Endometriosis Theories and Concepts

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Endometriosis Theories and Concepts

"Studying endometriosis is like nailing Jell-O to a tree."
Donna Vogel, National Institute of Health, Endometriosis 2000

Introduction

This document focuses on theories and concepts that date back at least to 1870 (Waldeyer) following Rokitansky's 1860 histologic description of what we now call endometriosis. A theory may be useful at several levels including guiding research, acting as a framework for education, understanding possibilities in endometriosis, explaining why changes occur in endometriosis, and explaining why a treatment works. However, a theory is only a theory and does not determine if a treatment works. The success of a treatment is based on evidence, not on theory. A discussion of the *tomato effect*, or how theory can interfere with treatment, is covered in this file.

No theory is completely adequate. It generally takes eight theories and concepts to introduce what I have seen and many more to discuss what I have read and published. Since theories change, this file will be periodically updated and posted at the addresses above.

The seven, non-exclusive theories and concepts needed to discuss what I have seen are:

- Retrograde menstruation with peritoneal dispersion, attachment, infiltration, and growth
- Hematogenous dissemination rather than retrograde, with dissemination through diaphragmatic foramen, for pulmonary endometriosis
- Differentiation of precursor (stem) cells into endometriotic cells with subsequent replacement of endometrial cells by endometriotic cells
- Fibrotic collagen reaction with muscular metaplasia as part of metaplasia or local reaction
- Age dependent changes in appearances and depth of infiltration
- Immunologic maturation and competence
- Surgical scar or traumatic vaginal tear implantation
- Inflammatory induction might include menstrual debris, trauma, or infection

I understand that some physicians would criticize me for not including Müllerian theory (location present at birth) as a primary consideration. Please note that my list covers cases that I saw in my practice. I never saw a male case and Rei (2018) found only 17 cases in men in the world literature from 1971 to 2018. Also, male cases are limited to the genital and lower abdomen areas and not the diffuse areas seen in women. Thus, male cases are in the normal Müllerian area or compatible with local invasion or local lymphatic or hematogenous metastasis. In addition, I never saw a case of an accessory and cavitated uterine masses (ACUM, Acién 2012). ACUM is an organoid Müllerian anomaly that is an example of how a Müllerian remnant can look. On the other hand, female cases can be more easily explained with retrograde, hematogenous, or lymphatic spread accompanied by immune system maturation than a theory that can require that the entire body be of Müllerian origin.

The "Theories and Concepts" section is needed to introduce what I have read and published. "Theories and Concepts" covers the source of the '**cell of origin,'** methods of '**dissemination (metastasis),**' and why, how, and when the original cell '**transitions'** to endometriosis. Of these concepts, the '**transition'** appears to hold the most promise for future research and therapy. Note: Previous version included 'dissemination and metastasis' as part of the 'cell of origin.'

- The **Cell of Origin**
  - Endometrium - Degree of Differentiation
    - Whole Tissue Endometrial Fragments
    - Precursors in normal whole tissue endometrial fragments
    - Precursors in traumatized endometrium
    - Mesenchymal Cells
    - Stromal Stem Cells
    - Epithelial Stem Cells
  - Embryonic Müllerian Remnants
    - Organized Fragments
    - Stem Cells
    - Müllerian Remnants (any congenital)
    - Müllerianosis (organoid)
    - Mülleriosis (non-organoid and projected to include transition)
  - Metaplastic Theories
    - Peritoneal / Coelomic / Mesenchymal Stem Cells
    - Bone Marrow Stem Cells
    - Endometrial Stem Cells
- **Dissemination (Metastasis)** theories and concepts
    - Retrograde Menstruation
    - Hematogenous Dissemination
    - Lymphatic Dissemination
    - Traumatic / Surgical Dissemination
    - Embryonic Dissemination
      - Primary Müllerian area is in the normal location, not disseminated.
      - Secondary Müllerian System is dissemination.
        - Pelvic peritoneal area
        - Other body areas

