Endometriosis Concepts and Theories

Mobile Summary

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The complete document with updates and references is at
https://www.danmartinmd.com/files/endotheory.pdf

"Please don't refer to endometriosis, adenomyosis, or fibroids as "benign disease" – nope, not benign, they are "common and morbid"."

Linda G Griffith, Ph.D., 2020

"Studying endometriosis is like nailing Jell-O to a tree."

Donna Vogel, MD, Ph.D., 2000

Symptoms suggesting endometriosis were reported in 1855 BC (Egyptian Papyrus). Hippocrates (400 BC) noted that "part of the vagina hardens.” Intraabdominal lesion and history compatible with endometriosis were noted in 1690 (Shroen). The histology of endometriosis and adenomyosis was described in 1860 (Rokitansky) and theory reported in 1870 (Waldeyer).The difficulty of recognition was documented in 1899 (Russell).

A theory may be useful at several levels including guiding research, acting as a framework for education, understanding possibilities in endometriosis, explaining changes that occur in endometriosis, and explaining why treatment might work. In contrast, the *Tomato Effect* discusses how

some theories have interfered with treatment. *Medical Reversal* is a parallel concern that can interfere with useful treatment.

No concept or theory is entirely adequate. I needed only Sampson's retrograde theory in 1970 (Sampson 1921 & 1927, Ridley 1961) and added Müllerian remnants in 1992 (Batt 1985, Koninckx and Martin 1992). The number I needed increased to five by 2017. Now it takes eighteen to introduce what I saw in patients or published and more to discuss what I have read.

Summary

- Endometriosis is heterogenous with more than 65 published, overlapping, visual and anatomic phenotypes and

many microscopic, biochemical, histochemical, immunological, genetic, and epigenetic phenotypes. It presents with heterogenous signs, symptoms, and behaviors and has a non-uniform response to hormonal, surgical, and anti-inflammatory therapy. The prevalence varies from 0.9%–22% overall, 2.1% to 77.1% in infertile women, and 1.4% to 50.0% in fertile women (Simpson 1980, Guo 2006). It can regress, progress, or remain stable. There is debate about diagnostic criteria. Possible components of the criteria include endometriotic (endometrial-like) glands and stroma, transition from a cell of origin to an endometriotic cell, vascularization, bleeding, fibrosis, or the presence of

CD10, IFITM1, BER-Ep4, Calretinin, CD34, antiendometrial antibodies or other characteristics.

- There are age-dependent, diagnosis, symptom, sign, and imaging differences in appearances, depth of infiltration, and volume of lesions.
- The diffuse locations of endometriosis may be explained by retrograde menstruation, peritoneal dispersion, attachment, infiltration, and growth; peritoneal or pleural metaplasia; and hematogenous or lymphatic dissemination of Müllerian or non-Müllerian stem cells.
- Nodular rectovaginal lesions of 4 cm can be asymptomatic while 0.08 mm lesions have been associated with pain.

Tenderness can be 27 mm from a visible lesion.

- Endometriosis can be hidden deep or in plain sight. Clinically unrecognized endometriosis was described as early as 1899 and nodules as large as 5 cm have been discovered beneath adhesions or scar and in ovaries, the retroperitoneum, tubes, lymphatics including nodes, open pockets, cryptic pockets, large and small bowel, appendices, epiploic fat, mesentery, and omentum. Surface endometriosis may not be visualized on the peritoneum when it is microscopic including stem cells.
- Coelomic metaplasia, immune overload, escape from immune

surveillance, immune maturation, neuroimmune maturation, inflammatory induction, and stem cells may play a role in both women and men.

- Pulmonary, pleural, and mediastinal endometriosis may be a) retrograde menstruation with dissemination through diaphragmatic fenestrations or infiltration through the diaphragm, b) hematogenous dissemination, c) diaphragmatic lymphatic dissemination, or d) coelomic metaplasia of the pleura.
- Retroperitoneal, retrocervical, and cul-de-sac endometriosis may be a) Müllerian remnants, b) pelvic

lymphatics, c) retrograde with retraction, or d) hematogenous.

