

Perspective

Understanding Endometriosis: Clarifying Sampson's Theories with a Personal Perspective

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Abstract

Endometriosis is classified as a benign gynaecological disease, but it actually demonstrates several pathogenic processes which are the hallmark of carcinomatosis; namely metaplasia, metastasis and implantation with variable degrees of invasiveness. Whilst metaplastic processes were suggested by earlier authors, the latter two, more important, pathogenic mechanisms were described by John Sampson. To this day respected experts describe the two related conditions of endometriosis and adenomyosis as having an enigmatic pathogenesis involving endocrine, immunologic, proinflammatory, and proangiogenic processes. However, I would contend that these processes are secondary to Sampson's two separately developed theories for which he described abundant histological photomicrographic data to demonstrate the underlying mechanisms. The first theory/ mechanism involves a process of venous embolization of "heterotopic endometrial tissue" described in 1925, the same year when Sampson coined the term endometriosis, and which he applied in his extensive publications thereafter. The second theory/ mechanism involves retrograde menstruation via the fallopian tubes followed by implantation on peritoneal surfaces, described by him initially in 1927, and fully reported in 1940 as a commissioned article following an invited presentation to the American College of Obstetrics and Gynecology to specifically expand on this second theory. For unclear reasons, most authors reporting studies on endometriosis have focussed on the implantation theory and minimised its relevance as it fails to explain many forms of endometriosis outside the peritoneal cavity. Having reviewed Sampson's entire body of publications, I believe all eight locations of endometriosis, both common and uncommon, can be explained from his extensively reported studies.

Keywords

- Müllerian metaplasia; Endometrial metastasis; Endometrial implantation; Invasive endometriosis; Heterotopic endometrial tissue; Uterine vasculature

INTRODUCTION

Affecting around 10% of women, endometriosis is classified as a benign gynaecological disorder. However, in many cases the disease bears resemblance to carcinoma with similar pathogenic processes including metaplasia, metastatic phenomena and the implantation of endometrium in various sites remote from the uterine cavity. These are often attended with variable degrees, sometimes very deeply, of adjacent tissue invasion. This article will describe the evidence for these statements from the perspective of New York gynaecologist, John Sampson who wrote exquisitely detailed articles across the first 40 years of the twentieth century. These were accompanied by numerous unique Figures comprising photomicrographic plates, also rather uniquely involving, in its day, the new technology of X-rays.

Clinical Scope of Endometriosis

For those clinicians who have devoted their professional

lives to managing women with gynaecological disorders, the one condition of endometriosis requires managing individual women across their individual lifetimes, from the onset of dysmenorrhoea in early teens through to the stabilisation of pelvic symptoms during the menopausal years. For many women and their gynaecologists, the years of shared pain is halted at the time of hysterectomy with bilateral salpingo-oophorectomy; but many women who I have managed over our respective lifetimes, have avoided the pelvic surgery and continue on progestogen suppression therapy (namely medroxyprogesterone acetate; Provera) into their seventies. This extends utility of an inexpensive, readily available progestogen, initially applied to create amenorrhoea during the years of menstrual cycling; into the menopausal years to avoid hot flushes and other hypo-estrogenic symptoms, as well as ensuring the well of pelvic pain is truly capped. For many women have found that estrogen therapy given during menopause can re-ignite the process of endometriosis from where-ever it is hiding.

For the optimal management of women with endometriosis, this required embracing both Advanced Laparoscopic Surgery as well as In Vitro Fertilization (IVF) and also acquiring a broader knowledge of endocrinology to understand all those processes impacting on the Reproductive System [1-3]. In 44 years of gynaecological clinical practice this has introduced me to women with endometriosis involving not only the common sites, being ovaries and pelvic areas, especially around the utero-sacral ligaments in the cul-de-sac (Pouch of Douglas), but also cases with pleural and diaphragmatic deposits, and cases with lesions in both the upper and lower abdominal areas noting a predilection for endometriosis granulomas within the appendix. Less commonly there have been cases with deposits in ligamentous structures including inguinal and umbilical sites as well as abdominal wall scars and deeply invasive nodules involving the bladder and ureter as well as extraperitoneal recto-vaginal invasion, the latter challenging the surgical skills of gynaecologists beyond that of any other disease process. Extending from these described limits, endometriosis can sometimes appear pre-menarchal, probably bedding down during neonatal menses, lying dormant until the earliest rise of serum estrogens at the thelarche re-ignites the nasty process even before the first menses appear. Assisting women with endometriosis to achieve pregnancies is also part of the close clinical management process required of the person-dedicated gynaecologist.

Current assisted reproductive processes undertaken by my clinical group indicates that those women with endometriosis Grades III and IV (AFS: American Fertility Society classification), and those with Deep Invasive Endometriosis involving the Recto-vaginal septum area (DIER) should be maintained in a state of amenorrhoea until ready to undertake an IVF treatment cycle; reverting back to Provera therapy for amenorrhoea if the fresh embryo transfer fails to generate a pregnancy [4-6]. Cryopreserved embryos can be transferred later in a controlled HRT regimen, again reverting to Provera suppression therapy if pregnancy fails to ensue [7,8].

CLINICAL SCOPE OF ADENOMYOSIS

Although adenomyosis is classified as a separate disease, this delineation is simply one of anatomical siting as the underlying cellular pathology is the same. This will become clear as we examine the works of the early pioneer gynaecologists, especially Thomas Cullen and John Sampson. However, to complete this introduction, both endometriosis and adenomyosis are noted to have similar negative effects on fertility, but the latter has added limitations regarding implantation and placentation as well as a chronic irritation effect during pregnancy, further increasing the likelihood of pre-term delivery [9]. Nodular forms of adenomyosis can be excised prior to pregnancy with beneficial effects demonstrated, but diffuse adenomyosis remains a high-level challenge similar to that of DIER [10]. Surgical procedures of myolysis and wedge resection of large areas of diffuse adenomyosis have been undertaken with improved outcomes for achieving IVF pregnancies, but the increased risks of uterine scar disruption in late pregnancy introduces a separate hazard requiring particularly careful management [11].

CURRENT PROGRESSIVE MANAGEMENT OF ENDOMETRIOSIS AND ADENOMYOSIS

Against the aforementioned background, the evolving ideas regarding the management of women with endometriosis is to avoid surgical procedures [12,13], maintain the condition in a suppressed state and consider oocyte vitrification for fertility preservation whilst the woman is young, preferably under age 32 years [14]. This approach is beginning to show promising outcomes for pregnancy as well as control of the disorder [15].