- **Transition** from endometrium to endometriosis

  The transition appears to hold the most potential for future research and therapeutic options. Transition involves the cellular, histological, biochemical, immunological and other changes that distinguish endometriosis from endometrium. Those changes involve the local environment, inflammation, epigenetic changes, genetic changes progenitor cell differentiation, biochemical changes immunologic changes, apoptosis, autophagy, reactive oxygen species, fibrosis, muscular metaplasia, macrophage migration inhibitor factor, clonality, microRNA, signaling, nerve activation, cancer-associated driver mutations, fibroblast to myofibroblast transdifferentiation, neurogenesis, angiogenesis, genetic dysregulation and more that are covered in this document

The articles listed in this review are only a small part of what is published. A PubMed search at https://www.ncbi.nlm.nih.gov/pubmed/?term=endometriosis on 10/17/18 listed 25,716 articles that include many parts of the endometriosis story. That is an increase of 243 article since 8/14/18 (3.8 articles daily). The concerns include theories, results of treatment, biochemical testing, immunologic testing, inflammatory reaction, spontaneous resolution of endometriosis, stages, phenotypes, aromatase production, hormonal levels, embryology, neonatal development, genetics, epigenetics, organoid development, stromal type endometriosis, endometriosis in men, bone marrow stem cells in endometriosis, differentiated stem cells, primordial germ cells, programmed death (apoptosis) and transitions into mesenchymal cells.

Theories and Concepts

This list is a 'watch this space' work in progress. I am currently investigating 2 more articles from the 19th century and several from the 20th and 21st centuries.

1. Waldeyer 1870 – Metaplasia from the germinal epithelium of an ovary. If Waldeyer considered the germinal epithelium as a precursor to ovarian serosa, this might be the first recognition of a progenitor. The germinal epithelium of an ovary had also been considered as the precursor to eggs. See Iwanoff 1898 for coelomic metaplasia and Lauchlan 1972 for metaplasia from secondary Müllerian system.
2. Cullen 1896, Russell 1899, Batt 2007, Acién 2012, Batt 2013, Laganà 2017 – Müllerianosis (Mülleriosis) as a remnant or fragment of Müllerian tissue in or near the normal area of embryologic Müllerian development. See Nerune 2016 & Rei 2018 persistent Müllerian duct in men.
3. Iwanoff 1898, Meyer 1903, Sampson 1921, Suginami 1991, Matsuura 1999 – Coelomic metaplasia of ovarian serosa may be the same concept as Waldeyer's metaplasia from the germinal epithelium.
4. Cullen 1914 – Endometriosis has fibrous and muscular components like adenomyoma.
5. Hueter, 1918, Meyer, 1919 – Inflammatory metaplasia
6. Sampson 1921 – Peritoneal implantation from internally menstruating ovaries
7. Meyer 1923, Gruenwald 1942 – Coelomic metaplasia from the peritoneum
8. Halban 1925, Jerman 2015 – Lymphatic spread (metastasis) of the endometrium
9. Halban 1925 – Hematogenous vascular spread (metastasis) of the endometrium

10. Sampson 1927, Nap 2004, Nap 2012 – Updated retrograde menstruation theory includes:
    - Cell of Origin - Endometrial fragments or cells
    - Dissemination - Retrograde menstruation of tissue fragments or cells
    - Peritoneal dispersion
    - Attachment
    - Inflammation
    - Infiltration
    - Growth
        - Fibrosis
        - Entrapment
        - Muscular metaplasia

