Endometriosis Concepts and Theories

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"Studying endometriosis is like nailing Jell-O to a tree."
Donna Vogel, MD, PhD, NIH Endometriosis 2000

Introduction

This document focuses on symptoms since 1855 BC (Egyptian Papyrus), histology of deep infiltration since 1860 (Rokitansky), theory since 1870 (Waldeyer), difficulty in recognition since 1899 (Russell), and other concerns and theories. 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 treatment might work. However, the

success of a treatment is based on evidence, not on theory. The *tomato effect* discusses how theory can interfere with treatment.

No concept or theory is entirely adequate. It takes fifteen to introduce what I have seen or published and many more to discuss what I have read. This is a work in progress and will be periodically updated and posted at the addresses above.

- Endometriosis is not homogenous with more than 40 published, overlapping, visual and anatomic phenotypes and an uncounted number of biochemical, histochemical, and immunological phenotypes. It presents with heterogenous signs and symptoms and has non-uniform responses to

hormonal, surgical, and anti-inflammatory therapy.

- Retrograde menstruation, peritoneal dispersion, attachment, infiltration, and growth can explain intraperitoneal and infiltrating endometriosis.
- Pulmonary, pleural and mediastinal endometriosis may be a) retrograde menstruation with dissemination through diaphragmatic foramen, b) hematogenous dissemination, or c) diaphragmatic lymphatic dissemination.
- Retroperitoneal, retrocervical, and cul-de-sac endometriosis may be a) Müllerian remnants, b) pelvic lymphatics, c) retrograde with retraction, or d) hematogenous.

- Distal (e.g. spinal) endometriosis may be hematogenous or lymphatic.
- Differentiation of original endometrial cells or precursors into endometriotic cells with subsequent replacement of endometrial cell populations by endometriotic cells is complex involving biochemical, immunologic, epigenetic, genetic, etc. changes.
- Sites of reimplantation are surgical scar, vaginal tears and possibly peritoneal incisions.
- Inflammatory stimuli may include menstrual debris, surgical trauma, and infection.
- Fibrotic collagen reaction with muscular metaplasia starts as part of a local reaction.

- Immunologic maturation and development of immunocompetence limit growth.
- There are age-dependent changes in appearances and depth of infiltration

Retroperitoneal, rectovaginal, and retrocervical endometriosis may be Müllerian remnants (Koninckx 1992, Donnez 2001, 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 rare. 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. Also, if organoid, a Müllerian remnant could be expected to look like an accessory and cavitated uterine mass (Acién 2012). In contrast, the location of female cases can be explained with retrograde, hematogenous, or lymphatic 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 intraabdominal surgery as an inflammatory or fertile site for peritoneal implantation.

Concepts and Theories covers the source of the *cell of origin*, methods of *dissemination (metastasis)*, and why, how, and when the original cell *transitions* to endometriosis. Some unified theories include *cell of origin, dissemination and metastasis* as one concept. This discussion separates considers those to be as least partially independent.

- **Cell of Origin**
  - Endometrium as Müllerian Tissue - 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 (non-Müllerian)
  - Peritoneal / Coelomic / Mesenchymal Stem Cells
  - Bone Marrow Stem Cells
  - Endometrial Stem Cells

- **Dissemination (Metastasis)**
  - Retrograde Menstruation
  - Hematogenous Dissemination
  - Lymphatic Dissemination
  - Traumatic / Surgical Dissemination
  - Embryonic Dissemination
    - The primary Müllerian area is in the usual location, not disseminated.
    - A theoretical secondary Müllerian System is used to explain dissemination.
      - Pelvic peritoneal area
      - Other body areas

- **Transition**

  The transition from endometrium to endometriosis appears to hold the most potential for future research and

therapeutic options. Transition involves the cellular, histological, biochemical, immunological. epigenetic, genetic, and other changes that distinguish endometriosis from the endometrium. Those changes involve the local environment, inflammation, infection, immune system maturation, immune system competence, endotoxins, epigenetic changes, genetic changes progenitor cell differentiation, biochemical changes immunologic changes, apoptosis, autophagy, reactive oxygen species, fibrosis, muscular metaplasia, macrophage migration inhibitory 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 10/26/18 listed 25,797 articles that include many parts of the endometriosis story. That is an increase of 324 articles since 8/14/18 (3.7 articles daily).