ENDOMETRIOSIS AS AN "ENIGMATIC" DISORDER

At the European Society for Reproduction and Embryology (ESHRE) meeting held in Vienna in 2019, a pre-congress course on Endometriosis involved eight experts covering the subject in-depth including the latest ideas on pathogenesis. They each continued to view the two related conditions of Adenomyosis and Endometriosis as having an enigmatic pathogenesis. However, they were in agreement regarding definitive diagnosis, confirming laparoscopy as the established gold standard since the early 1970's, but increasingly assisted by pelvic ultrasound since the 1980's and magnetic resonance imaging since 2004 for the better definition of deep tissue invasion.

However with respect to understanding the causation of endometriosis, and to seek a useful biomarker, experts examined the current evidence concerning genetic biomarkers, studies on the transcriptome (including the challenges and promises of RNA diagnostics); the extensive studies on both proteomics and metabolomics; as well as the search for a non-invasive diagnostic test. Whilst the promises from genome-wide analysis for transcriptomic and RNA diagnosis was highly expectant, the research has proven complex with various analytical problems and confounders, long non-coding RNA (lncRNA) shows promise but not yet validated; similarly short non-coding micro RNA's (miRNA's) show promise, albeit with overlap and conflicting results, also awaiting validation. Both proteomics and metabolomics have been explored extensively. Of the more than 20,000 proteins in the human proteome, the plasma proteins fall into three classes - functional plasma proteins, tissue leakage proteins and signal proteins. The human metabolome contains at least 114,000 small molecules but so-far there has not emerged a single reliable biomarker or even a panel of useful biomarkers. The Cochrane library concluded in 2016 there is not enough evidence to recommend testing for any plasma or urine biomarker for the non-invasive diagnosis of endometriosis [16]. More recently the ideas on pathogenesis have moved towards a genetic or epigenetic hypothesis, but again without strong supportive data [17]. A current detailed review of endometriosis in the New England Journal of Medicine summarises "the development of endometriosis involves interacting endocrine, immunologic, proinflammatory, and proangiogenic processes ... but whether these factors are pathogenic (causal) or merely represent a feature of the pathophysiological process typically measured years after symptom onset, remains uncertain." [18].

All this continues to perpetuate the notion that endometriosis is truly an enigmatic disease, but is this so? I would contend

that closely reviewing important historical data can change this perception.

THE EARLY WORK OF JOHN SAMPSON - DECIPHERING THE UTERINE VASCULATURE

On 11 May 1911, John Sampson presented a paper to the American Gynecological Society in Atlantic City. It was entitled "The blood supply of uterine myomata (based on the study of 80 injected uteri containing these tumors)". A further paper which added 20 more injected uteri was presented at the annual session of the Clinical Congress of Surgeons of North America on 15 November 1911 and was subsequently published in the journal *Surgery, Gynecology and Obstetrics*, March 1912 [19]. Sampson continued to expand on the study of injected uterine specimens, presenting a larger series of 150 uteri with fibroids for which he had personally performed hysterectomy operations [20], and about which he was very familiar with the clinical aspects of those patients. Sampson offered this body of work to explain that "changes in the circulation of the uterus caused by these tumours contribute more to their symptomatology and interfere more with the health of the individual than the blood supply of the tumours themselves."

Sampson's procedures on the hysterectomy specimens is best described in his own words: *"The injection mass used was 15 per cent gelatin which contained in suspension either a pigment or some material (usually bismuth subcarbonate) which was impervious to the X-ray. In 52 specimens, either the arteries or veins, or both, were injected with a pigment (if both were injected, Venetian red was used for the arteries and ultramarine blue for the veins). In the remaining 98 specimens, one vascular system was usually injected with a mass impervious to the X-Ray, and the other system was usually injected with a coloured mass. Stereoscopic radiographs of the specimens injected with the mass impervious to the X-ray were found to be of great value in the study of the various phases of this subject."*

APPLYING X-RAYS IN MEDICINE

Several physicists working in the 19th century with partially evacuated glass tubes (Crookes tubes and Lenard tubes) through which electricity was passed, recognised energy waves emanating from the tubes. However, it was physicist Wilhelm Conrad Röntgen who fortuitously discovered and named them as X-rays in 1895, sending pictures of his wife's hand (with rings) to friends and colleagues around the world on Christmas day of that year. Hospitals were quick to introduce the technology. Before the end of the century, hospitals in Britain, beginning with Glasgow, established radiology departments and proudly reported their skills at identifying kidney stones and of finding lost pennies swallowed by children. Military doctors could now find the placement of bullets and associated bone damage within the bodies of gunshot survivors. At carnivals, people could have their skeletons displayed until the practice was restricted once the dangers of unshielded X-rays were revealed. During World War I dual Nobel prize-winner Madame Curie (who pioneered research on radioactivity, isolated isotopes and discovered the elements polonium and radium) set up France's first military radiology centre and developed mobile radiology facilities which

she manned and for which she trained female radiographers. This popularised X-ray technology and within hospitals uptake was sequentially rapid so that by 1930 X-rays were a routine part of patient diagnostics worldwide [21].

PLACING SAMPSON IN THE CONTEXT OF HIS ERA

In the context of this background summary of X-Rays, one can consider that Sampson's work, which commenced around 1905 for presentation in 1911 [19,20], was indeed pioneering with a new technology. Indeed, even the application of electricity, used to power up the Röntgen (Roentgen) tubes, was also in its infancy. The historic alternating current powerline established from Niagara Falls to Buffalo, New York had occurred just a decade prior (1896), utilising large-scale hydroelectric generators built by George Westinghouse after he had bought the patents for alternating current from Nicola Tesla.

John Albertson Sampson (1873-1946), graduated at Johns Hopkins University in 1899 where he had been exposed to the lectures of Thomas Stephen Cullen (1868-1953) who was the Director of Gynecological Pathology from 1903 and who later became the Professor of Clinical Gynecology from 1919. Sampson became Professor of Gynecology at the Albany Medical College in New York in 1899 working his entire career at the Albany Medical Hospital on the shared campus. He was clearly an innovative pioneer in the application of X-ray technology. The 150 hysterectomy specimens described above enabled Sampson to categorise them according to the underlying pathologies embracing myomata (n=79; 53%), pelvic inflammatory conditions (n=20; 13%), dysfunctional uterine bleeding (n=16; 11%), ovarian cysts (n=12; 8%), carcinoma of the cervix (n=8; 5%), carcinoma of the uterine body (n=5; 3%), prolapse (n=5; 3%), ectopic pregnancy (n=3; 2%) and single cases of hydatidiform mole and uterine sarcoma. This enabled Sampson to describe the vasculature of both the normal and pathological uterus [19,20].