    Revisions of dispersion (retrograde menstruation, lymphatic, hematogenous, traumatic, surgical), congenital (Müllerianosis (organoid), Mülleriosis (non-organoid), secondary Müllerian system) and metaplasia theories have been expanded to include the role of stem cells, replacement of endometrial cells by endometriotic cells, differentiation of stem cells into endometriotic cells, and other concerns reviewed in the references that follow.
11. Novak 1931 – Metaplasia due to hormonal stimulation
12. Geist 1941 (reviewed in Brosens 2011) – Geist advocated the use of androgens in gynecological disorders. Brosens (2011) is a free download at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135985/
13. Karnaky 1948, Karnaky 1969 – Karnaky proposed the use of a synthetic estrogen, diethylstilbestrol (DES), to produce amenorrhea and suppress endometriosis.
14. Clark 1948 –16-year-old with endometriosis in left horn of bicornuate uterus.
15. Fallon 1950 – Endometriosis can be colorless and amenorrheic.
16. Meigs 1953 – Meigs recommended early and frequent childbearing as prophylaxis.
17. Levander 1955, Merrill 1966, Lauchlan 1972 – Induction of endometriosis due to activation of mesenchymal cell metaplasia by degenerating endometrium that arrives in the pelvis.
18. Nora 1956, Steck 1965, Kaunotz 1979 – Direct implantation in surgical scars, amniocentesis needle tract or traumatic vaginal tears.
19. Fallas 1956 – Cervical and upper vaginal agenesis associated with retrograde menstruation and severe endometriosis.
20. Kistner 1958 – Kistner proposed a state of "pseudopregnancy" to reproduce the improvement noted in endometriosis during and after pregnancy. He postulated that decidualization that results in necrosis and elimination of superficial endometriotic implants.
21. Freidman 1959 – Müllerian epithelium noted in exophytic bladder in male. This AFIP slide was reported in Oliker 1971.
22. Kantor 1963 – Endometriosis due to retrograde menstruation may be a different disease than endometriosis due to embryonal rests. Two phenotypic disease theory.
23. Merrill 1966 – Merrill factor is a metaplasia-inducing substance such as estrogen and a factor liberated from degenerating endometrium. (quoted in Suginami 1991)
24. Melicow 1967 – First report of prostatic endometrial cancer in male.
25. Karnaky 1969, Jansen 1869 – Diagnosed endometriosis in the absence of hemosiderin

26. Karnaky 1969, Redwine 1987, Davis 1988, Koninckx 1991 – Based on age distributions, there is a 4 to 20-year progression from an initial water blister lesion (clear papule) to red to hemorrhage to scar to scar with blue dome cysts (black only appearance) to deep infiltrating endometriosis.
27. Karnaky 1969 – Endometrium and endometriosis respond differently to antiestrogen therapy. He further notes that the differences in humans were not seen in monkeys and questions if monkey research might be on normal transplanted endometrium and not endometriosis. He felt this supported the theory of coelomic metaplasia.
28. Oliker 1971 – This is the first report of endometriosis in a 46 XY male. See Friedman 1959 for Müllerian epithelium, Melicow 1967 for prostatic endometrial cancer, and Nerune 2016 for male pseudohermaphroditism. Seventeen reports of endometriosis or endometrial cancer were summarized in Rei 2018. Most were older and on estrogen therapy.
29. Lauchlan 1972 – Differentiation of tissue in a secondary Müllerian system may be responsible for endometriosis outside the normal Müllerian developmental area. He felt that pelvic endometriosis was most compatible with retrograde while distal, non-abdominal sites might be hematogenous dissemination or metaplasia. He also noted that endometriosis is histologically different than endometrium with a mixture of cell types. See Cullen 1914 for fibrous and muscular components. *(Author's Note: Many peritoneal endometriotic lesions are outside the normal Müllerian area including ileum, appendix, cecum, lateral gutters, and diaphragm. Those and extra-peritoneal distal sites could require classifying the entire body as Müllerian.)*
30. Schifrin 1973 – Early report of endometriosis in 15 teenagers. Also see Clark 1948.
31. Kistner 1975 – Surgery improves pregnancy rates.
32. Mettler 1979 – Reported on ovarian cyst resection but concluded that more than "*coagulation of endometriotic foci cannot be performed via the laparoscope*."
33. Goldstein 1980 – Endometriosis in adolescents as young as 10.5 years old with petechial lesions. Karnaky 1969 discussed young girls. Also see Schifrin 1973
34. Goldstein 1980, Redwine 1988a – A "close-up" or "near-contact" view is better for recognizing subtle appearances of endometriosis. Redwine's (1988a) "near-contact" is more descriptive of the technique.
35. Simpson 1980 – Genetic predisposition is generally seen as an observation, not a theory.
36. Semm 1980 – Laparoscopic partial excision needs to precede coagulation with large nodules.
37. Dmowski 1981 – Dmowski proposed that the immune system was involved in the development of endometriosis
38. Halme 1983 – Halme noted an increased activation of pelvic macrophages in infertile women with mild endometriosis
39. Martin 1983, 1985, 1986, 1987, 1988, 1989 – The CO2 laser can be used laparoscopically for excision of deep endometriosis.
40. Halme 1984, Halme 1988 – Halme noted that retrograde menstruation was very common. Therefore, there were other factors that influenced endometriosis.
41. Semm 1984 (German), Semm 1987 (English) – "*The surgical excision of endometriosis implants is still considered the optimal treatment of pelvic endometriosis."*

