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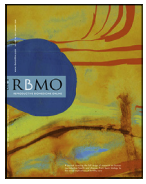

COMMENTARY

Pathogenesis of endometriosis: Look no further than John Sampson

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ABSTRACT

Rather than consider endometriosis as an enigmatic disease, reading John Sampson's two theories/mechanisms explains virtually all cases affecting the female. It is true that Sampson's most recent publication, in 1940, which talks about retrograde menstruation via the fallopian tubes, clearly fails to explain many types of endometriosis, particularly that located in extra-pelvic sites. However, his earlier publications of 1911 and 1912, on radiographic studies of hysterectomy specimens that had been injected with various gelatin/bismuth/pigment mixtures examining the unique uterine vasculature, were more important. These studies enabled him to describe 'the escape of foreign material from the uterine cavity into the uterine veins' in 1918 and subsequently to demonstrate metastatic or embolic endometriosis in the first of his two important publications in 1927. Later in that same year, in response to 'academic banter' from other historic gynaecologists, he published a second article that indicated his studies had been redirected to explore the retrograde tubal menstruation idea; this required undertaking his hysterectomies during menses. That work led to his 1940 presentation at the invitation of The American College of Obstetricians and Gynecologists to focus on the second theory/mechanism of endometriosis. This appears to have caused his more important first theory/mechanism to have been forgotten.

INTRODUCTION

Over the past year we have carefully read the 18 published works of American gynaecologist John Albertson Sampson (1873–1946) that we were able to trace, in order to better understand the vascular make-up of the human uterus and the mechanism by which intramural leiomyomata cause dysfunction. In this respect his publications of 1912, 1913 and 1918 provided unique insight into the venous drainage system, explaining how even relatively small fibroids, remote from the endometrial cavity, can cause adverse symptoms (*Sampson, 1918*; *Yovich et al., 2019*). We also discovered that Sampson's pioneering research endeavours uncovered two mechanisms that explain the pathogenesis of virtually all cases of both pelvic and non-pelvic endometriosis, but his work these days is poorly presented.

John Sampson receives a distorted appraisal because of an article he published in 1940 entitled 'The development of the implantation theory for the origin of peritoneal endometriosis' (*Sampson, 1940*). That article is often cited to indicate that Sampson's theories fail to explain endometriosis in unusual locations, such as the umbilicus and other extra-genital areas, as well as deep invasive recto-vaginal septum endometriosis, pre-menarchal and very severe adolescent endometriosis and settings such as post-hysterectomy or other absent uterus scenarios.

Consequently, there is a plethora of articles reflecting studies pursuing the idea of metaplasia involving Müllerian remnants or even various stem cells, one recent report describing a genetic/epigenetic theory (*Koninckx et al., 2019*). With due respect to the erudite authors, we would contend that such studies are not required for understanding the

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Pelvic venous network
Retrograde menstruation
Uterine venous drainage

pathogenesis of endometriosis, except perhaps for the extremely rare case of endometriosis found in men, or women who have congenital absence of the uterus. However, neither of these scenarios has been identified among our collective experience of more than 4000 cases of endometriosis managed over a 46-year experience. Apart from pelvic endometriosis, our cases include umbilical endometriosis, endometriotic nodules in abdominal scars, in the pelvis post-tubal ligation and post-hysterectomy, in round ligament remnants and even in the chest cavity in two cases suffering catamenial pneumo-thoraces. Furthermore, we have been impressed with the pristine pelvic appearance of the several cases of Müllerian agenesis we have managed over that period.