The concerns include theories, results of treatment, biochemical testing, immunologic testing, inflammatory reaction, fibrosis, muscular metaplasia, spontaneous resolution of endometriosis,

stages, phenotypes, aromatase production, hormonal levels, miRNA, 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.

Concepts and Theories

1. Kahun Medical Papyrus 1825 BC vs. 1855 BC– Discussed in Redwine 2012 and Nezhat 2012 as the oldest known medical text. This hieroglyphic text discusses pelvic pain but is not sufficiently specific to determine if the

pelvic symptoms were those of endometriosis. Additional historical findings include Hippocrates’ (400 BC) notation that "a part of the vagina hardens" may be the first description endometriotic nodules. Johnston's (1977) description of an isolated rectal stricture has the characteristics of rectal endometriosis while Rutter (1808) added the scirrhous characteristic and Seymour (1830) noted a rectovaginal location. Chocolate cysts with iron noted on chemical analysis and probable endometriomas or hemorrhagic corpus lutea (see Martin 1990) were reported by Lobstein (1820). Also, see Hippocrates (466 – 377 BC), Müller 1830, and Knapp 1999.

Redwine DB. Googling Endometriosis -

The Lost Centuries. https://drive.google.com/file/d/0B8niPVY6iWUqemJ3SDd3UWxOc3c/view Nezhat C, et al. Endometriosis: ancient disease, ancient treatments. https://www.fertstert.org/article/S0015-0282(12)01955-3/fulltext

2. Hippocrates's (466 – 377 BC) – From Whiteley 2003 and in Redwine 2012 - Hippocrates's theories were based purely on observation and experience. His observation "… when, in a woman who has not given birth, the menses stay away or are not able to find a way out, disease occurs, and this happens—either the mouth of the womb closes, or it doubles back upon itself, or a part of the vagina hardens" may be the first description of nodules. Kathleen

Whiteley PhD thesis (2003) http://uir.unisa.ac.za/handle/10500/1620

3. Müller 1830 – Johannes Müller published his treatise on the embryology of vertebrate genitalia, entitled Bildungsgeschichte der Genitalien aus anatomischen Untersuchungen an Embryonen des Menschen und der Thiere. Müller elevated the developmental anatomy and pathology of the müllerian organs to a prominent scientific level. (From Batt R. *Intellectual Development of Carl Von Rokitansky*. 2011)
4. Rokitansky1860 – Rokitansky published the first description of the histology of uterine and ovarian lesions compatible with endometriosis, adenomyosis, and endometrial polyps.

He used the term “Ein Ovarial-Cystosarcom” for what we now call an ovarian endometrioma. The gross and microscopic characteristics were seen in a 68-year old in 1859. Rokitansky is generally credited with having performed 30,000 autopsies during his career. (From Batt R. *A History of Endometriosis*. 2011)

5. Waldeyer 1870 – Metaplasia from nests of cell in 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 the secondary Müllerian system.

6. 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 natural area of embryologic Müllerian development. See Nerune 2016 & Rei 2018 persistent Müllerian duct in men.
7. 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.
8. Von Recklinghausen 1896 (quoted in Casler 1919) – The Wolffian theory proposes that adenoma (later called

endometriosis) result from intermingling when the Wolffian and Müllerian ducts cross in fetal development.

9. Russell 1899 – Clinically unrecognized, intraovarian endometriosis was discovered in an ovary with adhesions. See Sampson 1921 and 1927 for endometriosis within adhesions.
10. Clark 1908 (quoted in Kelly 1931) – Clark developed useful electrosurgery.
11. Cullen 1914 –Fibrous and muscular components like adenomyoma are present.
12. Hueter 1918, Meyer 1919 – Inflammatory metaplasia

13. Sampson 1918, Sampson 1927 – Discusses venous dissemination (metastasis) of intrauterine contents.
14. Lockyer 1918 – This first classification was of the anatomic location of adenomyomas that were later called endometriosis.
15. Casler 1919 – Report of cyclic bleeding from ovarian adenoma (later called endometriosis) through a vaginal fistula after hysterectomy. Also discusses Von Recklinghausen's Wolffian theory of intermingling when the Wolffian and Müllerian systems cross in fetal development.
16. Sampson 1921 – Discusses peritoneal implantation from internally menstruating ovaries, differences between normal endometrium and

"adenomas of endometrial type" both "in structure and function," and adenomyosis as different than adenomyoma. "Adenomas of endometrial type" preceded his use of the term endometriosis. Adhesions between the rectum and uterus had adenoma of the endometrial type in 72% of cases.