42. Malinak 1984 – Recurrence rates are likely higher than published due to asymptomatic recurrence.
43. Vernon 1986 – There are differences in prostaglandin production in the four (4) surface phenotypes examined. "*Petechial implants may be more pathologically influential than older implants*." "*A patient who presents with severe, progressive dysmenorrhea but is shown at laparoscopy to have minimal disease may have exaggerated pain symptoms as a result of the presence of the more biochemically active, petechial implants, whereas a patient with extensive disease may have minimal pain symptoms due to the presence of primarily inactive, powder-burn implants.*" See Davis 1993
44. Redwine 1987, Martin 1989, Albee 2008 – Any abnormality of the pelvic peritoneum, no matter how small, how subtle, or what color, may be endometriosis.
45. Halme 1988, Hill 1992, Northick 2016 – Lack of immunologic competence results in an inadequate response of the peritoneal defense system to the normal retrograde flow that is present in most women. The inadequate response results in evasion of apoptosis of endometrial cells, and endometriosis continues to live.
46. Redwine 1988b – Providers should consider theory "in order to select treatment." See Goodwin (1984) on the Tomato Effect for the opposite view.
47. Batt 1989 – Medial ureteral position due to an attenuated uterosacral ligament or as the medial border of a large fossa associated with endometriosis is congenital.
48. Martin 1989 – 13 of the 20 laparoscopic surface appearances of endometriosis were phenotypic. In 2018, we do not know if only some or all these have similar or contrasting characteristics. Vernon (1986) used four other descriptive superficial phenotypes.
49. Martin 1989, Davis 1993 – The type of procedure should consider the depth of infiltration. The definition of deep decreased from 5 mm in 1989 to less than 3 mm in 1993. Clinically, this definition was not overly useful as it could only be determined if the lesions were excised and processed for specific depth measurements. The concept then changed over several years to peritoneal and infiltrating lesions. Infiltration and pain were generally associated with fibrosis and depth. (Ripps 1991, Ripps 1992, Khare 1996, Vigano 2017, and Liu 2017). Furthermore, even superficial appearance could be associated with infiltration to 4 mm. (Koninckx 1991)
50. Cornillie 1990 – In-phase cyclic changes are different in deep (≥5 mm), intermediate (2 to 4 mm), and superficial (<1 mm) endometriosis
51. Cornillie 1991 – The presence of endometrial protein PP14 positivity varies in deep (≥5 mm), intermediate (2 to 4 mm), and superficial (≤1 mm) endometriosis.
52. Koninckx 1991, Gordts 2017 – Deep endometriosis is endometriotic disease. Superficial endometriosis is either stopped by the immune system or converted into endometriotic disease.
53. Portz 1991, Vitale 2018 – Reactive oxygen species (ROS) or free radicals may increase growth and adhesion of endometrial cells in the peritoneal cavity, promoting endometriosis and infertility
54. Ripps 1991 – Pain and tenderness are associated with fibrosis (scarring) of implants.
55. Suginami 1991 – Suginami concluded that the multiple sites or endometriosis were most compatible with coelomic metaplasia.