TWO DISTINCT MECHANISMS/ THEORIES

Sampson's 1940 article covers his second theory and mechanism by describing the effect of retrograde menstruation sometimes establishing endometriotic lesions on the ovaries and within the surrounding pelvic peritoneum. This probably covers the majority of cases of pelvic endometriosis. However, this was not Sampson's first theory, which was described in the first of two articles he published in 1927 entitled 'Metastatic or embolic endometriosis due to the menstrual dissemination of endometrial tissue into the venous circulation' (*Sampson, 1927a*). He had been documenting this story of menstrual and post-partum material entering the venous circulation since 1918. In fact, when he tried to force endometrial tissue out through the fallopian tubes by clamping the cervix, Sampson found it was almost impossible, endometrial tissue preferentially entering the venous circulation (*Sampson, 1918*).

SECOND MECHANISM/THEORY

In his second article published in 1927, Sampson started to plan his hysterectomies to coincide with menses and thereafter developed his implantation theory. In his own words (*Sampson, 1940*):

> 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.

Earlier, *Sampson (1927b)* had written: '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, the tubal spill is surmised to have occurred prior to the complete (tubal) occlusion.'

Sampson strengthened this view over the years, citing from his 1927 article (*Sampson, 1927b*, *1940*) that 'one of the outstanding features of patients with peritoneal endometriosis is that the tubes are usually patent'. Sampson describes a three-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 and shedding from the endometriotic lesions during menstruation. This nearby spread, in his opinion, was like a metastatic process (similar to some cancers he had managed), although we might believe another mechanism could be operating, related to the pelvic venous vasculature network (see later). What readers of the 1940 article (*Sampson, 1940*) should appreciate is noted in the concluding two lines of Sampson's summary: 'There are many other interesting unsolved problems associated with the pathogenesis and life history of endometriosis of all types. Since it is my desire to adhere strictly to the text which has been assigned me, I have not discussed any of these.' This comment relates to the fact that The American College of Obstetricians and Gynecologists had commissioned Sampson to expand on his most recent (second) theory, that concerning retrograde menstruation with peritoneal implantation. The text of that 1940 oral presentation is faithfully documented in the article of the same year.

FIRST (ORIGINAL) MECHANISM/ THEORY

The 1940 presentation was never intended to replace Sampson's original (first) theory about menstrual dissemination into the venous circulation from the uterine cavity (*Sampson, 1927a*). In Sampson's eyes, the mechanism was clearly demonstrated from his radiographic studies on hysterectomy specimens following injection of a gelatine/bismuth suspension into the endometrial cavity as well as the uterine arteries (with Venetian red) and veins (with ultramarine blue) (*Sampson, 1913*, *1918*). From pioneer studies on 150 injected uteri beginning in 1911, 15 figures were presented in the 1918 article which showed how the normal endometrium protected against venous entry during contractions, but damaged endometrium (from inflammation, curettage or uterine pathologies) enabled entry of 'foreign materials' into the uterine veins. Sampson continued his studies, publishing an extended series of 67 figures under the title of 'Metastatic or embolic endometriosis due to the menstrual dissemination of endometrial tissue into the venous circulation' (*Sampson, 1927a*). Sampson's findings explain adenomyosis as well as those unusual endometriotic deposits occurring in the umbilicus or within the recto-vaginal septum extending into the posterior fornix. In fact, Sampson had already published articles about these, including 'pelvic adenomas of the endometrial type' (*Sampson, 1921*), 'intestinal adenomas of endometrial type' (*Sampson, 1922*), 'inguinal endometriosis' (*Sampson, 1924, 1925a*) and 'heterotopic or misplaced endometrial tissue' (*Sampson, 1925b*). These reports ensued well before he started thinking about his future retrograde menstruation and peritoneal implantation theory, and which would require a change in the timing of his hysterectomies.