17. Sampson 1922, Halban 1924, Jerman 2015 – Lymphatic spread (metastasis) of the endometrium
18. Meyer 1923, Gruenwald 1942 – Coelomic metaplasia of cells from the peritoneum
19. Sampson 1924 – Discusses multiple appearances including red raspberries, purple raspberries, blueberries

raspberries, hemorrhagic blebs, and clear blebs.

20. Sampson 1925 – Discusses endometriosis phenotypes, true endometrial (Müllerian) tissue derived from the uterine or tubal mucosa, pseudo-endometrial tissue which arises from remnants of the Wolffian body, and metaplasia of the peritoneal serosa. He concludes that endometriosis is a Müllerian derivative. This may be the first mention of “endometriosis.”
21. Jacobson 1925 – Early discussion of “Sampson's syndrome” and “endometriosis.”
22. Sampson 1927, Nap 2004a, Nap 2004b, Nap 2012 – Sampson suggested retrograde menstrual as a, not the, source of endometriosis. He suggested

additional theories, such as celomic metaplasia and venous dissemination might cause some lesions. He added the transition from endometrium to endometriosis to his 1921 observation that endometriosis was different in "both in structure and in function". Retrograde menstruation theory includes:

- Endometriosis differs from endometrium in structure and function. Histologically normal endometrium and endometriosis can coexist, and a transition can be seen. See Koninckx 2018 for the transition from endometrium to endometriosis.
- The 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

His 1927 article also discussed endometriosis within the adhesions of hemorrhagic cysts.

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.

23. Hunter 1927 – Early research on grafting of endometrial fragments.
24. Weller 1927 – Early report of umbilical endometriosis.'
25. Ferguson 1929, Nora 1956, Steck 1965, Kaunotz 1979, Rock 1981, Donnez 1984 – Direct implantation of endometrium or endometriosis in surgical scars, drain sites, amniocentesis needle tract or traumatic vaginal tears may be from denuded surface, trauma, or inflammation.

26. Novak 1931 – Metaplasia due to hormonal stimulation
27. Sampson 1940 – Discusses the detail needed for research including attention paid to small implants, sketches, selection of sections to be submitted, supervision of technicians, and giving cutting instructions. Noted that endometriosis can remain small and superficial. See Goldstein 1980 on close-up view, Redwine 1988a on near-contact laparoscopy, and Martin 2006 on STARD.
28. 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/

29. Karnaky 1948, Karnaky 1969 – Karnaky proposed the use of the synthetic estrogen diethylstilbestrol (DES) to produce amenorrhea and suppress endometriosis.
30. Clark 1948 –16-year-old with endometriosis in left horn of bicornuate uterus.
31. Fallon 1950 – Endometriosis can be colorless and amenorrheic.
32. Scott & TeLinde 1950 – Early discussion of excision and fulguration (ablation)
33. Meigs 1953 – Meigs recommended early and frequent childbearing as prophylaxis.
34. Levander 1955, Merrill 1966, Lauchlan 1972, Thomas 1996 –

Induction of endometriosis due to activation of mesenchymal cell metaplasia by degenerating endometrium that arrives in the pelvis.

35. Fallas 1956 – Cervical and upper vaginal agenesis associated with retrograde menstruation and severe endometriosis.

36. 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. Also, see Klemmt 2006 & Aoyagi 2017.

37. Freidman 1959 – Müllerian epithelium was noted in an exophytic

bladder in a male. This AFIP slide was reported in Oliker 1971.

38. Kantor 1963 – Endometriosis due to retrograde menstruation may be a different disease than endometriosis due to embryonal rests. Two phenotypic disease theory.

39. Merrill 1966 – “Merrill factor” (quoted in Suginami 1991) is a metaplasia-inducing substance such as estrogen and a factor liberated from degenerating menstrual endometrium. Also, see Thomas 1996.

40. Melicow 1967 – First report of prostatic endometrial cancer in a male. See Oliker 1971 for the first report on endometriosis.