56. Ripps 1992 – Pain and tenderness are related to the depth and volume of implants.
57. Koninckx 1992 – Deep endometriosis has 3 phenotypes: superficial (<3 cm), intermediate3 to 5 cm) and deep (0.5 cm or deeper)
58. Rier 1993 – Environmental toxins such as dioxin may increase the risk of endometriosis by modulating the immune response of altering tissue-specific responses to hormones.
59. Hoshiai 1993 – Serial laparoscopies confirm that some get better, some worse and some get better then worse. Dee Evers 1994 and "Pimple Model."
60. Haney 1993 – Endometriosis is associated with a localized sterile inflammatory process, growth factors, cytokines, and activated macrophages in the peritoneal fluid.
61. Davis 1993, Vercellini 1991 – Adolescents with functional pain, cyclic pain, abdominal pain, nausea, constipation, and diarrhea during menses have the largest proportion of red lesions. See Vernon 1986.
62. Adamyan1993 Batt 2014 – All rectovaginal endometriosis is retrocervical. Some retrocervical endometriosis is not rectovaginal.
63. Adamson 1994 – Surgery or no treatment is better than medical therapy for fertility.
64. Evers 1994, Koninckx 1994, Harrison 2000, Nap 2004 – Endometriosis in its superficial form is generally transient, self-limiting, and cause little or no long-term damage. This has been called the "Pimple Theory." Almost everyone has pimples, most are mild and resolve spontaneously, some get worse. some come and go (Hoshiai 1993, unpublished observation in Rhesus monkeys at Harlow Primate Center 1992 - see Rier 1993), they are inflammatory, they can get better on medication (estrogenic BCPs, Accutane, antibiotics), they can cause scarring, and some are treated with surgery (dermabrasion).
65. Wild 1994, Nisolle 2000, Witz 2002 – Endometrial stromal cells and epithelial cells can attach to the peritoneum within one hour and the mesothelium can be replaced by 24 hours. These observations were in research animals. Research as this level in humans will likely continue be unethical without a major paradigm shift in technology.
66. Sutton 1994 – Pain relief at three months is not significantly different between patient who had endometriosis removed and those who had a diagnostic laparoscopy only. At six months the placebo response had resolved and pain recurred in the diagnostic only group.
67. Perper 1995 – Menstrual cramps (dysmenorrhea) are related to the number of implants.
68. Fernandez 1995 – Bone marrow-derived cells are found in endometriosis.
69. Khare 1996 – Differences in collagen types suggest that ovarian endometriosis may be metastatic while pelvic wall-infiltrating endometriosis is metaplastic.
70. ASRM 1997 – Eight laparoscopic phenotypes
71. Nisolle 1997 – Peritoneal, ovarian, and rectovaginal nodules are three different entities
72. Gaetje 1997 – Invasion based on E-cad- epithelial cells
73. Leyendecker 1998 – Intrauterine tissue injury and repair at the endometrial-muscularis interface (TIAR) due to intrauterine trauma.
74. Starzinski-Powitz 2001, 2003 – Differentiation of stem cells into endometriotic cells
75. Redwine 2002 – 38 differences between endometriosis and eutopic endometrium in humans
76. Gazvani 2002 – The peritoneal environment can influence the development of endometriosis.

