follicular cysts:

1. In which there are a well developed theca interna layer and an extremely poorly marked stratum granulosum layer.

2. In which representatives of both layers are well marked.

Blood cysts, then, may result from hemorrhage occurring in the corpus luteum and its derivatives. It
4. Luteal Origin of Tarry Cysts of the Ovary

results in hemorrhage into the stratum granulosum and from this there is rupture into the central cavity. In case of the typical atretic follicle, hemorrhage takes place in the theca interna cell alve and may rupture into the surrounding tissue. Pressure inward pushes the stratum granulosum before it so that blood does not usually occupy the cavity of the follicle. However, it should be emphasized that these structures need not be typical in appearance and may represent any stage in the development.

Tarry cysts of follicular origin may also occur. Due to changes in blood of the preceding cyst. Since there are two main varieties of follicular cysts, so two principal forms of tarry luteal cysts of follicular origin may be differentiated: (a) the tarry granulosa luteal cyst-cells probably from theca interna, and (b) the tarry granulosa luteal cyst also has cells of stratum granulosum. The cells occurring in the walls of these cysts are of atypical luteal character and since they become replaced gradually by connective tissue, all stages may be found between the easily recognizable cyst containing well marked (if atypical) luteal cells and the one in which few luteal cells are to be found.
4. Luteal Origin of Tarry Cysts of the Ovary.

King thus believes that the lining of heterotopic epithelium may be found in both the corpus luteum cysts and the cysts of follicular origin as has been described above. The epithelium has the same characteristics as in the corpus luteum cysts in that it may be columnar, cuboidal, or flattened in shape and there is present a subepithelial stroma.

A summary of the various types of cysts may be given as follows:

1. Corpus Luteum Cysts: Corpus albicans cysts, follicular cysts which may become hyaline.
2. Blood cysts of various types.
3. Tarry cysts:
   (a) Corpus Luteum Cysts.
   (b) Tarry thecal luteal cysts.
   (c) Tarry granulosal luteal cysts.

It must, however, be remembered that there may be many variants of the typical descriptions that have been given above. Any of these cysts may possess an epithelial lining. King states that the majority of the cysts do not have a typical appearance. Different stages of regression of the luteal cells may be observed in various portions of the cyst wall. The epithelium does not extend
4. Luteal Origin of Tarry Cysts of the Ovary.

throughout the whole extent of the wall, and it is usual for the epithelium to be present only in those parts in which luteal cells are absent. Thus, should the section happen to be in a plane at an angle, it will be apparent that one section, taken at one end of the cyst may show only the epithelium in the wall and the one taken at the other end may show only luteal tissue in the wall. A confusion will then arise. He believes that this is the difficulty that Sampson had and for this reason does not agree with Sampson on this point. Phagocytic cells are often present in large numbers in the walls of the cysts, and it is important that they be distinguished from luteal cells. He believes that many of the sections of so-called endometrial tissue are not necessarily characteristic of uterine endometrium and in fact may simulate other tissues in the body. These glands are epithelial lined and have a stroma beneath the epithelium. There are crypts in the walls of these tarry cysts and these are lined almost invariably, by columnar epithelium, even when the surfaces of the main cavity are lined by flattened cells or where even these are absent. These projections of the central cavity may extend for a considerable distance and owing to a meandering course, the plane of section may cut these in
4. Luteal Origin of Tarry Cysts of the Ovary.

one or more planes. The appearance of "glands" thus obtained is not uncommon in the walls of these cysts. The subepithelial stroma is particularly abundant about these glands, so that it is these more particularly which give a close imitation of endometrium. An important feature is the projection of these cysts beyond the boundaries of the original cyst wall, i.e., beyond the area containing hyaline tissue. Thus it is possible to discover "glands" in ovarian tissue without any proximate evidence of derivatives of luteal or follicular bodies. If not careful, such a gland would be regarded as of "endometrial" origin, that is of implantation type. The invasive properties of this epithelium are extremely important from point of view of results of rupture of the cysts with spilling of their contents into the peritoneum.

From this it is noteworthy that King agrees with Sampson on the further dissemination of the endometrial tissue from the ovary into the peritoneum but he disagrees with their origin into the ovary. Sampson believes that they arise from implantations of endometrial tissue of the uterus through the tubes while King believes that the origin is different.

The origin of the epithelium of these structures
4. Luteal Origin of Tarry Cysts of the Ovary

has various hypotheses to explain its occurrence. King considers three:

(1) From surface epithelium of the ovary. That the epithelial lining of the walls of some of the luteal cysts is continuous with the presumably developed from the surface epithelium is easily demonstrated in some examples. The ease with which the surface epithelium grows into any space in the ovary communicating with the surface renders such an explanation reasonable for these cases. The majority of cysts can't come into this category, however, since most of the graffian follicles do not rupture and consequently their cavities do not become continuous with the exterior.

(2) From endothelium of vessels lying in connective tissue lining the wall of the cysts. The endothelium is known to change shape in this fashion, the evidence in the case of these cysts is not in any way conclusive. This suggestion is similar in kind to that made by Schiller in which aberrant endometrium arises by metaplasia of lymphatic endothelium.

(3) From luteal cells or their progenitors. Fraenkel suggested originally that the cells arise from luteal cells. Observations that King has made point in this direc-
4. Luteal Origin of Tarry Cysts of the Ovary

tion. Certain well known phenomena suggest this origin also:

(a) A columnar epithelium may be found in simple atretic follicles. Continuity between these cells and cells of the degenerating stratum granulosum may be observed,

(b) The life history of the epithelium (The formation of glands, the effects of rupture of the cysts, and the development of tumors) more strongly suggests an epithelial (luteal) origin.

King (37) believes that the epithelium probably arises by metaplasia from cells which are present in the ovary, and not from cells of another organ by a peculiar process of transplantation.

King (37) in conclusion summarizes his opinions on five groups of cysts:

(1) Ovarian cysts have been discussed above but in brief he believes they arise from the epithelium and cells of other cysts.

(2) The peritoneal cysts are produced in almost every case, by implantation of epithelium in the peritoneum (a different proposition from the regurgitation of pieces of tissue of dubious viability through the fallopian tubes) from tarry cysts. Even the vaginal cysts may be explained
4. Luteal Origin of Tarry Cysts of the Ovary

by the burrowing of the "glands" through the vaginal vault from the pouch of Douglas, which is an early site for implantation after rupture of cysts. The burrowing propensities of the glands in the tarry cysts has been noted above. These peritoneal cysts depend on the cysts of the ovary and do not present any serious difficulty in the hypothesis of the luteal origin of the tarry cysts. It should be noted, however, that the serosal hypothesis must also be considered in the explantation of peritoneal tissue, especially in the umbilicus.