Sampson clearly regarded endometriosis as a metastatic process, bearing strong behavioural resemblance to ovarian carcinomatous peritoneal implants, which he also studied (*Sampson, 1924*, *1931*; also *1925b*, *1936*, *1938*). In 1927 he concluded:

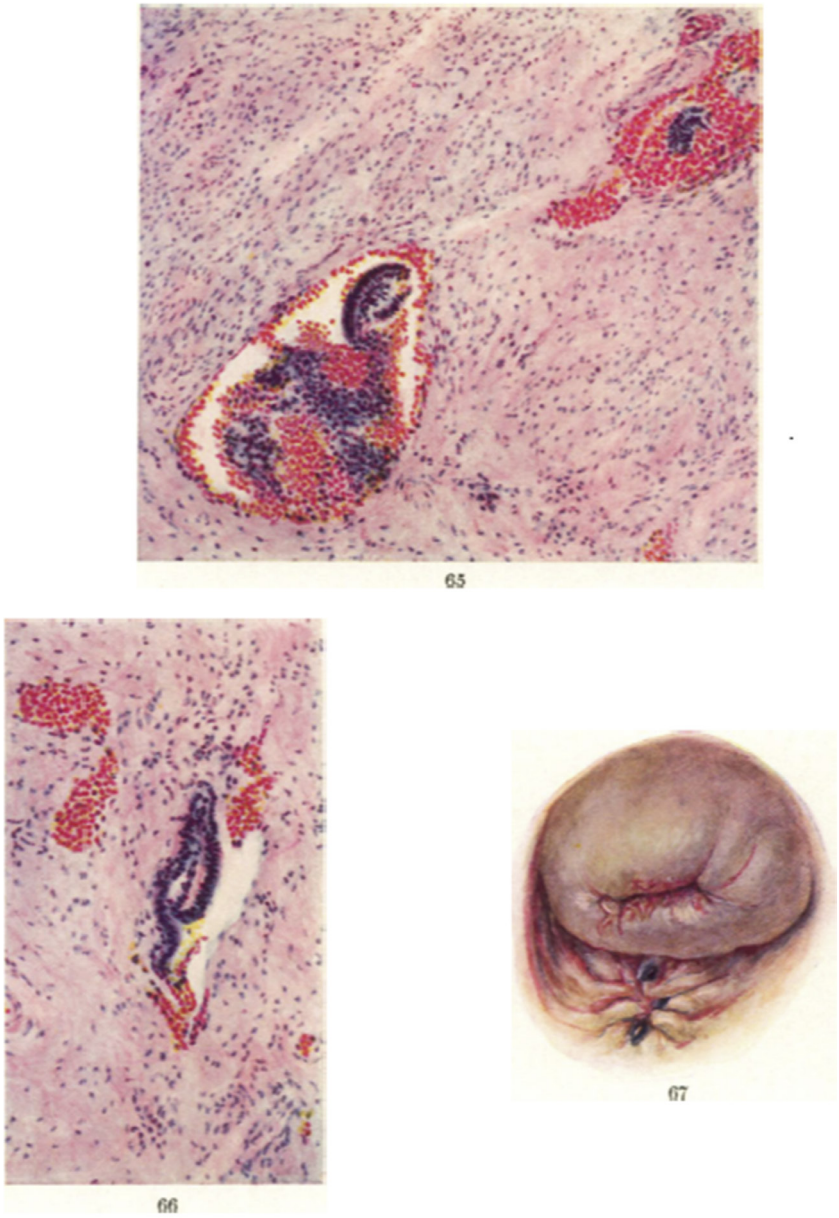

FIGURE 1 Copy of Plate 41 from *Sampson (1927)*. Figure 65 (coloured micrograph × 130) shows menstrual emboli in two veins within the myometrium, well distant from the endometrial cavity. Figure 66 (coloured micrograph × 130) shows menstrual emboli implanted in a vein from the posterior vaginal wall. Figure 67 (natural size) shows the cervix and vaginal wall with endometriotic emboli invasive in sub-epithelial areas.

- 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 (this could include metaplastic Müllerian remnants).
- 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 favourable to its existence.

In fact, the mechanism supporting the dissemination of endometrial tissue into the uterine veins required an aberration in the submucous collecting veins displaying a feature Sampson described as 'receiving sinuses' that could harbour pieces of endometrial slough, which thereafter travels to peripheral venous plexuses within the myometrium. This area could well coincide with the recently described junctional zone, which tends to be rather thick in those women who develop adenomyosis (*Van den Bosch et al., 2015*).