41. Karnaky 1969, Jansen 1869 – Diagnosed endometriosis in the absence of hemosiderin
42. 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.
43. 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.

44. 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.

45. Lauchlan 1972 – Differentiation of precursor 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 from 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.)*

46. Schifrin 1973 – Early report of endometriosis in 15 teenagers. Also, see Clark 1948.

47. Kistner 1975 – Surgery improves pregnancy rates. "*Early implantations on the surface of the "peritoneum should be excised. Electrocoagulation is*

not recommended because of the possibility of subsequent adhesions to the small intestine or the adnexal structures.”

48. Cohen 1975 – Early report of biopsy and cautery.
49. Malinak 1979 – Nodules and large implants require excision. Small lesions with no nodules or infiltration can be fulgurated (coagulated). Recurrence rates were 12% to 40%.
50. Mettler 1979 – Reported on ovarian cyst resection but concluded that more than “*coagulation of endometriotic foci cannot be performed via the laparoscope*.” See Semm 1980. Note: Mettler and Semm were co-workers at the University of Kiel.

51. Goldstein 1980 – Endometriosis in adolescents as young as 10.5 years old with petechial lesions. Karnaky 1969 discussed young girls. Also, see Schifrin 1973
52. 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.
53. Simpson 1980 – Genetic predisposition is generally seen as an observation, not a theory.
54. Semm 1980 – The depth of coagulation is not adequate for large nodules, and laparoscopic partial excision needs to precede coagulation for those.

55. Semm 1981 – Professor Semm presented partial excisional techniques at the 10th Annual AAGL meeting in Phoenix, Arizona circa November 7. 1981.
56. Dmowski 1981 – Dmowski proposed that the immune system was involved in the development of endometriosis.
57. Rock 1981, Donnez 1984 – There is an increased risk of tubal endometriosis, especially after coagulation. Tubal surgery may be the surface disruption, traumatic or inflammatory event that facilitated the growth of endometriosis.
58. Daniell 1982 – Development of CO_2 laser vaporization for endometriosis. See Martin 1983 for development of CO_2 laser excision.

59. Halme 1983, Canis 2017 – Halme noted an increased activation of pelvic macrophages in infertile women with mild endometriosis
60. Martin 1983, 1985, 1986, 1987, 1988, 1989 – Development of laparoscopic CO_2 laser excision techniques for deep endometriosis. The difference between vaporization for excision, vaporization to turn the lesion into an aerosol plume, and coagulation (fulguration) was discussed and refined.
61. Halme 1984, Halme 1988– Halme noted that retrograde menstruation was more common than endometriosis. Therefore, other factors influenced the development of endometriosis.
62. Semm 1984 (German), Semm 1987 (English) – "*The surgical excision of*

endometriosis implants is still considered the optimal treatment of pelvic endometriosis.”

63. Malinak 1984 – Recurrence rates are likely higher than published due to asymptomatic recurrence.

64. 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

65. Taylor 1986 – Clarifies that CO_2 laser thermal burn is more significant than penetration at low power densities with thermal coagulation of 2.7 mm at 30 watts/cm2. Also, see Luciano 1987.
66. Thomas 1987 – Hormonal suppression with gestrinone after laparoscopy decreases the risk of progression compared with no suppression. Spontaneous regression occurred in both groups.
67. Luciano 1987 – The thermal effect of CO2 laser and electrosurgery are similar at high power density. Depths of

coagulation less than 0.2 mm at > 58,000 watts/cm^2. See Taylor 1986.

68. Redwine 1987, Martin 1989, Albee 2008 – Any abnormality of the pelvic peritoneum, no matter how small, how subtle, or what color, may be endometriosis.

69. Martin 1988 – Deep excision to the vagina with colpotomy. Drs. Richard "Pete" Hollis, Harry Reich and Gordon Davis were instrumental in the development of these techniques.

70. Halme 1988, Hill 1992, Giudice 2004, Northick 2016, Pavone 2016, Koninckx 2018 – 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 immunologic response results in evasion of apoptosis allowing endometriosis cells to continue to live. According to the peritoneal immune surveillance hypothesis, only women with a local and/or systemic immune defect develop “endometriosis.” In Koninckx 2018 this would be called “endometriotic disease.”

71. Redwine 1988b – Providers should consider theory “*in order to select treatment*.” See Goodwin (1984) on the Tomato Effect for the opposite view.