3. Incision cysts fit any theory.

4. Adenomyomata of the uterus and rectovaginal septum; believes that they may fall in any category.

5. Umbilical cysts; difficult problem for all views and King seems to favor the serosal theory for the explantation of these cysts.
5. Hormonal Theory of Origin

The theory of hormonal origin of endometriosis has many supporters, all of whom are not well agreed for some have a tendency to lean to the coelomic theory and others to the implantation theory but all agree that basically all are dependent on the hormonal influence of ovarian origin. Some of the chief adherents will be used in discussing this theory of origin and there will be no attempt to comprehensively cover this field.

Jeffcoate and Potter (34) believe that endometriosis is a manifestation of ovarian dysfunction. They state: "It is agreed that one single theory can not account for the occurrence of these tumors in all sites. For, these who adhere to the serosal cell heteroplasia view can not explain the origin of perineal endometriomata, except by assuming implantation of endometrial cells, while the finding of endometrial elements in the umbilicus can hardly be ascribed to the implantation of fragments of the uterine lining." Their work is more concerned with the primary source of the endometriosis. "It is usual for authors to mention that two factors are concerned in the formation of these tumors: (1) The source of the ectopic endometrium, (2) some factor which determines its development. Thus, if an endometrioma of the ovary is due to retrograde menstruation, then there must be some agent, or environment
5. Hormonal Theory of Origin

which decides whether the implanted endometrial structures shall grow or perish. Sampson realized this and states that 'the escaping cells need suitable soil'. Likewise, if the ovarian lesion originates by heteroplasia of the cells of the germinal, or other epithelium, then there must be some factor which first instigates the change in cell structure, and subsequently produces uncontrolled growth of the new tissue. Similarly, there must be some cause for the unlimited outgrowth of the mucosa in uterine endometriosis."

They believe it is of great significance from every point of view to determine the conditions which cause the morphological and functional changes in coelomic cells and their subsequent proliferation, or which decide whether fragments of transplanted endometrium shall live or die. The mass of glands and stroma found in endometrioma is histologically and functionally similar to true endometrium; its integrity depends on the presence of active ovarian tissue in the body, it reacts to pregnancy by forming decidual cells, and it has been shown to undergo phases typical of the menstrual cycle. It is now known that the ovarian influence is exerted by way of hormones, and Gleave has proved that, in rabbits, the presence of oestrin is essential for the maintenance of the lesion.
5. Hormonal Theory of Origin

They continue, "If these statements be accepted, it is reasonable to regard the condition of endometriosis as one in which there is an excessive formation of endometrial tissue in the body." There, according to their view, it is logical to conclude that an over-production of oestrin by the ovary is the most important factor in the development of endometriomata in any site. Hence, a clinical and pathological study of all patients suffering from endometriosis was made with the object of determining, in each case, the presence or absence of these forms of ovarian dysfunction characterized by an excessive secretion of the folliculin hormone.

They name three ovarian conditions in which an abnormally large amount of follicular hormone is produced:

1. An anovular ovarian cycle with the formation of one or more follicular cysts, as in metropathia hemorrhagica. In such cases, owing to the absence of follicular rupture, a corpus luteum is not formed and consequently progestin is not secreted, for long periods of time.

2. Unusually frequent ripening; often more than one follicle at a time. This leads to rapid formation of one or more corpora lutea, and hence both oestrin and progestin are formed in excess. This is the hyperfollicular type of ovarian disorder.
5. Hormonal Theory of Origin

3. A true functioning neoplasm, innocent or malignant, or granulosa cells; the folliculoma or cell tumor.

Their work deals with 113 specimens obtained from 111 patients. In their method of diagnosis they used gross and microscopic estimation of ovaries, uterine mucosa and endometrioma as well as determining the clinical features of the condition. They demonstrate a close relation between ovarian dysfunction and endometriomata. They believe that the disordered ovarian mechanism is the cause and not the result of the endometriosis, for the following reasons:

"(1) The majority of the patients had menstrual irregularity and sterility for a considerable time before the operation. In many cases, although it is impossible to present exact statistics, menorrhagia or metrostaxis, often warranting operative interference, was present before the endometriomata developed. Moreover, in at least three instances, operations for follicular cysts in the ovaries had been performed previously.

"(2) It is an established principle of clinical gynecology that ovarian tumors, with the exception of folliculomata and advanced bilateral malignant disease, rarely, if ever, produce menstrual upset. It is unlikely, therefore, that ovarian endometriomata, frequently insign-
5. Hormonal Theory of Origin

Significant in size, would produce ovarian dysfunction. Moreover, there is evidence of upset in ovarian rhythm in almost all cases irrespective of involvement of the gonads by the endometrioma. There was not any ovarian lesion in 42 per cent of this series of cases.

"(3) Clinical, pathological, and experimental data, collected from numerous sources, have made it an axiom of endocrinology that endometrial changes are secondary to the ovarian function and not visa versa."

They find that in endometriomatous lesions of the uterus and pelvic ligaments and occasionally in those of the ovary, there are usually in addition to the epithelial elements, variable amounts of fibromuscular tissue. Such mixed tumors are often termed endometrio-fibromytomata or endometrio-fibriomata. In their investigation a distinction has not been drawn between those tumors containing both epithelial connective tissues and those in which only glands and stroma were present. We believe that the hypertrophy and hyperplasia of the fibrous and muscle cells is brought about by the same factor as causes endometrial growth, that is, oestrin. This hormone is known to control the growth, and to maintain the integrity, of uterine muscle and, on theoretical grounds, it is reason-
5. Hormonal Theory of Origin

able to suppose that over-development of this tissue is
due to over-action of the ovarian principle.

They state the hypothesis "that all forms of
overgrowth of the mucosa or muscle of the uterus are due
to the same principle is not only supported by clinical
and pathological data, but also explains satisfactorily
the simultaneous development of endometriomata, fibromy-
omata, and endometrial hyperplasia."

They conclude that "no matter what mechanism may
be involved to explain the origin of the initial endome-
trial elements in endometriomatous lesions, their subse-
quent development is due to overactivity of the follicule
or secretory apparatus in the ovary. This same underlying
disorder accounts for the frequency with which overgrowth
of fibromuscular tissue and uterine mucosa occurs in
association with endometriosis." They are, however, unable
to explain the specific responses, such as to what deter-
mines the peculiar manifestations exhibited in individual
cases.

They are of the opinion that this conception of the
etiology of endometriosis explains more adequately than
does any other, the symptomatology and pathology of the
disease. Moreover, it accounts for the frequent recurrence
5. Hormonal Theory of Origin

of these tumors in patients subjected to conservation operation, and explains why the site of election is the ovary and why these neoplasms never develop when ovarian function has ceased. This applies to removal of the ovaries by operation or their destruction by exposure to rays, but does not necessarily mean that endometriomata do not arise after menopause. This is because the menarche, although characterized clinically by amenorrhea is rarely, if ever, associated with immediate cessation of the secretion of oestrin and the gonadotropic hormones. They are certain that the cause of the alteration in the behavior of the follicular apparatus lies in the pituitary gland.