What remains a mystery, however, is why such venous material (FIGURE 1) does not continue to migrate peripherally and end up in the general venous drainage via the internal iliac and ovarian veins to finish in the inferior vena cava. We believe current studies should pursue the idea that there exists a general pelvic venous network that enables blood to travel to other sites, even retrograde (like a functional, if not anatomical, portal system) enabling implantation in remote sites and organs (FIGURE 1). In support of this idea we cite the work of *Bulletti et al. (1997)*, which shows that radioactive-labelled (tritiated) progesterone pessaries placed in the vagina can concentrate in the endometrium to enhance the

implantation process. The mechanism requires retrograde dispersal and appears to be more than simple diffusion, and which might relate to the concept of the uterus acting like a 'pelvic heart' forcing blood into pelvic veins during contractions but enabling some retrograde flow during uterine relaxation as there are no valves in the pelvic veins (*Sampson, 1913*).

SAMPSON'S CONSIDERATION OF THE TWO MECHANISMS

A second publication from Sampson in 1927, comprising 60 new figures and entitled 'Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity' (*Sampson, 1927b*), arose in response to objections, criticisms and academic banter from eminent gynaecologists such as Robert Meyer and Emil Novak. Sampson had shown that menstrual tissue could not be disseminated by lymphatics and that the venous system was the most likely carrier. However, he did begin to consider the theoretical idea of 'the menstrual dissemination of endometrial tissue through the tubes from the uterine cavity' (*Sampson, 1927b*). At the time this idea was not favoured by Sampson or other eminent gynaecologists such as Novak, for four reasons stated by the latter (*Novak, 1926*; *Sampson 1927b*): (i) menstrual blood rarely, if ever, escapes from the uterine cavity into the tubes; (ii) the lumen of the interstitial portion of the tube is too small for bits of endometrial tissue to pass through it; (iii) endometrial tissue, set free by menstruation, is dead or dying and therefore incapable of implantation; (iv) several days must be required for endometrial tissue to be carried from the uterine cavity through the tubes, and, therefore, there is little chance that such 'degenerative tissue' … should grow where it falls.

It was Sampson who took up the studies required to show that these four points were not indisputable and, by timing his hysterectomies with menstruation, showed that menstrual tissue could sometimes undergo retrograde flow down the fallopian tubes, particularly in the presence of uterine pathologies such as myomata. Furthermore, such menstrual endometrium could sometimes be viable and potentially implant on the peritoneum or the ovarian surface (*Sampson, 1940*).

CONCLUSION

In conclusion, we believe that Sampson's early works should be carefully read by all doctors in training so that his full descriptions can be evaluated. In particular all specialist gynaecologists and those doctors and health practitioners assisting women with the pelvic conditions of endometriosis, adenomyosis and fibroids should understand the unique features described by Sampson and which provide an essential understanding of the pathogenesis of these conditions. We gynaecologists involved with training the next generation should ensure these articles are made available, along with the interplay among contemporaneous gynaecological giants such as Robert Meyer, Emil Novak, Joseph Halban, Carl von Rokitansky, William Graves, Ernst Wertheim, Joe Meigs, William Blair-Bell and Thomas Cullen, who each offered critical 'banter' to Sampson during the evolution of his theories. Emil Novak, 2 years after Sampson's death, stated that John Sampson was, with Robert Meyer, one of the two greatest contributors to American gynaecology. Wider dissemination of Sampson's articles should avoid future specialists continuing to stumble around in the dark with incomplete evidence concerning the so-called 'enigmatic' condition of endometriosis. Furthermore, the current generation of gynaecological trainees must search more deeply for information than that afforded by the current digital libraries or by only focusing on those studies which meet modern evidence-based medicine standards. To our mind there is still much to learn from historical experts with their vast, hands-on experience.

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