72. 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.

73. Martin 1989 – The diagnosis of endometriosis at laparoscopy increased from 42% in 1982 to 72% in 1988. The greatest change was in "subtle" lesions, which increased from 15% in 1986 to 65% in 1988. Thirteen 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.
74. 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)

75. Cornillie 1990 – In-phase cyclic changes are different in deep (≥5 mm), intermediate (2 to 4 mm), and superficial (<1 mm) endometriosis

76. Martin 1990 –The gross characteristics of a chocolate cyst are not always predictive of the histology. However, those with a flattened

appearance and red or red and brown mottled ridges generally were endometriosis, and those with a dark uniform base, an intracavitary clot, or a yellowish rim generally were corpus lutea or albicans. See Lobstein (1820) in Redwine 2012.

77. Cornillie 1991 – Endometrial protein PP14 positivity varies in deep (≥5 mm), intermediate (2 to 4 mm), and superficial (≤1 mm) endometriosis.

78. Koninckx 1991, Koninckx 1994, Gordts 2017, Koninckx 2018 – Deep endometriosis is endometriotic disease. Superficial endometriosis is either stopped by the immune system or converts into endometriotic disease.

79. Koninckx 1991 – Infiltration found in 4% of superficial appearing vesicles at 5-6 mm and 3% of polyploid lesions at 3-4 mm. The data is in table 3.
80. Portz 1991, Vitale 2018 – Reactive oxygen species (ROS) or free radicals may increase the growth and adhesion of endometrial cells in the peritoneal cavity, promoting endometriosis and infertility
81. Ripps 1991 – Pain and tenderness are associated with fibrosis (scarring) of implants.
82. Suginami 1991 – Suginami concluded that the multiple sites or endometriosis were most compatible with coelomic metaplasia.

83. Ripps 1992 – Pain and tenderness are associated with implants having a mean depth of 5.3-mm and a volume of 1,213 mm^3.

84. Koninckx 1992 – Endometriosis has three phenotypes. Types I and II can present as superficial (<3 cm), intermediate 3 to 5 cm) and deep (0.5 cm or deeper) lesions. Type III a form of adenomyosis externa with most of the volume hidden in a retroperitoneal location and is generally deeper than 1.0 cm.

85. Thomas 1993 – The only clear recommendation for treatment is in symptomatic patients. The short-term effects of medication and surgery may be placebo. But, see Thomas 1996.

86. 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. See Umezawa 2011 for diesel fuel toxicology.
87. Hoshiai 1993 – Serial laparoscopies confirm that some get better, some get worse, and some get better and then worse. See Evers 1994 and the "Pimple Model" (Martin 2005)
88. Haney 1993 – Endometriosis is associated with a localized sterile inflammatory process, growth factors, cytokines, and activated macrophages in the peritoneal fluid.
89. Davis 1993, Vercellini 1991 – Adolescents with functional pain, cyclic

pain, abdominal pain, nausea, constipation, and diarrhea during menses have the greatest proportion of red lesions. See Vernon 1986.

90. Adamyan1993 Batt 2014 – All rectovaginal endometriosis is retrocervical. Some retrocervical endometriosis is not rectovaginal.

91. Chan 1993 – Vitamins E and C constitute a strong line of defense in retarding free radical induced cellular damage. Also see Agarwal 2005, Mier-Cabrera 2009, Nishihara 2018.

92. Adamson 1994 – Surgery or no treatment is better than medical therapy for fertility.

93. Oosterlynck1994 – CA-125 levels, but not natural killer activity, decrease

after excision. These data suggest that natural killer activity is a primary deficiency in women with endometriosis and the elevated CA-125 is a consequence of endometriosis. See Margatho 2018 for response to etonogestrel (ENG) implant and levonorgestrel-releasing intrauterine system (LNG-IUS)

94. Evers 1994, Koninckx 1994, Koninckx 1999, Harrison 2000, Nap 2004a, Koninckx 2018 – Endometriosis in its superficial form is generally transient, self-limiting, and cause little or no long-term damage. This has been called the “Pimple Model" (Martin 2005) as almost everyone has pimples, most are mild and resolve spontaneously, some get worse, and

some come and go. (Hoshiai 1993 and Martin 1999) Some are inflammatory, can get better on medication (estrogenic BCPs, Accutane, antibiotics), can cause scarring, and are treated with surgery (dermabrasion). Koninckx endometriotic disease theory (1999) of the transition of some transient subtle to deep infiltrating and ovarian endometriomas evolved into the genetic/epigenetic theory (2018). See Halme 1988 and others for immune competence models that explain why transient is not the common pathway.