Jeffcoate and Potter summarize their results:

1. The view is put forward that the development of endometriomata irrespective of the primary source of the endometrial elements, is due to an excessive production of oestrin by the ovaries.

2. In a clinical and pathological study of 111 cases of endometriosis, the presence of follicular overactivity is demonstrated in the majority.

3. Endometriosis is regarded as being analogous in many respects to hyperplasia of the uterine mucosa.

4. It is suggested that the same ovarian conditions

give rise to the frequently associated overgrowth of fibromuscular tissue.

5. It is claimed that this theory explains more adequately than does any other all the known clinical and pathological features of the disease.

Witherspoon (69) in July 1935, discusses the "Hormonal Origin of Endometriosis." He is of the opinion that, although the two most generally accepted theories of initial origin of endometriosis are the Implantation theory and the Serosal theory, neither of them can explain the occurrence of endometrioma at all the known sites. The theory of heteroplasia of the serosal cell can not explain the perineal endometrioma while endometriosis of the inguinal canal is difficult to ascribe to the theory of implantation of fragments of the uterine lining. His work is concerned with the stimulus which makes the tumors grow. He states: "The actual origin of the endometrioma is unimportant, whether from implantation of a living graft or from cellular metaplasia; the all important question is the determination of the cause of the igniting factor which controls the cellular change or which stimulates the endometrial implant of proliferation."

The hypothesis he assumes is that the fundamental cause has its origin in the excessive stimulation of the
aberrant tissue by the ovarian follicular hormone, That the action of this hormone is not confined to the uterine endometrium alone, as demonstrated by the endometrial changes during the normal menstrual cycle, but influences the genital tract as a whole, is easily proved. When this hormonal action of the endometrium is abnormal, however, causing endometrial hyperplasia, it is equally abnormal in its action on ectopic endometrial tissue and causes, by means of cellular metaplasia of the potential serosal cells or by tumor proliferation of an aberrant endometrial implant, the formation of an endometrioma.

Through the work of Schroeder and Meyer in Germany, Shaw in England, and Graves (73), Fluhman (18), Novak (49), Mertzlof (49) (43) and Burch (5) (6), in this country, the cause of endometrial hyperplasia has been thoroughly investigated. That the persistent and excessive stimulation of the ovarian follicular hormone, in the absence of any corpora lutea and with a possible anterior hypophyseal action in the background, is the cause of the endometrial hyperplasia has been established by these observers. Burch (5,6) and his co-workers produced endometrial hyperplasia in spayed mice by injection of the estrogenic principle, while Hofbauer (29) by implantation of the substances of the anterior lobe or by injection of anterior hypophyseal
extracts, demonstrated endometrial changes similar to those of endometrial hyperplasia. The general acceptance is at present that endometrial hyperplasia is the result of the unopposed and continued action of an excessive amount of the estrogenic principle derived from the multiple follicular cysts of the ovary.

Witherspoon (69) states that the "morphological and functional characteristics of an endometrioma and of the uterine endometrium are similar; the integrity and function of the endometrioma are dependent on the presence of active ovarian tissue, since castration causes regression of the tumor; the endometrioma presents decidual reaction during pregnancy; it undergoes the phases of the menstrual cycle; changes dependent on the ovarian hormones, and as proved by Gleave (22) in rabbits, the presence of the estrogenic principle is essential for the maintenance of the lesion."

Since the ovarian follicular hormone is the cause of endometrioma and that of the uterine endometrium are similar, it is logical to deduce that the igniting factor of endometrioma which brings about the cellular metaplasia or the proliferation of the endometrial implant is the estrogenic principle. That such is the case is all the more firmly established by the fact that in many instances
5. Hormonal Theory of Origin

the endometrioma presents hyperplasia which is typical histologically of endometrial hyperplasia and also by the high incidence of the association of endometrioma with uterine endometrial hyperplasia in an endometrioma, accompanied with similar changes in the uterine mucosa, according to Witherspoon, indicates the endometrioma can be caused only by the factor which determines the mucosal changes; the ovarian follicular hormone.

Witherspoon makes a distinction between endometrial hyperplasia or hypertrophy and the formation of a true tumor. In hypertrophy of hyperplasia the etiological factor is an abnormally high concentration of the ovarian follicular hormone in the circulation, acting apparently on normally susceptible tissue. On the other hand, in the formation of a tumor, as in a case of endometrioma, the increased amount of the estrogentic principle in the blood acts on a hypersusceptible tissue which has the capacity to concentrate the hormone at the site of the tumor and to react to the proliferation.

In former contribution on the relationship between endometrial hyperplasia and uterine fibroids, Witherspoon (71) noted the high incidence of ovarian endometrial implants (30). At that time the suggestion was made that these three conditions might possibly have a common etio-
logic background. These figures have been rechecked
and combined with recent observations, and it has been
found that ovarian and uterine endometriomas were asso-
ciated with endometrial hyperplasia and uterine fibroids
in 64 per cent of the forty-four cases studied, a figure
too high to indicate a mere coincidence.

Other authors likewise have called attention to
the frequent association of endometrial hyperplasia, endo-
metrioma and uterine fibroids. From the above work of
Jeffcoate (34) it is seen that in a series of 113 cases
of endometriosis 79 women (71 per cent) present endome-
trial hyperplasia while 31 (28 per cent) presented uterine
fibroids. Allen (2) in his study of endometrioma was
impressed with the high incidence of the association of
this condition with menstrual irregularities due to endo-
metrial hyperplasia (70 per cent) and uterine fibroids
(41 per cent) and the prevalence of relative sterility
(80 per cent). Smith (30) in 59 cases of endometrioma,
noted associated endometrial hyperplasia in 42 per cent
and uterine fibroids in 52 per cent of the patients.

Witherspoon (78) noted that not only the uterine
and the aberrant endometrium is stimulated to hyperplasia
and the tumor proliferation by the estrogenic principle,
5. Harmonal Theory of Origin

but the uterine musculature also is affected. Because uterine fibroids are slow-growing tumors, the stimulation of the ovarian follicular hormone must be effective over a long period of time in order that the formation of the fibroid can occur. Geschickter, Lewis, and Hartman (20) have gone a step further in describing the action of the estrogenic principle. Their conclusion seems to indicate that gynecomastia in the male and virginal hypertrophy and the formation of fibroadenoma in the female breasts are dependent on the pathological variations in the action of the ovarian follicular hormone on the epithelium of the mammary ducts; and that prolonged and interrupted stimulation by the estrogenic principle rather than brief, high, concentrated stimulation, is necessary for the production of these abnormal conditions of the breast.

Witherspoon (70) states that: "It therefore seems logical to deduce that the multiple follicular cysts of the ovaries, in the absence of corpora lutea, which cause, through the hyperplasia or hypertrophy, endometriomas, uterine fibroids and mammary fibro-adenomas."