NORMAL UTERUS WITH NORMAL MENSTRUATION

With a long-standing interest in dysfunctional uterine bleeding [22], I personally examined all the pictures presented by Sampson in an attempt to explain new observations about fibroids and the relevance of their location with respect to their symptomatology, in particular with reference to infertility and assisted reproduction outcomes. Consistent with my own longstanding view that all intramural fibroids can cause disturbance of uterine function, including menorrhagia or fertility-related issues as well as pregnancy losses at all gestational stages, my team reviewed the early articles from John Sampson, in particular the unique venous drainage mechanism from the endometrium which explains how menstrual loss is contained in normal physiology but which can be excessive when the protective 'anaemic' zone is disturbed. By adding the subsequent knowledge from hysteroscopy studies of the 1970's, including those of Osamu Sugimoto (Figure 1) [23], and advanced imaging techniques including recent sonographic morphologies combined with magnetic resonance imaging [24], we discovered "lost" or "unrealised" information from John Sampson which

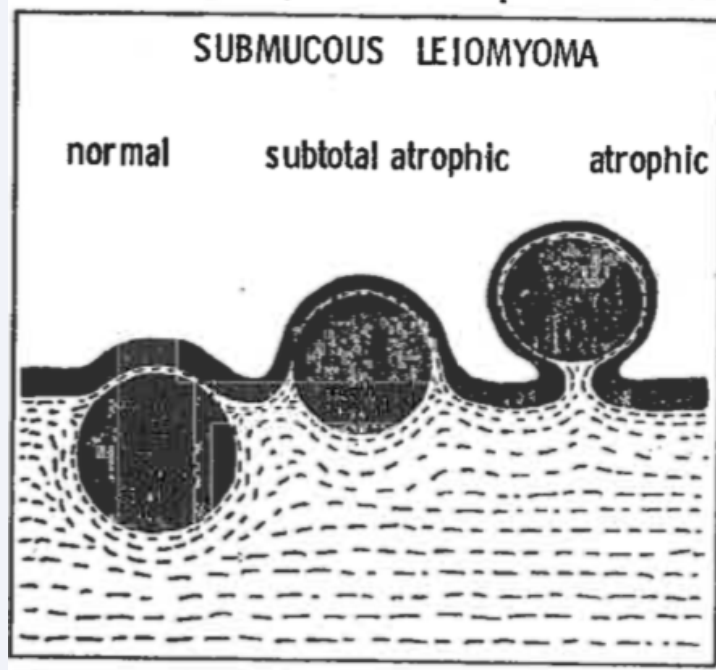


Figure 1 Relationship between submucous leiomyoma and overlying endometrium. Figure from Yovich, 1978 [22] derived from Sugimoto, 1978 [23]. Hysteroscopic views of the endometrium overlying myomata which protrude into the uterine cavity invariably reveal a thin, atrophic appearance rather than hyperplasia, negating the endometrium as the cause for myoma-related menorrhagia.

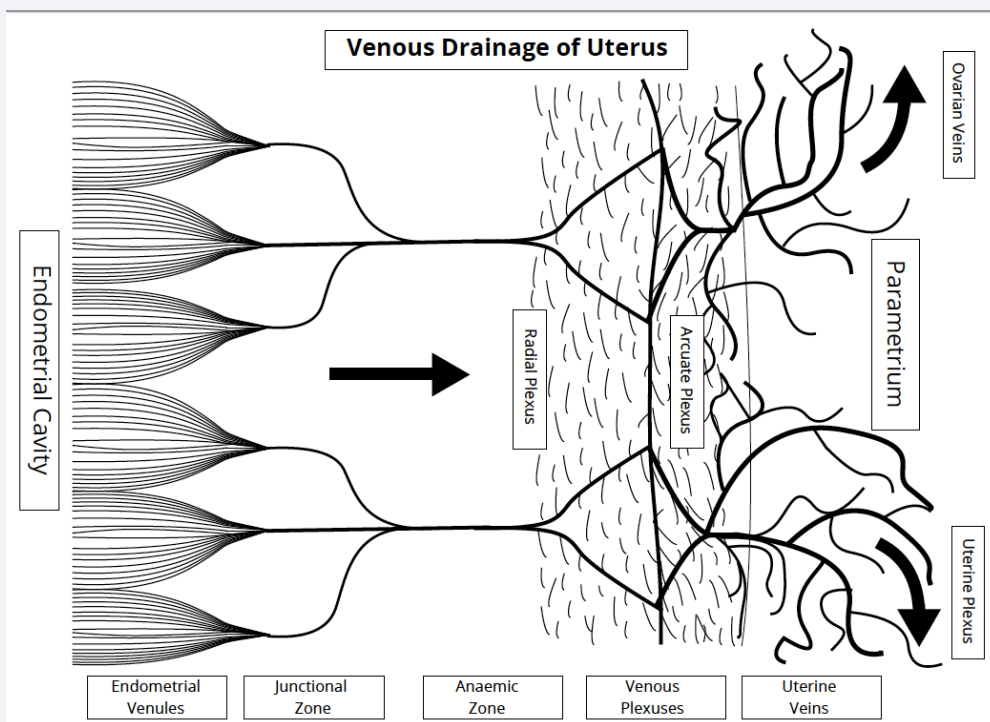


Figure 2 Stylised diagram by Yovich JL. Depicts the venous system of the uterus in part-cross section. It incorporates Sampson’s findings of the “anaemic” zone where endometrial blood is “received” through only a few narrow veins. This region acts as a valve-like protective layer which ensures that during uterine contractions venous blood preferentially travels towards the less resistant radial and peripheral plexus regions which act somewhat like a sponge. However, the flow mechanism can be disrupted by intramural pathologies such as fibroids and adenomyosis which can cause congestion, oedema and menorrhagia by backpressure on the endometrium. The junctional zone reflects the more recently described ultrasonic and MRI findings, but may, in fact, represent peri-endometrial oedema reflective of disruption to the normal venous outflow, depicted by the bold arrows.

better explains the current data (Figure 2) [25]. We implored that Sampson's data required resurrection and "at the very least this knowledge needs to immediately enter the training education of medical students, doctors and specialists worldwide". In a similar vein, we now wonder whether Sampson's studies on endometriosis had been properly interpreted and whether those important historic articles should be reviewed.