95. 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 to be unethical without a significant paradigm shift in technology.

96. Sutton 1994 – Pain relief at three months is not significantly different between a 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.

97. Shapiro 1994, Landin-Romero 2018 – Eye desensitization and reprocessing that was initially used for trauma and substance abuse has since been exported to areas including pain management.

98. Perper 1995 – Menstrual cramps (dysmenorrhea) are related to the number of implants.
99. Fernandez 1995 – Bone marrow-derived cells are found in endometriosis.
100. Abu-Hijleh 1995 – Diaphragmatic lymphatics drain into retrosternal (parasternal) lymphatic trunks that carry lymph to the great veins after it filters through mediastinal lymph nodes may be the source of mediastinal cases such as Yasukawa 2018.
101. Khare 1996 – Differences in collagen types suggest that ovarian endometriosis may be metastatic while pelvic wall-infiltrating endometriosis is metaplastic.

102. Thomas 1996 – There is evidence of some improvement of endometriosis spontaneously, it was more marked with gestrinone therapy. The striking finding was that there is a tendency for endometriosis to worsen over time if untreated, but this does not occur in women on gestrinone therapy.
103. ASRM 1997 – Eight phenotypic laparoscopic appearances
104. Nisolle 1997 – Peritoneal, ovarian, and rectovaginal nodules are three different entities
105. Gaetje 1997 – Invasion based on E-cad- epithelial cells
106. Leyendecker 1998 – Intrauterine tissue injury and repair at the

endometrial-muscularis interface (TIAR) due to intrauterine trauma.

107. Knapp 1999 – Dr. Knapp concluded that 17th and 18th-century reports of ulcerated, inflammatory lesions were compatible with endometriosis despite no histology with glands or stroma or characteristics compatible with current descriptions. On the other hand, his descriptions of symptomatology are better and consistent with endometriosis. See Redwine 2012 & Nezhat 2012 for symptomatology in 1855 BC vs. 1825 BC

108. Martin 1999 – Discusses retroperitoneal endometriosis in a Rhesus monkey that converted to surface endometriosis when she bled and opened the cystic lesion,

rectovaginal nodule was not seen at laparoscopy or laparotomy, a 14-year old who progressed from a flat peritoneum to pockets at age 15, the patient with the two perirectal pockets with only one having an entrance, and deep endometriosis that failed to respond to coagulation. Of note, the 14/15-year old was treated with suppression for several years, had three children, and was doing well at age 35.

109. Starzinski-Powitz 2001, 2003 – Differentiation of stem cells into endometriotic cells

110. Martin 2001 – The retrovaginal (RV) zone is increased due to contraction of the RV pouch and may be lengthened RV septum. See Takeuchi 2005 for a conclusion that the

septum fractured rather than lengthening

111. Donnez 2001, Squifflet 2001 – Retroperitoneal adenomyotic disease (RAD) results from metaplasia in Müllerian remnants. See Koninckx 1992, Signorile 2010, and Signorile 2012

112. Rier 2001 – TCDD-exposed rhesus monkeys with endometriosis exhibit long-term alterations in systemic immunity associated with elevated serum levels of specific PHAH congeners. Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) correlated with increased peripheral blood mononuclear cells (PBMC) tumor necrosis factor-alpha (TNF-alpha) secretion in response to stimulation by

T-cell mitogen and decreased cytolytic activity against NK-sensitive target cells.

113. Redwine 2002 – 38 differences between endometriosis and eutopic endometrium in humans.

114. Gazvani 2002 – The peritoneal environment can influence the development of endometriosis.

115. Kats 2002 – Macrophage migration inhibitory factor is higher in early (subtle red) than in late (blue, black, or white) lesion appearances.