There are two clinical features, functional uterine hemorrhage and sterility, that are associated with endometrioma, and their occurrence is explainable by the
5. Hormonal Theory of Origin

hypothesis just stated according to Witherspoon. Menstrual irregularities frequently accompany endometrioma, yet the source of the bleeding cannot, many cases, be ascribed to the endometrial tumor. However, such hemorrhage can easily be explained by the associated endometrial hyperplasia of the uterine mucosa. Likewise the high frequency of sterility with endometrioma is due to the presence of the multiple follicular cysts of the ovaries in the absence of ovulation and of the formation of corpora lutea.

Witherspoon (69) concludes "The hypothesis that all forms of overgrowth (hyperplasia, hypertrophy or tumor proliferation) of the uterine endometrium and musculature, of the aberrant endometrioma and of the mammary glands are due to the same factor—the estrogenic principle— not only is supported by clinical and pathological data but it explains satisfactorily the simultaneous development of these conditions and their associated clinical features, uterine hemorrhage and sterility."

It can thus be seen that the various authorities are in agreement as far as the hormonal theory of origin is concerned. It can easily be seen that the same influence that stimulates the uterine mucosa to decidual reaction as
well as to a menstrual reaction is present and this has been proven to be the ovarian hormone folliculin.

It is then one step further to assume, as these men do, that overactivity of the hormone due to prolonged intermittent stimulation may be a means of promoting these tumors in as far as their further growth is concerned.

Moench (44) in 1929, while discussing the "Etiology of Adenomyosis and Uterine Fibromyoma: An Hypothesis", presents a theory of hormonal activity with response in the endometrium of local congestion as a result of the overactivity of the ovarian hormone. There are three facts known concerning adenomyosis. First, it occurs only in the female. Second, it occurs only during the sexual life of the woman. Third, it regresses after castration or atrophy of the ovaries. It thus appears that in some way or other the ovary is responsible for the adenomyosis. Considering the reaction of endometrium itself to ovarian influence, we find that before puberty there is no real endometrium and after the action of the ovaries is lost, the endometrium atrophies. It can now be definitely stated, according to this authority, that the monthly proliferative changes in the endometrium are based on follicular activity and that the secretory or premenstrual changes are due to corpus luteum activity. That the substance producing, for instance, the decidual reaction in
5. Hormonal Theory of Origin

the premenstrual endometrium is carried by the bloodstream, was shown even before Allen and Doisy (14) and Frank (19) and his collaborators and others, demonstrated a female sex hormone in the blood by the fact that it is around the small blood vessels in the form of a thinner or thicker mantle, that the stroma cells of the uterine mucosa first acquire their decidua characteristics. This is an important point.

He continues, "If then, the ovarian hormone carried by the bloodstream causes the endometrial changes, it is justifiable to assume, and this is supported by clinical and pathologic evidence, that the amount of hormone will, other things being equal, determine the amount of reaction shown by the endometrium. Increased follicular activity would lead to increased growth of the endometrium. Thus in the hyperplasia of the endometrium, I have seen follicular cysts of the ovary associated in most cases. In fact, from the histologic picture alone of a slide showing a definite hyperplasia of the endometrium, I have felt so certain that the ovaries would show small cystic degeneration that I have often advised examination of the patient and careful palpation of the ovaries, even under anesthesia if necessary, and the resection of the cystic organs,
5. Hormonal Theory of Origin

should they be present, which indeed they often were."

Shroeder, for example, states that in many of his case of hyperplasia of the endometrium, corpora lutea were lacking or subnormal, menorrhagia was not present, and even menstruation was decreased or absent. In such cases, of course, there would be accumulative action of the follicular substance without the respite caused by menstruation, and therefore continued proliferation would take place. At the same time certain authors found corpora lutea in the ovaries in most cases of endometrial hyperplasia. This also has been the experience of Moench. Whether or not we find corpora lutea does not make any difference in the underlying etiology, since the endometrium, even if lost at menstruation, can grow very fast, especially under the impulse of excessive follicular activity. He has seen a thin, dense endometrium completely covered by regenerated epithelium as early as the day after the cessation of the menstruation.

In some cases of endometrial hyperplasia, menorrhagia occurs, whereas this is absent in others. This also is not a contradiction. It depends on the amount of corpus luteum hormone carried by the blood supply of the particular part. Thus, follicular action, because it may be
5. Hormonal Theory of Origin

continued for months and thus be cumulative, and may be sufficient to cause endometrial hyperplasia while the corpus luteum action in the nature of things can not be thus cumulative. It may be insufficient to cause the endometrial changes necessary as a preliminary to menstruation, also that externally, at least, no sign of corpus luteum activity will become evident.

Hammond (28) has shown that in the ferret, which ovulates only on coitus, the same endometrial picture, the result of follicular activity is carried through estrus, if coitus and thus the formation of a corpus luteum is prevented. That menorrhagia also occurs without hyperplasia of the endometrium is no contradiction since other not directly related causes may of course lead to uterine bleeding.

The small cystic degeneration of the ovaries used to be interpreted as due to inflammation, but this is certainly not so. It is due to congestion, and the increased blood supply causes an increased number of follicles to ripen, and this in turn causes the endometrial changes. The fact that endometrial hyperplasia is more frequent around the fortieth year of life, Moench believes, we can explain by the fact that around that time many women are heavier, less active, and have perhaps a lessened muscular
5. Hormonal Theory of Origin

tonus, all of which causes would lead to pelvic congestion. Constipation should be stressed as a source of such congestion.

However, we have cases of endometrial hyperplasia where no evidence of gonads is present. He still believes we are dealing with exactly the same process as before. More ovarian hormone may reach a particular area, first, because more of this substance is present in the blood stream, and second, because congestion and slowing of the blood current allows more hormone to seep out by a process of osmosis in one particular spot. Thus, congestion would lead to hyperplasia, and uterine congestion is, indeed, often associated with endometrial hyperplasia. In some endometria, however, on one and the same slide different areas are seen which show different pictures of the menstrual cycle. Localized congestion or congenitally or otherwise abnormally situated or developed blood vessels and capillaries will explain just such an occurrence.

Since fibromyomas of the uterus grow only in the presence of the ovaries, and atrophy when these are lost, it seems perhaps not altogether unreasonable to interpret such tumors as being perhaps due to increased ovarian activity, coupled to local areas of congestion, due to congenital or acquired formal defects or simply to stasis.
If, on the other hand, there is diffuse congestion, it might cause the condition known as metropathia chronica.