SAMPSON'S OBSERVATIONS REGARDING THE ARTERIAL SUPPLY OF THE UTERUS

Sampson described: "The course of each uterine artery along the side of the uterus and its free anastomosis with the ovarian artery of the same side are well known (Figure 3A). From each uterine artery branches arise, at intervals, which penetrate the uterus; each one either divides into two branches, one supplying the anterior and the other the posterior uterine wall, or without dividing, it supplies either one or the other uterine wall. At the level of the internal os their course within the uterus is at right angles to the long axis of that organ; below this level it is inclined downwards, while above it is directed obliquely upward and the arteries themselves are larger. Frequently one intramural artery is much larger than the rest and appears as a terminal branch of the main uterine artery. This is known as the fundal branch. These arteries present many minor variations, but the general plan of their origin and course is the same. These main intramural arteries which I have called "arcuate" lie between the outer and middle third of the uterine wall, and each one supplies a quadrantal segment

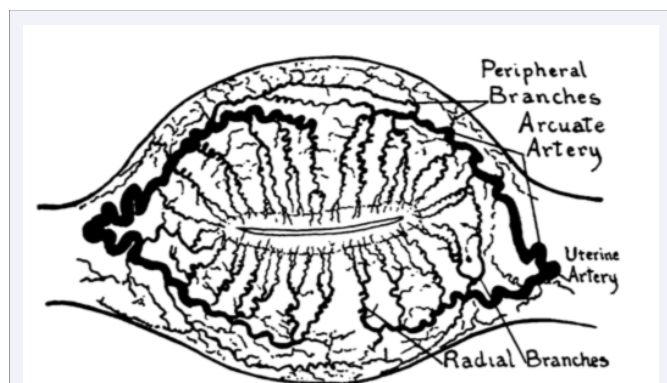


Figure 3 Diagrams derived from John Sampson article in the American Journal of Obstetrics and Diseases of Women and Children, August 1918. Fifteen figures are presented explaining the normal mechanism of menstruation along with "the escape of foreign material from the uterine cavity into the uterine veins". It can be seen that, in the normal situation, the uterus is well supplied with arterial blood; thereafter during contractions blood is pushed to the periphery and unable to return across the protective "anemic" zone, unless this area is disrupted.

A: The arterial system of the uterus, as seen in cross-section. The arcuate arteries, which arise in pairs from each uterine artery, divide the uterine wall into three zones, the outer, or peripheral zone, nourished by the peripheral branches; the narrow arcuate zone in which the arcuate arteries lie; and the inner or radial zone which is nourished by the radial branches, the latter terminating in the endometrium. Each pair of arcuate arteries supplies a segment of the uterine wall corresponding to a segment of the Mullerian duct on that side.

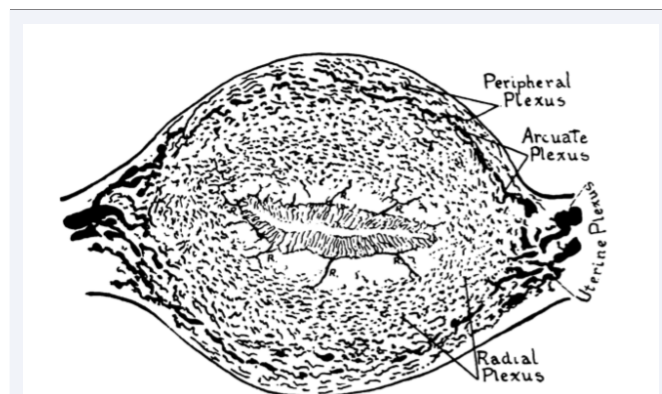


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B: The venous system of the uterus as seen in cross-section. The venous blood is conveyed by the arcuate plexus of veins (corresponding to the arcuate arteries) from the uterus into the uterine plexus, situated between the layers of the broad ligament. The arcuate plexus receives blood from both the peripheral and radial zones, there being a rich plexus of veins in each. The venous blood from the endometrial plexus is collected by venous sinuses at the base of the endometrium which empty into the plexus of the radial zone (R) through "receiving" sinuses. This area is relatively "anemic" and probably acts as a protective "controlling or constricting zone" to ensure blood flows along the direction of least resistance toward the periphery into the arcuate plexus then the uterine plexus.

of the uterus corresponding to a segment of either the anterior or posterior half of the Müllerian duct of that side. They terminate in median peripheral and radial (centripetal) branches. The peripheral terminal branches of some of the arcuate arteries of one side anastomose freely with similar branches of arcuate arteries of the opposite side, thus establishing a communication between the two main uterine arteries. Along the course of each arcuate artery, radial (centripetal) and peripheral (centrifugal) branches arise. The radial branches are the larger and more numerous. They supply the myometrium, mesial to the arcuate artery from which they arise, and terminate in the endometrium. The peripheral arteries nourish the peripheral portion of the myometrium. There is a free anastomosis of the arterioles of the peripheral branches of neighbouring arcuate arteries of the same side, and also of the arterioles of the radial branches near their origin from the arcuate artery, but the distal portion of the radial arteries are apparently end arteries.

The arterial system of the uterus enables us to divide the uterine wall into three zones: first, the peripheral (the outer third), which is nourished by the peripheral arteries; second, the arcuate, the narrow zone in which the arcuate vessels lie; and third, the radial (the inner two thirds) which is nourished by the radial arteries. The fine terminal branches of the radial arteries penetrate the base of the endometrium, and arterial capillaries were found to extend

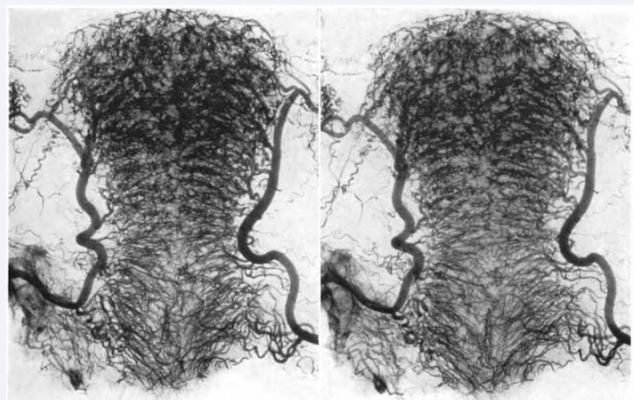


Figure 4 Stereoscopic radiograph from 1912 [19] displaying arterial supply of the entire uterus; from autopsy on 25 year-old nullipara with normal uterus. Front and rear views.

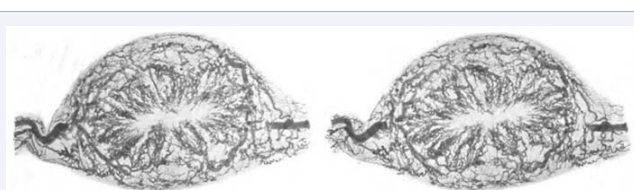


Figure 5 Stereoscopic radiograph of a cross-section of the uterus shown in Figure 4. A portion of each uterine artery appears in the slice along with a portion of six arcuate arteries with their branches.

only a short distance in the uterine mucosa" (Figures 4,5).