77. Kats 2002 – Macrophage migration inhibitory factor is higher in early (subtle red) than in late (blue, black, or white) lesion appearances.
78. Bulun 2004, Nothnick 2016 – Inflammatory reaction exponentially increases local aromatase activity. Nothnick is a free download at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4760268/
79. Petta 2005 – Levonorgestrel-releasing intrauterine system is useful for treatment of pain
80. Chan 2004 – Endometriosis is clonal
81. Marsh & Laufer 2005 and Cabana et al. 2010 – Inflammation may be a precursor, facilitator or early presentation.
82. Klemmt 2006, Akoum 2006, Klemmt 2007, Grümmer 2012, Klemmt 2018 – Changes in the eutopic (within the uterus in the normal location) endometrium can be associated with changes in ectopic endometrium (endometriosis). Klemmt (2018) is a free download at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5925869/
83. Batt 2007 – Choristoma is a neoplastic Müllerian tissue in non-Müllerian areas
84. Batt 2011 – Dr. Batt's book "*A History of Endometriosis*" presents the great leap forward that occurred from 1860 to 1946 from statistical grouping of signs and symptoms through treating symptoms to treating diseases. The pathophysiology of endometriosis was initially defined in an era when surgery was the only treatment. https://www.springer.com/us/book/9780857295842
85. Ohlsson Teague 2009 – MicroRNA-regulated pathways associated with endometriosis
86. Adamson 2010 – Fertility rates after endometriosis surgery are based 50% of the surgical findings and 50% on history. The Endometriosis Fertility Index is the only validated tool to determine fertility after surgery. https://www.fertstert.org/article/S0015-0282(09)03714-5/fulltext
87. Surrey 2010 – Add back therapy adds to patient acceptance & safety of GnRH therapy
88. Acién 2012 – Accessory and cavitated uterine masses (ACUM) are non-inflammatory, organoid examples of how Müllerian remnants can appear.
89. Redwine 2012, Nezhat 2012 – Clinical descriptions suggesting the presence of endometriosis were first written almost 4000 years ago in the Egyptian Kahun Papyrus
90. Batt 2013, Laganà 2017 – Müllerianosis as an organoid remnant of Müllerian tissue in the normal area of embryologic Müllerian development. Organoid remnants are not what is more commonly called endometriosis.
91. Batt 2013 – Hamartoma is a neoplastic Müllerian growth in the normal Müllerian area.
92. Brosens 2013 – Endometriosis is a progressive disease
93. Raposo 2013 – Extracellular vesicles involved in intercellular communication (signaling)
94. Becker 2014 – Six surgical phenotypes: clear, red, white, blue/black, brown, and vascular. Becker is a free download at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4230690/
95. Batt 2015 – Ron Batt's 2015 presentation on the four forms of Müllerianosis – embryonic endometriosis, adenomyosis, endosalpingiosis, and endocervicosis is at: https://player.vimeo.com/video/125963026
96. Kobayashi 2014 – Infectious precursors or infectious induction of endometriosis.
97. Gargett et al. 2014, Brosens 2015 – Perinatal retrograde dissemination is like Sampson but suggests an earlier occurrence shortly after birth.
98. Forte 2014 – Chromosomal anomalies and instability can alter gene expression

99. Khan 2014 – Three patterns of occult microscopic endometriosis (OME) based on patterns of Ber-EP4 (epithelial cell marker), CD10 (stromal cell marker), Calretinin (mesothelial cell marker), estrogen/progesterone receptors (ER/PR) and Ki-67 (cell proliferation marker).
100. Guo 2015 – Repeated tissue injury and repair (ReTIAR) due to cyclic bleeding in endometriosis.
101. Laux-Biehlmann 2015 – Pain due to activation of peripheral nerve endings in response to retrograde and extra-uterine menstruation
102. Koninckx 2016 – There are four phenotypic types of endometriosis: subtle, typical, cystic ovarian, and deep.
103. Nerune 2016 – Persistent Müllerian Duct Syndrome (PMDS), a rare form of internal male pseudohermaphroditism in men. This includes references from 2009. Also see Melicow 1967 and Oliker 1971 for 46 XY males,
104. Laganà 2017 – "Unus pro omnibus, omnes pro uno" is a combination of many concepts into a process that begins during embryogenesis. Components include Hox (homeobox) genes, Wnt (wingless) genes, Müllerian derivatives and remnants, genital ridge leakage during organogenesis, human embryonic stem cells (hEmSC), endometrial stem progenitor cells (hESP), stem/progenitor cells residing in adult uterus, mesenchymal stem cells from bone marrow, and embryonic ectopic implantation.
105. Gordts 2017 – Whether the original cell comes from the endometrium, endometrial pale cells, other stem cells, bone marrow cells, embryonic cells, neonatal cells, adult cells or another source of endometrial or potentially endometrial cells is not important as the genetic and epigenetic changes that are associated with the specific phenotypes of endometriosis.
106. Liu 2017 – Epithelial-mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, smooth muscle metaplasia, fibrosis, vascularity, hormonal receptors, and proteins involved in epigenetic modifications. Differences may result from the different lesional microenvironments.
107. Makiyan 2017 – Congenital primordial germ cells remnants can be the source.
108. Anglesio 2017 – Cancer-associated driver mutations can be present in deep infiltrating endometriosis.
109. Vigano 2018 – Fibrotic condition with endometrial stroma and epithelium.
110. Klemmt 2018 – Other stem cell concerns include lack of apoptosis, evasion of immunosurveillance, angiogenesis, neurogenesis, exosomes, plasticity, stem cell signaling, aberrantly activated signaling pathways, stem cell migration, immunogenicity, peritoneal cavity homeostasis, dysregulation of Wnt and Hox genes, phenotype and microRNA analysis. Free download at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5925869/
111. Brosens 2018 – Progression requires active neo-angiogenesis.
112. Panir 2018 – Non-coding RNA is associated with endometriosis.
113. Foster 2018, Luo 2018, Matsuzaki 2018 – Endometrial implant survival, growth, evasion from apoptosis, and immune dysregulation are estrogen-dependent processes. Either autophagy or apoptosis can be a cause of cell death.
114. Matsuzaki 2018 – Using autophagy inhibition may decrease the chance of recurrence.
115. Baranov 2018 – A genetic program governs the origin of stem cells, transition into mesenchymal stem cells, invasion of the peritoneum and progression to endometriotic