Moench (44) states in addition: "Many cases . . . showed inflammation at the site of adenomyositis and there can be no doubt that inflammation or irritation is a stimulus to growth." "In every case of adenomyositis that I have observed there is . . . either clinically or histologically, an evident congestion present. I believe that this fact and not inflammation per se is the crux of the matter. Lahm has seen cytogenetic-like stroma develop in areas which showed convolutions and dilatation of the sub-serosal connective tissue of the uterus, either on the basis of congestion or due to certain formal defects in the tissue structure at this point, thus causing a relaxation of the blood vessels. Thus we may see adenomyositis at points where, for one reason or another, increased ovarian activity was applied, either because of increased follicular activity or because of localized congestion, or, and most probably, because of both factors."

He believes that in acute or chronic inflammations of the pelvic organs we see no invasion of the uterus because there is not sufficiently long enough action of the hormone and because there is such disturbance of blood supply that their action can not be locally applied. The
5. Hormonal Theory of Origin

ovarian activity in such involvements is really depressed and not simulated. That inflammation, however, often is the initial stimulus to heterotopic epithelial growth is shown by the frequency with which adhesions are found in such cases and these may be primary and not secondary to the growth.

Moench (44) is of the opinion that as far as the invasion of the uterine wall by the endometrium, especially late in life, is concerned, we have the same factors at work as was discussed under endometrial hyperplasia. Aside from this we may assume that the irregular corpus luteum production also has its effect, and that uterine muscle changes in addition may lead to changes in the tissue balance and allow of penetration of the endometrium. This is to him more logical to assume, as has been done, that the basalis, in the course of the many years of its regeneration of endometrium, has acquired an activity which causes it to invade the uterine musculature because it no longer forms endometrium. The basalis, according to his observations, shares in the final atrophy upon loss of ovarian activity, just as much as the rest of the uterine lining, and deficient ovarian function does not cause hyperplasia of the endometrium. . .
5. Hormonal Theory of Origin

There is one more point to consider, namely, the question as to why the lower parts of the pelvis and the ovaries are especially often the seat of adenomyositis. If congestion plays any role, naturally the lowest parts of the coelom would be most frequently affected. The ovary is very prone to congestion and often prolapses. Adhesions also occur frequently. Again the blood and lymph vessels enter the hilus and become very convoluted thus further leading to congestion. In addition, it is probably true that tissues nearer to the source of the blood contains more ovarian hormone than further away.

In conclusion he states "that while the theory is necessarily hypothetical, certain clinical and pathologic evidence seems to support it. I believe it to be at any rate more logical than the "menstrual blood" conception of Sampson."
6. Metastatic Theory

This theory of histogenesis assumes that there may be dissemination of endometrial tissue through lymph and venous channels. It is not, however, to be understood that the supporters of this theory assume that this is the only means of dissemination. Sampson, who is a supporter of this theory, believes that it is merely one means of spread, the major means being by menstrual dissemination through the tubes.

In 1924, Halban (26) published a preliminary communication of the lymphatic origin of misplaced endometrial tissue. He believed that in the invasion of the myometrium by its mucosa bits of epithelium may be set free in the lymph spaces between the muscle bundles of the myometrium and wander through these to the superficial lymphatics beneath the serosa of the uterine wall and from there spread by lymph channels to other pelvic structures including the inguinal glands. He offers in support of this view the fact that characteristic uterine glands have been found in the regional nodes of the uterus.

Wertheim believed that the glands in the pelvic nodes were metastatic from adenoma of the cervix. Ries (68) in 1897, was the first to describe epithelial glands or ducts in the pelvic lymph nodes. He found them in iliac lymph nodes removed at operation of carcinoma of
6. Metastatic Theory

the uterine cervix. There was an associated adenomyoma of both uterine horns and also an invasion of the uterine endometrium of the left uterosacral ligament by epithelial glands similar to those found in the lymph nodes. He compared the epithelial lining of the glands in both situations to that of the glands of the uterine mucosa. He also suggested the possibility that the glands in the lymph nodes might have been metastatic either from those in the uterine adenomyoma or from those in the uterosacral ligament. He concluded, however, that remnants of the wolffian body which had led to the formation of the uterine adenomyomas, according to the Recklinghausen theory, were also responsible for the glands or ducts in the uterosacral ligament and in the lymph nodes. Wälfring (58) in 1901, published a similar case which was associated with adenomyoma of the uterine ends of both tubes.

Sampson (58) in 1925, in discussing Heterotopic or Misplaced endometrial tissue, stated that he believed that many peritoneal lesions are metastatic through lymph channels secondary to the mucosal invasion of the uterine wall. He believes that endometrial tissue may metastasize through lymph vessels reached by mucosal invasion of the uterine wall. He, however, does not believe as Halban
6. Metastatic Theory

does that the metastatic theory satisfactorily explains the majority of the peritoneal lesions. Endometrial tissue is so situated, sometimes, that if it came from the mucosa lining the uterine cavity or from the lesions of a peritoneal endometriosis it must have reached its present location by metastasis through the lymph vessels or veins. Examples of this type are found in the groin, vulva, possibly the umbilicus, and maybe the vagina and the pelvis. All cases of vaginal endometriosis seen by him were situated in the vault of the vagina, posterior to the cervix and were directly continuous with a peritoneal endometriosis in the posterior culdesac. The only situations in which he has seen possible metastatic lesions have been in the groin and in the pelvis. In three cases of inguinal endometriosis studied by Sampson at operation, the structure of the endometrial contents was identical with that of those found in the uterine wall, which arise from the invasion of the myometrium by the mucosa lining the uterine cavity. There was a reaction against the invasion by a hyperplasia of the tissues of the groin, the connective tissue being most affected.

In all three cases the nodule in the groin reacted to menstruation as was indicated by its being tender at that time, and also by the presence of cavities filled
6. Metastatic Theory

with blood and blood pigment in its tissues. There was no gross evidence of pelvic endometriosis in these cases. A summary of the evidence that endometrial metastasis through lymph vessels from both a primary uterine and from a peritoneal endometriosis may occur:

1. Endometrial tissue, like carcinoma, wherever situated at times invades the host.

2. Have a strong, almost positive, evidence that like carcinoma it may escape into the peritoneal cavity, causing peritoneal implantations and also may be transplanted into the tissues of the body.

3. We should expect that any tissue with such activity and tendencies would metastasize through lymph vessels if it could reach the lumen of these vessels and fragments of it be set free.

4. We should also expect that if metastasis of benign endometrial tissue occurred, it would be found in situations reached by lymph vessels from the body of the uterus and from structures invaded in peritoneal implantations; thus, in its distribution corresponding to the metastasis of carcinoma of the endometrium and of pelvic carcinoma.

5. In the invasion of the uterine wall by its
6. Metastatic Theory

mucosa, endometrial tissue is sometimes found in the superficial portions of the uterine wall, apparently in lymph channels or veins. He has observed the same in the tube from the invasion of its wall by its mucosa.

6. He has found endometrial tissue protruding into the lumen of other organs, secondary to peritoneal endometriosis with invasion of these structures.

7. Should endometrial tissue protruding into the lumen of lymph vessels react to menstruation fragments of this tissue could be set free into its lumen and might be carried to other parts of the body reached by this vessel.