SAMPSON'S OBSERVATIONS REGARDING THE VENOUS SYSTEM OF THE UTERUS

Sampson's early studies during 1911-1912 [19], advanced the understanding underlying the control of menses and thereafter emerged a better understanding behind the mechanism of abnormal uterine bleeding, not only that associated with myomata but also from other causes where the endometrium is disturbed [20]. In his increasing focus on the venous system, Sampson discovered that, in certain circumstances, foreign material from the uterine cavity could appear in the uterine veins [26]. By this stage Sampson was starting to describe the uterus as a "pelvic heart" with alternating cavities (endometrial or venous) depending upon the pressure effect from contractions. Blood flow between the cavities was controlled by the "anemic zone" acting as a "controlling or constricting zone". However, the presence of receiving sinuses could disturb this control, enabling blood to be forced into the endometrial cavity during contractions, (causing menorrhagia). Conversely the myometrial venous plexus could receive foreign material (endometrial slough or inflammatory debris via these receiving sinuses. Sampson also described that "during menstruation, if there is any loss of tissue it is usually only from the compact layer, leaving behind the spongy layer. This spongy layer from the very nature of its structure would act as a valve (probably at times imperfect), preventing any back flow into the receiving sinuses beneath it."

In 1913 Sampson wrote [20]: "menstrual flow is preceded by changes in the venous plexus of the endometrium permitting the escape of blood into the tissues of the latter. The duration of the flow and the amount of blood lost is probably dependent upon many factors, such as changes in the endometrium, the time necessary for the repair of the altered endometrium, the degree of venous congestion of the uterus and the ability of the uterus to control its venous circulation. In the normal uterus there is a rich venous plexus of the endometrium, and also of the myometrium, which communicate with each other by a few slim channels which pass through a relatively anemic zone (Figure 3B). Valves are not present, and therefore when the uterus is relaxed the venous blood in the myometrium could easily be forced back into the plexus of the endometrium, and if the latter was injured (physiologically or otherwise) it would escape into the uterine cavity. In normal circumstances, myometrial contractions force the blood through the few venules which cross the anemic zone, from which it cannot return, and thus prevent bleeding into the uterine cavity. Those few venules in the anemic zone also become compressed during uterine contractions adding to the regulatory mechanism which prevents backflow in normal circumstances" (Figure 3B).

In 1918 [26], Sampson wrote: "The uterus may be considered a muscular venous sponge – the veins for the most part being spaces (sinuses), between the muscle bundles (Figure 10). The arrangement of these spaces is determined by the uterine musculature and their size by various normal and pathological uterine conditions and the degree of relaxation of the uterus. When contracted, the spaces (venous sinuses) would be small; when relaxed, dilated and filled with venous blood. From a study of the injected specimen we recognize how the venous blood is collected from the various portions of the uterus and how it escapes from that organ (Figure 9). Beginning with the endometrium we find a rich venous plexus (seen best in the premenstrual condition), with collecting sinuses at the base, which empty into the venous sinuses of the radial zone of the myometrium, and these in turn into the arcuate veins which are similar in their course to the arcuate arteries. The arcuate veins also receive venous blood from the venous sinuses of the peripheral zone. The blood in the arcuate veins empties into the uterine plexus of veins situated between the layers of the broad ligament on either side of the uterus. From this plexus the blood is conveyed to the ovarian veins, round ligament (epigastric) and uterine veins. The sinuses of the radial zone which receive the blood from the endometrium are deserving of special attention. Some of these are relatively large, radiate from the base of the endometrium and empty into the deeper portion of the venous plexus of the radial zone. I have called these sinuses the "receiving" sinuses (Figure

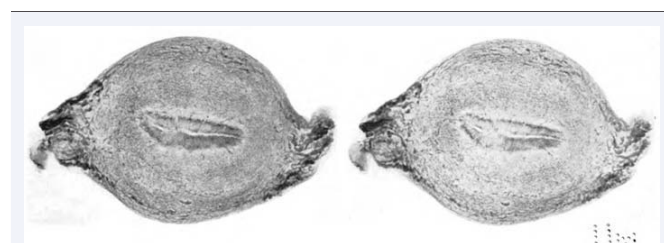


Figure 6 Stereoscopic radiograph. Venous supply of a cross-section of the body of the uterus. Operative specimen of a nullipara age 30 years with normal uterus.

6). Blood would pour from these sinuses into the uterine cavity if the endometrium was injured and the uterus relaxed – blood and foreign material could easily escape from the uterine cavity into these sinuses if the endometrium was removed, the uterus relaxed and pressure in the uterine cavity greater than that in the sinuses.”

In considering the cause for the aberrant peripheral flow, Sampson considered several causes. Certainly, myomata could be an underlying cause, but also endometrial damage from infection and, even curettage. So too, obstruction of the cervix from blood clot or placental tissue might be a cause. At this stage of his studies Sampson had progressed from studying fibroids (being the main cause of his collection of hysterectomy specimens), to understanding the mechanism underlying menorrhagia, to now developing his theory of the pathogenesis of puerperal sepsis. Sampson also later focussed on the retroverted, retroflexed uterus as contributing to the causation of endometriosis/adenomyosis within the rectovaginal septum. He postulated that during menses, the contractions were forced against a partially blocked (kinked) cervix causing an increased pressure within the uterine cavity, attempting to force the menses through. However,