- Hematogenous sites may include pulmonary, spinal, dermal, and other distal sites.
- Early endometriosis may start with normal Müllerian (endometrium or remnants) cells or non-Müllerian (peritoneal) stem cells. These undergoes reactive, biochemical, hormonal, immunologic, and genetic changes in developing later and more severe forms of endometriosis. Bone marrow stem cells may engraft previous foci of endometriosis. Peritoneal metaplasia may be recruitment into preexistent endometriosis.

- Sites of surgical transplantation include C-section scar, surgical excision scar including peritoneal excision sites, drain sites, episiotomies, and vaginal tears.
- *Inflammatory* stimuli can include estrogens, menstrual debris, surgical trauma, and infection.
- Fibrotic collagen reaction (fibrogenesis) with muscular metaplasia and starts as part of a local inflammatory reaction with prolonged exposure to activated platelets or immune cells leading to increased expression of α-smooth muscle actin as part a pathologic process that Guo (2018) characterizes as wounds

undergoing repeated tissue injury and repair (ReTIAR).

- Neuroimmunologic maturation, decreased immunologic load, control by the hypothalamic-pituitary-adrenal axis, homeostasis of the sympathetic nervous system, immunocompetence, apoptosis, autolysis, and autophagy limit infiltrative or expansive growth.
- Clonality, genomics, repeated tissue injury and repair (ReTIAR), peritoneal metaplasia as recruitment into preexistent endometriosis, engrafting of bone-marrow stem cells into endometrium or endometriosis, neuroimmunologic maturation, neuroendocrine axis interaction, and

homeostasis of the sympathetic nervous system also appear important.

Retroperitoneal, rectovaginal, and retrocervical endometriosis may be Müllerian remnants (Batt 1985, 2011a, 2013, & 2015; Redwine 1988, 2002, 2018; Koninckx 1992; Donnez 2001; and Signorile 2009, 2010 & 2012), lymphatic metastasis, the result of retrograde with retraction, or hematogenous metastasis. However, hidden, retroperitoneal endometriosis in women and any endometriosis in men are rarely reported and, until Badescu et al. (2016) found unrecognized endometriosis in 100% of 26 bowel endometriosis cases, hidden endometriosis was considered as uncommon or rare. That series was

recently updated to clarify that nonvisualized nodules as small as 2 mm can be palpated at laparotomy in 25% of bowel resections with 14% of those at or beyond the anticipated staple line (Roman 2021). A similar microscopic finding in tubes is reported by McGuinness et al. with tubal endometriosis found grossly in 12 (12%) and microscopically in 34 (35%) of 97 women.

Rei (2018) found only 17 cases in men in the world literature from 1971 to 2018. The 17 male cases and retroperitoneal cases in women are limited to the genital and lower abdomen areas and are therefore not a model for the diffuse locations of female endometriosis. Furthermore, Rei (2018) reported one

case compatible with coelomic metaplasia. Also, if organoid, a Müllerian remnant could be expected to look like an accessory and cavitated uterine mass (Acién 2012), endomyometriosis (La Greca 2021), or a uterus-like mass (Clement 2007). In contrast, the location of most female cases of endometriosis, including retroperitoneal, can also be explained with retrograde, hematogenous, lymphatic, or extensional dissemination.

Furthermore, various forms of trauma such as delivery, uterine curettage, intraabdominal surgery, retroperitoneal menstruation, intraperitoneal hemorrhage, or occult pelvic inflammatory diseases may mitigate the ongoing course and chance of recurrence. That might even

include surgical treatment of endometriosis may cause inflammation and increase implantation.

This review covers the source of the ***cell of origin***; methods of ***dissemination (metastasis)*** if not in situ: the stimulus or stimuli for the ***induction*** or activation of the transition; why, how, and when the cell of origin (early endometriosis) ***transitions*** to late endometriosis; and the mechanisms of ***inactivation and clearance***. Some theories combine some or all the components. This discussion considers those to be at least partially independent.