8. Epithelial glands with a microscopic structure identical with those of the uterine mucosa have been found in the pelvic lymph nodes. Some of these could have been metastatic from a uterine or peritoneal endometriosis, as they were associated with these lesions. If derived from a primary uterine adenomyoma we would expect to find them not only in the pelvic but also the lumbar nodes.

Sampson also believes that there is a dissemination through venous channels. In a study of menstruating uterus in which the veins had been injected he demonstrates that not only the natural protection against the escape of foreign material into them from the endometrial uterine
6. Metastatic Theory

cavity, but also suggests that the protection may not always be adequate against their invasion by menstrual blood. Sampson (61) in 1927, in a histologic study of uteri removed at various stages of menstrual cycle in which veins have been injected demonstrates the mechanism by which endometrial tissue may be disseminated from that organ. The uterine mucosa contains venous capillaries which sometimes are dilated to from sinuses. These sinuses empty into similar sinuses (endothelial lined spaces without definite walls) of the myometrium and the latter empty into the arcuate veins which convey the venous from the uterine tissue into the venous circulation outside of that organ. During menstruation the venous capillaries rupture and blood escapes into the surrounding tissues. This suggests that at times menstrual blood in the uterine mucosa might at times escape back into the lumen of the ruptured capillaries and sinuses from which it came and carry with it endometrial tissue into the venous circulation.

Sampson (60) in 1927, in a histologic study of sections of uteri removed during the various stages of the menstrual cycle in which the veins had been injected with bismuth demonstrated that there are venous capillaries and large venous sinuses in the uterine mucosa and that
6. Metastatic Theory

the later empty into similar sinuses in the uterine wall. During menstruation blood escaped from the mucosal vessels into the surrounding tissues and bits of the mucosa are often set free in the extravasated blood. These studies suggest that this menstrual blood containing fragments of endometrial tissues, at times, escapes through a ruptured mucosal sinus into the venous circulation of the uterus. In this article he takes special note of the endometriosis of the uterine wall. Sections of misplaced endometrial tissue, wherever situated and irrespective of its origin, also suggest that a like dissemination of fragments of this tissue may occur during menstruation. In menstruating uteri bits of the uterine mucosa at times actually escape into the venous circulation of the uterus through these channels. He found the escape into veins of the contents of two extopic endometrial cavities in an endometriosis of the posterior vaginal wall.

In one uterus removed during menstruation in which bits of endometrial tissue were found in the blood in veins and venous sinuses of the uterine wall, multiple embolic or metastatic-like growths of endometrial tissue also were present in these vessels. By serial sections
it was shown that these growths either arose from or were implanted on the walls or linings of these vessels and did not arise from the invasion of the latter by endometrial tissue from without. These embolus-like growths of endometrial tissue must have originated either from the actual anchoring and implantation of endometrial tissue similar to that found free in the vessels of the specimen. The study of the entire uterus demonstrated that, while some of the endometrial emboli lying free in the vessels of the uterine wall might have arisen from the menstruation of ectopic endometrial tissue in that organ, the latter ordinarily were derived from the mucosa lining the uterine cavity. In endometriosis of the posterior vaginal wall of this case, similar endometrial emboli and embolic vegetations of endometrial tissue were present there in veins about misplaced endometrial cavities and the actual escape of the menstrual contents of two of these cavities into a vein was seen.

In a second uterus, also removed while the patient was flowing, somewhat similar lesions were found in which their embolic origin was not as definitely established as in the above case. Nevertheless, Sampson believes that they had similar origin.

Sampson (60) is of the opinion that if these observations are correctly interpreted, they show that bits of endometrial tissue disseminated by menstruation from the
6. Metastatic Theory

mucosa lining the uterine cavity and also from ectopic endometrial foci, are not always dead but are sometimes alive and are capable of becoming implanted on the endothelial surface of nearby veins and venous sinuses. They further suggest that bits of endometrial tissue carried by menstrual blood into the venous circulation might cause metastatic growths of endometrial tissue at a distance from the original focus, and also that similar fragments of endometrial tissue carried by menstrual blood escaping from any source into the peritoneal cavity at times might cause the lesions of peritoneal endometriosis.

Sampson (60) concludes "Fragments of endometrial tissue, at times, are disseminated into the venous circulation during menstruation, from the mucosa lining the uterine cavity, and also from ectopic endometrial foci. Metastatic or embolic endometriosis arises from the implantation of these emboli in nearby veins. Endometrial tissue set free by menstruation, therefore, is sometimes not only alive but may actually continue to grow if transferred to situations favorable to its existence.

Sampson (58) is of the opinion that the capillaries of the endometrium of the uterus are dilated and in trauma associated with menstruation, menstrual blood might escape into them and be carried to the venous sinuses of the uterine wall and even into the venous circulation beyond the uterus. If the uterus is removed with the preservation
6. Metastatic Theory

of one or both ovaries, from a woman suffering with the local and constitutional disturbances of menstruation, she is relieved of these. Anatomical and clinical studies would lead us to believe that these disturbances are, at least in part, due to the escape of menstrual blood with some of the chemical or cellular ingredients into the venous circulation and the reaction against this invasion. It is possible that endometrial tissue may metastasize through these channels and become lodged in the wall of the uterus or even outside that organ. It also suggests an explanation of the etiology of leiomyomas of the uterus. Apparently the epithelium, stroma, or connective tissue and smooth muscle cells of menstrual blood may offer a stimulant to muscle tissue. A muscle reaction occurs.

Sampson (61) in a histologic study of the endometrial tissue of a direct or primary endometriosis shows that this tissue contains venous capillaries similar to those of the mucosa lining the uterine cavity and that the reaction to menstruation of this misplaced endometrial tissue is similar to that of the former except that it is not constant or as general as that of the uterine mucosa. The endometrial tissue of direct endometriosis, in its invasion of the myometrium often penetrates the
6. Metastatic Theory

spaces occupied by the vessels and sinuses of the uterine wall but is separated from the lumina of the latter by their endothelial lining. This is emphasized by R. Meyer and Kitai in their descriptions of the relation of misplaced endometrial tissue to the lymphatics of the uterine wall. The studies of specimens, in which the veins have been injected, have convinced Sampson that the majority of the vessels of the uterine wall, which previously he had considered to be lymphatics, are venous sinuses. It might be assumed that in the menstrual reaction of this misplaced endometrial tissue, bits of it might escape into its own venous capillaries and even into the lumen of a sinus of the uterine wall along which the endometrial tissue sometimes grows in an extra- or retro-endothelial course. In one instance of endometriosis of the culdesac, presenting in the posterior vaginal vault (the so-called adenomyoma of the rectovaginal septum) the actual escape of the menstrual contents of two ectopic endometrial cavities into adjacent veins was found. As a result of this observation he believes that a similar condition occasionally may arise in any situation where endometrial tissue reacts to menstruation.