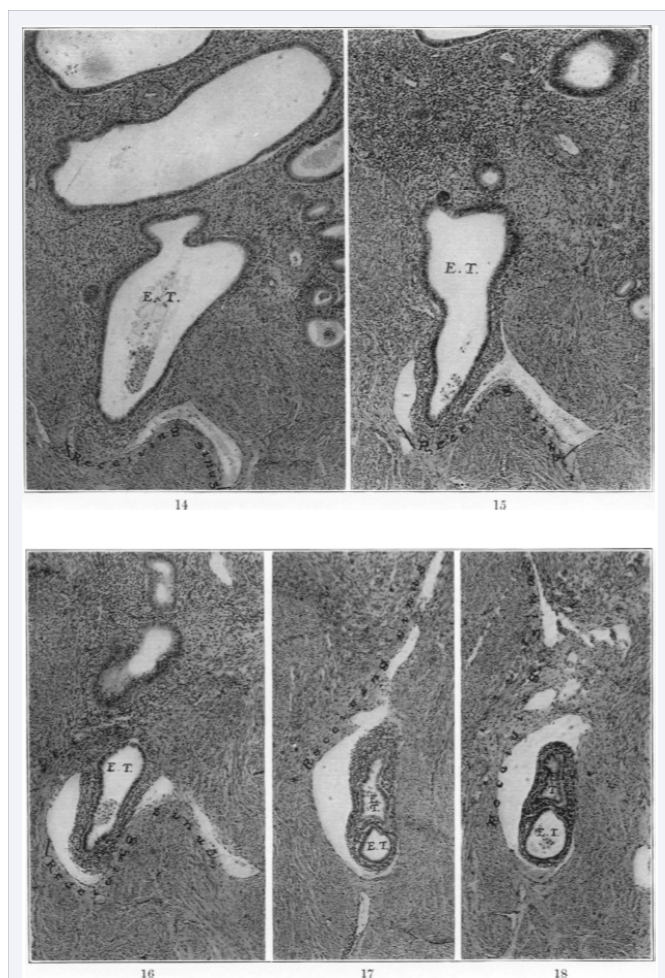


Figure 7 Plate 24 from American Journal of Pathology, 1927 [37]. Five micrographs showing endometrial tissue in receiving sinuses of the uterine wall, in some surrounded by stroma, in one with partial attachment or others completely free from any endometrial attachment.

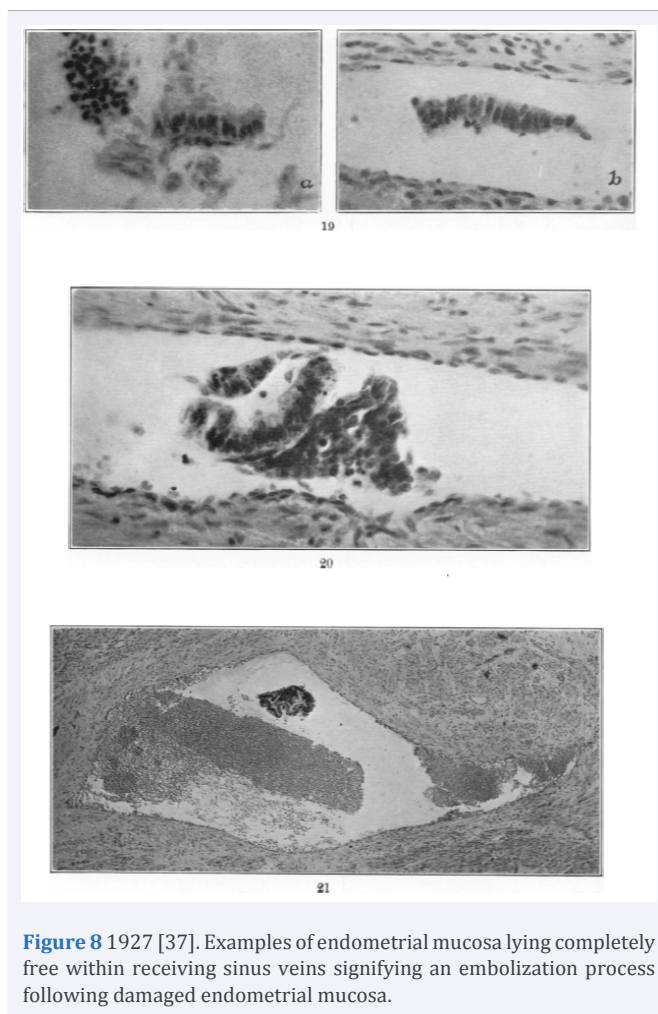


Figure 8 1927 [37]. Examples of endometrial mucosa lying completely free within receiving sinus veins signifying an embolization process following damaged endometrial mucosa.

the net effect was to force menstrual blood and debris into the receiving sinuses and across the normally protective anaemic zone so that endometrial tissue could implant in the periphery of the uterus or be distributed further (Figure 7,8).

HETEROTOPIC ENDOMETRIAL TISSUE/ ENDOMETRIOSIS

In 1925, Sampson presented at the Fiftieth Annual Meeting of the American Gynecological Society in Washington (May 4-6) concerning misplaced endometrial tissue which he thought should be termed endometriosis [27]. He stated that misplaced endometrial-type tissue may be divided into 2 groups: Firstly, true endometrial or Müllerian tissue, which is derived from the uterine and tubal mucosa; and secondly pseudo-endometrial tissue. The latter might arise from a) remnants of the Wolffian Body; or b) from metaplasia of the peritoneal serosa; or c) possibly from other sources. However, it is surprising to find Sampson including the Wolffian hypothesis which was the former theory of von Recklinghausen. With the support of William Welch and Robert Meyer, even Recklinghausen himself, agreed by 1903 that Thomas Cullen was correct, favouring a Müllerian origin for adenomyosis. The events preceding this are as follows:

In February 1916, Sampson described a myomatous uterus from a patient who was menstruating at the time of the operation.

On filling the uterine cavity with his radio-opaque gel, Sampson was surprised to find it escaped from the severed uterine and ovarian veins. As a result of his extensive studies Sampson considered that “menstrual changes in the uterine mucosa could be a means of the dissemination of bits of endometrial tissue into the uterine circulation and as a possible source of certain instances of misplaced endometrial tissue in that organ and outside it.

“At menstruation, some of the capillaries of the mucosa rupture and blood escapes into the tissues of the latter. Often bits of the mucosa may be found lying free in this extravasated blood. The histological study of the ectopic endometrial tissue in a direct or primary endometriosis (so-called adenomyoma of mucosal origin) shows this tissue contains venous capillaries similar to those of the mucosa lining the endometrial cavity (possibly not so large) and furthermore that this tissue, in its invasion of the myometrium, often extends in the spaces occupied by the vessels and sinuses of the uterine wall but is separated from the lumen of the latter by the endothelial lining of the vessel, as has been emphasized by Robert Meyer in his description of the relation of this ectopic endometrial tissue to the lymphatics of the uterine wall”.

SAMPSON HOWEVER, CONTENDED THAT THESE VESSELS WERE VEINS, NOT LYMPHATICS

“In one instance of an endometriosis of the cul-de-sac presenting in the posterior vaginal vault (a so-called adenomyoma of the recto-vaginal septum) the actual escape of the menstrual contents of two ectopic endometrial cavities into adjacent veins was found and furthermore, bits of endometrium were present lying free in the lumina of, and implanted on the lining of, veins about these cavities.”

“I have attempted to inject the lymphatics of the uterine wall and its mucosa but failed. Vessels which I have previously considered lymph vessels have corresponded to the venous capillaries and sinuses of uteri in which the veins have been injected.”