lesions. Baranov discusses the possibility that the stem cells could be disseminated during organogenesis or from the endometrium during retrograde menstruation.

116. Rei 2018 – Male endometriosis is rare. Rei found only 17 cases in men in the world literature from 1971 to 2018. Rei discusses Müllerian embryonal rests, induction, immune dysfunction, and coelomic metaplasia theories. Free download at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5833878/
117. Zhang 2018 – Metastasis-associated gene 1 (MTA1) may serve as a prognosis marker. The conclusion that a prognosis marker may be more important than a diagnostic marker was discussed at the 2017 World Congress of Endometriosis in Vancouver.

Müllerian Remnant, Dispersion & Unus Pro Omnibus, Omnes Pro Uno

Congenital (Müllerianosis (organoid), Mülleriosis (non-organoid), & secondary Müllerian system), dispersion (retrograde reflux, lymphatic dissemination, & hematogenous dissemination), and progenitor cell theories are all incomplete. Müllerian theory can explain origin in Müllerian areas, as occurs in men, and accessory and accessory and cavitated uterine masses (ACUM) (Acién 2012) but not the general distribution in women. And, Müllerian theory does not explain why a congenital remnant would cause an inflammatory reaction. In contrast, ACUM are non-inflammatory, organoid examples of how Müllerian remnants can appear. Also, Ron Batt considers Müllerian abnormalities to have eight forms. Four of those are congenital, and four are acquired. (Batt 2013) His presentation on this at the Endometriosis Foundation of America is at https://player.vimeo.com/video/125963026

Theories of the 19th & early 20th centuries did not investigate the intricate interactions that control or fail to control persistence, infiltration, and growth, in addition to the histologic, biochemical, and immunologic differences between endometrial and endometriotic lesions. Antonio Laganà's "Unus pro omnibus, omnes pro uno" (Med Hypotheses, 2017, 103:10-20) is a combination of many of those concepts into a process that begins during embryogenesis. Components include Hox (homeobox) genes, Wnt (wingless) genes, Müllerian derivatives and remnants, genital ridge leakage during organogenesis, human embryonic stem cells (hEmSC), endometrial stem progenitor cells (hESP), stem/progenitor cells residing in adult uterus, mesenchymal stem cells from bone marrow, and embryonic ectopic implantation.

Klemmt (2017) reviewed the molecular and cellular pathogenesis of endometriosis. A free, download is at:
https://www.researchgate.net/publication/316840373_Molecular_and_Cellular_Pathogenesis_of_Endometriosis

Subtle Inflammatory Lesions (Subtle Peritonitis)

An additional concern is raised by inflammatory lesions suggestive of endometriosis in adolescents and children. (Marsh and Laufer 2005, Cabana et al. 2010) Stroma can be difficult to recognize in inflammation and the conclusions that these are endometriosis is possible (Clement 2007).

Marsh and Laufer (2005) and Cabana et al. (2010) did not exclude infection as the source of the inflammation. If these are infectious, then antibiotics can treat active infection and potentially decrease long-term morbidity.

But, if these are sterile inflammatory lesions or if bacteria are present but part of a healthy microbiome, then antibiotics may interfere with a healthy microbiome (Power 2017).