Sampson (61) is of the opinion that if endometrial tissue disseminated by menstruation is viable we might expect to find embolic lesions of that organ. If these
lesions were found, they would furnish very strong evidence that they might have arisen from the implantation of endometrial emboli cast off by menstruation into the venous circulation. He found two such cases. Both patients were operated upon during their periods. Bits of endometrial tissue were found in the venous sinuses of both uteri. An embolic or metastatic growth of endometrial tissue was found in a venous sinus of one uterus and many such lesions in the other uterus. Sufficiently complete serial sections showed that these growths either arose from or were implanted in the walls or linings of these vessels and did not arise from the invasion of the latter by endometrial tissue from without. These embolic-like growths must have originated either from a localized metaplasia of the endothelial lining of the veins and venous sinuses or else from the actual anchoring and implantation of bits of endometrial tissue similar to those found floating about in some of the vessels of the uterus.

While an endometriosis of the direct type was present in a portion of the wall of each uterus, the distribution of the embolic lesions, as well as other histologic findings, indicated that the endometrial emboli, primarily responsible for the metastatic lesions, probably came from
6. Metastatic Theory

the mucosa lining the uterine cavity. Even if these emboli had been derived from the endometrial tissue of a direct endometriosis of the uterine wall, some traumatism would be necessary to rupture the endothelial lining of its veins and disseminate bits of endometrial tissue into their lumina. The reaction to menstruation is the most evident cause of such an injury. Curetage and termination of pregnancy by abortion of labor might also have caused spread. He is also of the opinion that an endometrial lesion could rupture into a vessel and thus have dissemination. The operation occurred on the second day of the menstrual period. Bits of endometrial tissue were found lying free in the veins about other endometrial cavities of the vaginal wall and embolic growths of endometrial tissue were also present in these vessels. The actual escape of the menstrual contents of two of these cavities into a vein was seen. This was an endometriosis of the posterior vaginal wall. He says that the only interpretation of the etiology of the embolic endometrial lesions in the veins about these endometrial cavities and that is they arose from the implantation of endometrial tissue, disseminated into the veins from the menstrual rupture of the walls of the endometrial cavities into these vessels. If so, endometrial tissue disseminated by menstruation in this instance must have been alive and
6. Metastatic Theory

capable of growing when transferred to suitable situations. He concludes that fragments of endometrial tissue, at times, are disseminated into the venous circulation during menstruation from the mucosa lining the uterine cavity and also from ectopic endometrial foci. Metastatic or embolic endometriosis may arise from the implantation of these emboli in nearby veins. Endometrial tissue set free by menstruation, therefore, is sometimes not only alive but may actually grow, if transferred to situations favorable to its existence. Apparently this theory would best explain inguinal and intraligamentary endometriosis.

It is thus seen that this theory is well supported and appears to be logical explanation for certain forms of endometriosis that occur.
CHAPTER IV
SUMMARY

Endometriosis is a disease process, occurring in women during the period of greatest sexual activity, of frequent incidence, characterized pathologically by wide distribution in peritoneal structure, with the formation of endometrial-like tissue in these situations, appearing morphologically and functionally identical.

This history of this condition dates back to 1860 when von Rokitansky first described an adenomyoma as a pathological entity. Since that time there have been numerous publications with presentation of this subject in great detail. Not much interest was manifested in the subject, nor its full significance recognized until 1921, when Sampson began his detailed investigations on this subject and wrote numerous articles on various phases of the conditions. Up to the time of Sampson's first article, in 1921, fewer than twenty cases has been published in the literature. Immediately following the appearance of this work reports of similar findings were published in England, Germany and this country.

The introduction of Sampson's work at once produced a great deal of interest in the subject, especially the consideration of the etiology of this condition. Sampson in his first article proposed a theory of origin of these tumors which has met with a great deal of opposition.
as well as support. Since this work of Sampson numerous theories or origin of the condition have been proposed. These have been considered in detail in this paper.

There are two theories of etiology that have received a great deal of support and seem the most plausible to the majority of the authorities, who may favor one or the other of these theories. First, The Implantation Theory of Sampson, and second, The Serosal or Coelomic Theory of Origin. Both sides are fairly well agreed that the hormonal stimulation provided by the ovarian hormone, folliculin, is of importance in considering the etiology of this condition, and this has been presented as a separate theory of origin in this paper. These theories of origin have been classified in relation to embryological development, i.e., embryonal and post-embryonal development. The theories of origin presented in this paper are:

A. Embryonal.

1. Wolffian Theory.

This theory was presented by von Recklinghausen in 1898. This theory assumes that the origin of the endometrial-like tissue in aberrant position is from the Wolffian duct structure. In embryonic life the Muellerian ducts cross the Muellerian ducts, and v. Reckling-
hausen, accepting the theory of displacement as a working hypothesis, saw in the close anatomical relationship between the ducts of the primodial kidney and the generative organs, sufficient ground for the possibilities of the transference of embryonal rests from one structure to another. In summing up his observations, v. Recklinghausen stated: "The epithelial constituents of the adenomata and cystadenomata of the fallopian tubes, of their interstitial portions, and of the outer peripheral layers of the uterus, are derived from rests of the Wolffian body, while the centrally located adenomyomata of the uterus arise from the uterine mucosa, or its equivalent, the Muellerian Ducts". This theory has received support by Dick, Meyer, and Lockyer. Later Meyer discarded this theory in favor of his Serosal Theory of Origin. This theory does not receive much support and recognition at the present time and Cullen and Meyer have done much to disprove this theory.


This theory assumes that the basis of endometriosis is certain aberrant portions or rests of the Muellerian duct. Cullen, in 1896, presented the Muellerian Theory of origin and has followed this quite closely. He assumes that there is deposit of a rest of the Muellerian duct on
SUMMARY

the ovary or some other structure in the embryological development of the individual with subsequent development of an endometrioma. Most of this is based on the premise that the origin of the müllerian duct is partly, at least, from the germinal epithelium, and thus well situated anatomic ally for the production of endometriomas in their various sites. The theory has received support from Russel and Norris chiefly, with Cullen presenting large amounts of material in support of his view. The theory is not given much credence at the present time.

B. Post-Embryonal.

1. Direct Uterine and Tubal Wall Invasion.

This form of origin assumes that the endometrium lining the uterus and the mucosa of the tube directly invades the wall with the formation of endometriomas in the muscular substance of the uterus and tubes. The direct uterine wall invasion by the endometrium was clearly recognized by Cullen as early as 1898. He was able to trace a direct connection between the endometrium and the endometrial-like lesions. This has received much support from Sampson and has been generally accepted by most authorities as the correct explanation in this site.