Sampson proposed the term “endometriosis” rather than müllerianosis or, endometrioma, endometriomyoma or müllerianoma as proposed by others; as, he believed, “in the majority of instances uterine mucosa is the chief source of these lesions.”

ENDOMETRIOSIS ARISING AS A METASTATIC PROCESS (FIRST MECHANISM)

At this stage Sampson was of the view that the invasion and dissemination of benign endometrial tissue employ the same channels as the invasion and dissemination of cancer. He had published two articles in 1921 concerning hemorrhagic cysts of the ovary and “adenomyoma” of the uterus, rectovaginal septum and sigmoid colon [28,29], in 1922 concerning ovarian hematomas of endometrial type [30,31], and intestinal adenomas of the endometrial type [32]. In 1924 Sampson described endometrial implants in the peritoneal cavity and their relation to ovarian tumours [33], and early in 1925 concerning endometrial adenomas in the groin [34], and endometrial carcinoma of the ovary [35]. These were in the lead-up to the afore-mentioned presentation, later in 1925. He also projected the view that leiomyomata may have a similar metastatic origin as

endometriosis, with the former establishing in peripheral areas of the uterus following venous dissemination of menstrual material from the endometrial cavity. These small deposits could enlarge according to the attendant arterial circulation established around them. In 1926, Sampson started using the term “endometriosis” publishing an article involving endometriosis of the sac of a hernia with attached pelvic peritoneal endometriosis [36].

Sampson classified endometriosis (misplaced endometrial or müllerian tissue) into four and possibly five groups, according to the manner in which this tissue reached its ectopic situation [27].

1. *Direct or primary endometriosis (müllerianosis), i.e., misplaced endometrial tissue in the uterine wall, which can be demonstrated to have arisen from the direct invasion of the myometrium by the mucosa. A similar condition occurs in the wall of the tube from its invasion by the tubal mucosa.*
2. *Peritoneal or implantation endometriosis. In this group implantation-like deposits of endometrial or müllerian tissue are found scattered throughout the pelvis, similar in their distribution to the peritoneal implantations of cancer, and like the latter often invading underlying structures.*
3. *Transplantation endometriosis. In this group endometrial tissue occurs in the scar of the abdominal incision after operations on the pelvic organs.*
4. *Metastatic endometriosis. This group includes extraperitoneal endometrial tissue in situations similar to those of the metastases from cancer of the pelvic organs, including peritoneal carcinosis.*
5. *Developmentally misplaced endometrial tissue. (Sampson admits that not all cases have a clear explanation).*

ENDOMETRIOSIS ARISING FROM IMPLANTATION (SECOND MECHANISM)

By 1927, Sampson had assembled 67 histological Figures on 41 Plates which demonstrated his theory in support of “Metastatic or embolic endometriosis, due to the menstrual dissemination of endometrial tissue into the venous circulation” [37]. His conclusions were threefold:

1. *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.*
2. *Metastatic or embolic endometriosis arises from the implantation of these emboli in nearby veins.*
3. *Endometrial tissue set free by menstruation, therefore, is sometimes not only alive but may actually continue to grow if transferred to situations favourable to its existence.*

Notwithstanding the above clear views about venous metastasis underlying the pathogenesis of endometriosis, Sampson published a second article later in 1927 entitled “Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity” [38]. This article included 60 further Figures, mostly comprising histological

photomicrographs and which indicated that peritoneal endometriosis sometimes arises from the implantation of endometrial tissue disseminated by menstrual blood escaping into the peritoneal cavity. This study prepares the way for the retrograde menstruation hypothesis and results from the professional academic banter among other gynecologic giants of the day including Robert Meyer, Emil Novak, William Blair Bell, Joseph Halban and Thomas Cullen. In order to respond to their challenges Sampson arranged to undertake hysterectomies during the woman's menstruation period. This did indeed indicate that retrograde dissemination of menstrual blood and endometrial, or even tubal, endothelium could occur, whereas he had found it impossible to force retrograde flow during non-menstrual phases of the cycle. This new idea that retrograde menstruation (via the fallopian tubes) could be another pathogenetic mechanism led to further articles supporting the hypothesis. He also published an article in 1930 describing endometriosis postsalpingectomy [39]. This followed from an examination of more than a hundred cases of salpingectomies, mostly for sterilization, where he showed that not all cases followed traditional epithelial healing processes, but many (20%) demonstrated endometriosis in the stumps; that is tissues of Müllerian derivation, rather than tubal epithelium. Sampson called these cases of endosalpingiosis, meaning endometriosis derived from tubal epithelium. Whereas the 1930 study detailed endometriosis in the tubal stumps (proximal fallopian tubes), a further article in 1932 described primary pelvic endometriosis arising from the tubal fimbriae in the ampullary end of the fallopian tubes [40]. In these latter two studies Sampson often noted widespread pelvic endometriosis, including endometriomata on or within the ovaries, occurring secondarily to the tubal endometriosis. Combined with the observations of his earlier report on peritoneal endometriosis [38], at this point Sampson started to strongly embrace the idea of endometriosis occurring by implantation from the surface [38-40].

SAMPSON'S PRESENTATION OF THE IMPLANTATION MECHANISM, 1940

Sampson's article of 1940 [41], is widely cited as representing his entire, embracing theory about the pathogenesis of endometriosis, but this is incorrect. The article arises from an invitation to present to the American College of Obstetrics and Gynecology, along with a commission to publish, specifically on his more recent studies concerning retrograde menstruation via the fallopian tubes and explain the implantation theory. As a commissioned article Sampson focussed on this second theory/mechanism of endometriosis and did not confuse the issue with the data from his earlier studies. This has been revealed in a recent commentary article [42].

Although I have indicated that Sampson strengthened his views about an implantation hypothesis from 1927, he actually began to consider the possibility following his studies on endometriomata involving the ovaries [28- 30]. In his 1940 article, Sampson wrote:

"Eighteen years have elapsed since the essential features of this theory were published. Ever since that time I have continued

to be greatly interested in endometriosis of all types, especially the peritoneal type, not only because it occurs more frequently than all others and is clinically the most important, but also because its pathogenesis is so tantalizingly alluring and elusive. For over 10 years I studied peritoneal endometriosis constantly and intensively, and since then intermittently according to the operative findings in individual cases. During the intensive study of this subject the distribution and character of its lesions were carefully noted at operation. Sketches were frequently made at that time. Great attention was made to small implants. When feasible these were excised. Drawings, many in color, were made of all specimens of endometriosis before they left the operating room floor. All material was fixed intact in formalin. After fixation, I selected the exact portions of the specimens which I wished to study histologically. The tissue was embedded in celloidin, since it causes less unequal tissue shrinkage than paraffin. I supervised the mounting of the embedded tissue and instructed the technician how it should be cut. A small notebook was carried, in which I jotted down 'inspirations' before they vanished. Studies of the peritoneal implantation of cancer cells escaping from carcinoma of the ovary and of the body of the uterus and also studies of the spread of these tumours in other ways, were initiated by my desire to investigate more intelligently the spread of benign Müllerian mucosa.