Cabana MD, Foster-Barber AE, Hong T, Martin DC, Shenkin B. Teen troubled by a trembling leg. Contemporary Pediatrics. 27(6):22-27, 201

Canis et al. (J Gynecol Obstet Hum Reprod. 2017, 46(3):219-227) considered "occult pelvic inflammatory disease" as a potential initiating event for endometriosis."

Cicinelli et al. (Fertil Steril 2017, 108:289-292) concluded that chronic endometritis might represent a facilitating factor in the development of endometriosis.

Clement PB. The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. Adv Anat Pathol. 2007 14(4):241-60

Gazvani et al. (J Endometriosis Pelvic Pain Disorders, 2013, 5:2-9) suggested that C. albicans may contribute to the pathogenesis of endometriosis by modulating cytokine production.

Khan et al. (J Endometriosis Pelvic Pain Disorders 2016, 8:2-7) found higher intrauterine microbial colonization with endometriosis.

Kobayashi et al. (Mol Med Rep, 2014, 9, 9-15. DOI:10.3892/mmr.2013.1755) concluded that infection and sterile inflammation are involved in endometriosis development.

Marsh EE, Laufer MR. Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly. Fertil Steril 83 (3):758-760, 2005

Power ML, Quaglieri C, Schulkin J. Reproductive Microbiomes: A New Thread in the Microbial Network. Reprod Sci. 2017 Nov;24(11):1482-1492. doi:10.1177/1933719117698577.

The Tomato Effect (Theory-Based Medicine)

The tomato effect in medicine occurs when an effective treatment for a certain disease is ignored or rejected because it does not make sense in the light of accepted theories of disease mechanisms and treatment of these diseases. The tomato effect can interfere with the acceptance of useful remedies. According to Goodwin & Goodwin (1984), the only three issues that matter in picking a therapy are:

- Does it help?
- How toxic is it?
- How much does it cost?

Goodwin & Goodwin's three issues can be updated to risks, benefits, costs, acceptability, availability, insurance coverage and other associated concerns of using a therapy.

Discussions of theory are not discussions about the effectiveness of treatment. The results of surgical or medical therapy stand on their therapeutic outcomes, not on an opinion or a theory.

Since early endometriosis can be transient or stable in some, if not most cases, observation or symptomatic care, such as hormonal suppression can be reasonable. Superficial endometriosis can respond to observation (Evers 1994, Koninckx 1994, Harrison 2000), medication or coagulation. Deep endometriosis will more likely require excision (Martin 1989). Excision was successful in my practice, just as it was for Dr. David Redwine. His reoperation rate of 55%, with only 19% having histologic endometriosis, was like mine in the 1980s. (Redwine 1991)

In the later years of my practice, although the persistent pain rate after surgery remained relatively constant, I stopped doing as many repeat laparoscopies. Sutton (1994) noted that three to six months of pain relief after surgery is non-specific and can be a placebo response. Performing a repeat laparoscopy for pain that occurred in the first six months after excision was

not commonly useful. I focused more on their questions and concerns, helping them with expectations, considering hormonal suppression, encouraging physical therapy, considering stress therapy, deciding about judicious use of narcotics, and more.

Evidence-Based Medicine

Evidence-based medicine, like theory, is dependent on the knowledge available at the time it is applied. When knowledge changes, the approach to a disease and its treatment can also change. "Medical reversal" is a term used to describe the phenomenon when the long-established medical practice changes due to new, emerging evidence. Vinay Prasad's *Ending Medical Reversal: Improving Outcomes, Saving Lives* (2015) discusses the problems that can occur with those changes. Although evidence-based medicine is more grounded than theory-based medicine, both are subject to change over time. Both are subject to the seven stages of a medical reversal: 1) promising report, 2) adoption by providers, 3) patients and payors accept the innovation, 4) insubstantial studies that superficially support the innovation, 5) randomized controlled trials, 6) denial if the trials do not support earlier observations and finally 7) acceptance.

These problems can be compounded by delay. Balas (2000) studied the components of delay such as the time needed to do the research, have the research accepted for publication, and have the change accepted by the general medical community. He calculated that it takes an average of 17 years for research evidence to reach clinical practice.

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