2. Implantation Theory.

This theory of origin was presented, in 1921, by Sampson and has been the subject of much discussion. It
SUMMARY

has gained considerable support but at the same time
has been rejected by many. The theory as presented
by Sampson postulates that during menstruation there is
a retrograde flow of menstrual material which contains
blood, fibrin, and epithelial cells, the viability of
which is the subject of much discussion. The cells then
become implanted on the ovary or on surrounding periton-
eal structures in the pelvis. Here this epithelium grows
and reacts like endometrium to hormonal stimulation. The
resulting growths are identical structureally and function-
ally with endometrium of the uterus. Gland-like struc-
tures are formed which are lined with an epithelium which
may be columnar, cuboidal, or flattened with nuclei at the
base or in the middle. Surrounding this there is a "cyto-
genic" stroma. During menstruation there is a menstrual
reaction with subepithelial hemorrhage and then subsequent
hemorrhage into the lumen of the glands. The contents
of the cyst are then the color of blood that has undergone
physiological changes. Hematomata may be formed in the
ovary due to the retention of menstrual blood. As these
continue to enlarge there may be rupture with further
dissemination of this material into the pelvis with
implantation. Thus the ovary may act as an intermediary
host. The theory also postulates that there may be direct
implantation on the peritoneum through or from the tubes. In this event the resulting involvement is not as invasive as when secondary to the ovary. These lesions are then characterized by the formation of extensive adhesions and may consequently cause obstructive symptoms.

There is also the possibility that an endometrioma may be formed by the direct invasion of the uterine wall with penetration of the wall and appearing on the serosa and eventually rupture of cystic contents into the peritoneum. There may also be invasion of the uterine and tubal walls from the serosal or peritoneal side of the structure with subsequent involvement of these structures. Sampson is of the opinion that all sites of endometriosis may be explained on this basis except certain extraperitoneal involvements.

Evidence is presented in support of Sampson's contention. Jacobsen, Cron & Gey, Heaney, and many others have given experimental evidence that the contentions of Sampson are possible and that there may be implantation of endometrial tissue. Implants have been made in the eye, abdominal wall, and other sites in rabbits and monkeys in an attempt to produce characteristic lesions. Some of the attempts have been successful and others have been met with failure.
SUMMARY

Novak is a strong opponent of Sampson and has presented much evidence to disprove the theory. He questions the retrograde menstruation that is so essential to the theory. Also he does not believe that the endometrial cells in the menstrual discharge have sufficient viability to grow and that they are degenerated cells. He also questions the occurrence of endometriosis in abdominal scars as a result of implantation.

Everett has presented much evidence in favor of the theory of implantation origin, especially in connection with tubal endometriosis. He is of the opinion that may of the lesions are as a result of tubal endometriosis and tubal epithelial invasion and at times metaplasia of tubal mucosa to form endometrial tissue.

From this it is evident that there is much confusion and the question still must be settled. King has also been a strong opponent to this theory and believes that many of the lesions are of luteal origin in the ovary and not as a result of implantation. He presents evidence of this effect and states he is of the opinion that morphological and physiological identity do not establish a positive endometrial identity.

3. Serosal or Coelomic Theory.

This theory is based on that fact that the epithelia of the female genital system are derived from the coelomic
epithelium of the urogenital folds, which in turn is a modification of the primitive peritoneum. These epithelia not only comprise the germinal epithelium of the surface of the ovary, the lining of the follicles, and possibly the ovary, but also these invaginations of the Muellerian duct represented by the endosalpins, endometrium, endocervix, and vagina. In other words, the entire epithelial apparatus has a common ancestor in the peritoneum. It is assumed that the coelomic epithelium does not use all of its developmental potentialities and that in later life it may awaken to new activity and produce differentiated structures identical with those which it produced when in the embryonic stage. Thus it is supposed that the germinal epithelium of the ovary may invade the ovarian substance and create endometrium. It is also believed that the pelvic peritoneum may at any point develop this innate tendency and produce the so-called ectopic endometriomata. There may be metaplasia of the structures with the subsequent formation of this endometrial tissue.

This theory has received wide acceptance and is equal in popularity with the implantation theory. The chief proponents of the theory are Meyer, Lauche, and Ivanoff. The work of Robinson, Novak, Enzer, Nicholson,
SUMMARY

and Spitz has been presented with evidence these authors have produced in support of this theory.

4. Luteal Origin of Tarry Cysts.

This theory was presented by E. S. J. King and seems to have considerable support. He believes that the endometrial involvements of the ovary are as a result of luteal cyst reaction with menstrual and decidua reaction of the resulting endometrial-like lesion. He contends that it is difficult to separate and distinguish between the true endometrial lesions and the cysts form from luteal origin. As these cysts react to menstruation they become enlarged and finally may rupture and it is noteworthy that from this point on the theory as presented by King is identical with that of Sampson. Thus the only point of difference between these two men is the primary origin of the endometrial-like structures in the ovary, one believing that they arise from implantations of endometrial cells on the ovary and the other believing that it originates from the luteal cysts of the ovary.


This theory assumes that the primary stimulus producing the endometrial lesions is the ovarian hormone, folliculin, which causes the lesions to be formed. The theory has many supporters, all of whom are not well agreed, for some have a tendency to lean to the coelomic
SUMMARY

theory and others to the implantation theory but all agree that basically all are dependent on the hormonal influence of the ovary. Jeffcoate and Potter believe that endometriosis is a manifestation of ovarian dysfunction. They think that an over-production of coelomic cells as proposed by the adherents of the serosal theory or prepares the peritoneum and other structures for the implantation of endometrial tissue as explained by the implantation theory adherents. Witherspoon is an active advocate of this theory of origin. It is well agreed that the hormone causes further growth of the lesions and the menstrual and decidua reaction.


This theory postulates that there may be venous and lymphatic dissemination of endometrial tissue to various sites. Halban and Sampson have been two very strong adherents to this theory. It is assumed that the primary origin is from the uterus where the venous and lymphatic sinuses are in close relationship to endometrium and where during menstruation there may be rupture of some endometrial tissue into the veins or lymphatics and subsequent spread of the lesions. Endometrial-like tissue has been found in the lymphatics, veins, and lymph nodes. Halban favors the lymphatic dissemination of this tissue while Sampson favors the venous dissemination and presents
SUMMARY

evidence to that effect. This theory is well supported and may be the correct explanation for endometriosis at certain sites.

In conclusion, it may be said that the probability is that no one theory can explain all sites of endometriosis and that more than one theory will be invoked to explain the various sites of involvement. It may be that, while one theory is the correct explanation for one site of involvement, another theory may account for a second site of involvement. The subject is still very confused and, as suggested by several authors, the correct solution may not have been suggested yet.


31. Jacobsen, V.C. Fate of endometrial emboli in the venous circulation of the rabbit, Arch.Path. 15:1, 1933.


60. Sampson, J.A. Metastatic or embolic endometriosis due to menstrual dissemination of endometrial tissue into the venous circulation, Am.J. Path., 3:93-109, March, 1927.