I enjoyed every bit of the study of endometriosis; there were an abundance of fresh material, excellent laboratory facilities, including well-trained technicians, an artist whose illustrations speak for themselves better than any words I might employ, a cooperative and skilled microphotographer and interested associates. My chief contribution was an insatiable curiosity which, stirred by difficulties and opportunities which were constantly arising, perpetuated my interest. The term endometriosis was introduced to indicate the presence of ectopic tissue which possesses the histological structure and function of the uterine mucosa. It also includes the abnormal conditions which may result not only from the invasion of organs and other structures by this tissue, but also from its reaction to menstruation.

Endometriosis may be divided into two main groups, direct (internal) and indirect (external). In the first the ectopic mucosa, usually situated in either the uterine or tubal walls, is continuous with the mucosa lining these organs. The ectopic mucosa in the second group has the same histological structure as that in the preceding one but is not continuous with normally situated Müllerian mucosa. If the mucosa in this group is derived from the latter it must arise from the transplantation to and the growth of bits of this tissue in new situations. This phenomenon may be accompanied in various ways.

Ovarian and other forms of peritoneal endometriosis arise from the implantation of bits of Müllerian mucosa, of either uterine or tubal origin, which have been carried with menstrual blood escaping through patent tubes into the peritoneal cavity, have lodged on the surfaces of the various pelvic structures. The ectopic mucosa in these implants, regardless of their size or situation, may become additional foci for the spread of the endometriosis by direct extension and also by the implantation of bits of Müllerian tissue which escape from them during their reaction to menstruation. This

latter phenomenon is most spectacular in the ovary where ectopic endometrial cavities may attain a much larger size than elsewhere, forming the well-known endometrial cysts of that organ.”

Material escaping through patent fallopian tubes, therefore, was considered as a possible cause of both ovarian and other forms of peritoneal endometriosis. Even in the occasional presence of hydrosalpinges, or previous salpingectomy, the tubal spill is surmised to have occurred prior to the complete occlusion. Sampson strengthened this view over the years, citing from his 1927 article that “one of the outstanding features of patients with peritoneal endometriosis is that the tubes are usually patent”. Hence, Sampson only observed the phenomenon of retrograde menstruation (via the fallopian tubes) sometime around 1927 when arranging his hysterectomies to coincide with menses. Sampson describes a 3-step staging for widespread peritoneal endometriosis; firstly, spillage from the fallopian tubes and implantation on ovarian and peritoneal surfaces; secondly, penetration to underlying structures; and thirdly, nearby spread following bleeding from the endometriotic lesions during menstruation.

ENDOMETRIOSIS VS CARCINOMATOSIS

Apart from endometriosis, Sampson published a number of articles concerning pelvic cancers and their metastatic spread in the 1930's [42]. He repeatedly observed that endometriosis bore great similarities to various cancers with peritoneal metastases although he accepted that endometriosis should be classified as a benign disease. His final publication (a year prior to his

death) covered his ideas on the pathogenesis of endometriosis within scars [43]. Sampson described in exquisite detail 17 cases occurring in laparotomy scars following salpingectomy (15 cases); one following myomectomy; the other following ventrosuspension. In all the excised tissues a combination of tubal endothelium was admixed with Müllerian glands indicating endosalpingiosis as well as typical endometriosis. Sampson surmised the causation was undoubtedly direct or indirect transplantation of the tubal tissues into the wound.

MY CONCLUSIONS CONCERNING THE PATHOGENESIS OF ENDOMETRIOSIS

I have gained an understanding about endometriosis from the two main mechanisms described by Sampson (S1 and S2) – firstly the venous embolism process, and secondly the retrograde menstruation with reimplantation process. An additional (third) mechanism, also described by Sampson in many of his articles (S3) involves that of coelomic metaplasia. I would propose an extension of the classification put forward by Noselle and Donnez in 1997 [44], to enable an understanding of the pathogenetic mechanism underlying all forms of endometriosis, in common and uncommon locations (Table 1). With respect to the uncommon sites, the baffling idea that pre-menarchal girls can have established endometriosis which becomes symptomatic as they approach puberty, can also have a rational explanation. I do like that proposed by the team from Leuven & Rome, led by Brosens which describes the likely origin as that related to neonatal menses [45]. All this reduces our tendency to present endometriosis as an “enigmatic” process. It is always a condition

Table 1: Describes all sites of endometriosis, both common (4 sites) and uncommon (4 sites) along with likely pathogenic mechanism from which they are derived. S1 refers to Sampson's first described mechanism of metastatic spread via the uterine veins; S2 refers to the implantation mechanism following retrograde menstruation via the fallopian tubes; S3 refers to metaplasia of coelomic epithelium or from Müllerian rests.

Prevalence	Site	Pathogenic Derivation
Common	Peritoneal	These mostly derive from S2 (retrograde flow), with some involving S3 (coelomic metaplasia)
	Ovarian	Sampson believed implantation adenomas in the ovary derive from either tubal or uterine epithelium, S2 theory with Müllerian invaginations. Donnez favours metaplasia of coelomic epithelium, S3
	Adenomyosis	S1, endometrium into uterine veins
	Rectovaginal	S1, extension from adenomyosis
Uncommon	Premenarchal	Probably relates to neo-natal menses. Likely S1 and S2, possibly S3 mechanisms
	MRKH*	Arises in Müllerian nodule with extension by S2, possibly S1
	males	Arises in Müllerian remnant (prostatic utricle) via S3 mechanism
	Remote sites	Catamenial pneumothorax may arise from endometriosis in the pleural cavity, probably derived via an S1 mechanism. Endometriosis in scars most often derived from direct implantation S2, especially of tubal epithelium.

*Mayer Rokitansky Küster Hauser (MKHR) syndrome from partial Müllerian agenesis. Although the pelvis at laparoscopy usually appears “empty” and pristine, one can easily identify the Müllerian nodules and I am aware these can respond to estrogen stimulation with enlargement and even develop nests of endometrium within.

with clearly recognisable features albeit with a complex pathogenetic derivation involving one or more of three well defined processes. Even the “most enigmatic” relatively common condition of deep invasive endometriosis involving the rectum (DIER) is seen to have a clearly definable pathogenesis [46]. Such an understanding should improve our concepts concerning the appropriate management of endometriosis in its various locations.

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