116. 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/

117. Petta 2005 – Levonorgestrel-releasing intrauterine system is useful for the treatment of pain
118. Takeuchi 2005 – Takeuchi saw no continuity between the rectovaginal septum and the lesion. Endometriosis in the contracting rectovaginal pouch may tear away from the septum, and the tissue behind the upper vagina may be loose connective tissue or scar rather than elongated septum.
119. Martin 2005 – The "pimple model" was presented as part of "Clinical and Research Aspects of Endometriosis" at the University of Tennessee Health Sciences Center, Department of Obstetrics and Gynecology rounds

November 15, 2005. Almost everyone has pimples, most are mild and resolve spontaneously, some get worse, and some come and go. (Hoshiai 1993, Martin 1999) Some are inflammatory, can get better on medication (estrogenic BCPs, Accutane, antibiotics), can cause scarring, and are treated with surgery (dermabrasion). http://www.danmartinmd.com/files/endouthsc2005.pdf

120. Chan 2004 – Endometriosis is clonal

121. Marsh & Laufer 2005 and Cabana et al. 2010 – Inflammation may be a precursor, facilitator or early presentation.

122. Agarwal 2005 – Before clinicians recommend antioxidants, randomized

controlled trials with sufficient power are necessary to prove the efficacy of antioxidant supplementation in disorders of female reproduction.

123. Klemmt 2006, Akoum 2006, Klemmt 2007, Grümmer 2012, Klemmt 2018 – Changes in the eutopic (within the uterus in the usual 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/

124. Martin 2006 – Discusses the use of standards for reporting of diagnostic accuracy (STARD) criteria such as specific and recorded features for a normal or abnormal laparoscopy,

histologic criteria, distance of observation, clinical palpation, exam under anesthesia, intra-operative palpation, and palpation with instrumentation.

125. Batt 2007 – Choristoma is a neoplastic Müllerian tissue in non-Müllerian areas

126. Kodati 2008 – Theory that menstrual, endometrial cells can adhere to peritoneum traumatized by Shigella or Shigella-like microorganisms.

127. Guo 2009 – There is a need for identification of prognostic biomarkers for recurrence.

128. Mier-Cabrera 2009 – A high antioxidant diet at 150% of the suggested daily intake of vitamin A

(1050 microg retinol equivalents), 660% of the recommended daily intake (RDI) of vitamin C (500 mg) and 133% of the RDI of vitamin E (20 mg) was associated with diminished peripheral oxidative stress markers and enhanced antioxidant markers in women with endometriosis.

129. Ohlsson Teague 2009 – MicroRNA-regulated pathways associated with endometriosis

130. Khan 2010 – Bacterial endotoxins such as lipopolysaccharide in the pelvis across the phases of the menstrual cycle. This lipopolysaccharide derived from higher colony formation of Escherichia coli in menstrual blood may promote the growth of endometriosis after its binding with toll-like receptor 4

(TLR4). Also see Khan 2016 for bacterial contamination hypothesis.

131. Chapron 2010 – Among 15 patients with non-operated associated asymptomatic posterior DIE lesions, a second surgical procedure indicated for pain symptoms was necessary for only one patient (6.7%).

132. Signorile 2010 & 2012 – Fetal tissue compatible with endometriosis on H&E, H&VG and immunohistochemistry stains (CD10, Era, CA125, cytokeratin 7, vimentin, and desmin) was found in the rectovaginal septum, proximity of the Douglas pouch, and the mesenchymal tissue close to the posterior wall of the uterus. This is the same anatomic area studied by Koninckx (1992) with Type

III being the most suggestive of a congenital rest and Donnez (2001) on metaplasia from Müllerian remnants.

133. Adamson 2010 –The Endometriosis Fertility Index is the only validated tool to determine fertility after surgery. Fertility rates after endometriosis surgery are based 50% of the surgical findings and 50% on history. https://www.fertstert.org/article/S0015-0282(09)03714-5/fulltext

134. Surrey 2010 – Add back therapy adds to patient acceptance & safety of GnRH therapy

135. Batt 2011 – Dr. Batt's book "*A History of Endometriosis*" presents the great leap forward that occurred from 1860 to 1946 from a 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

136. Umezawa 2010 – Prenatal and postnatal diesel exhaust exposure is toxic and enhances the activation of mast cells and prolongs the persistence of collagen fibers in the induced rat model of endometriosis.

137. Acién 2012 – Accessory and cavitated uterine masses (ACUM) are non-inflammatory, organoid examples of how Müllerian remnants can appear.

138. Redwine 2012, Nezhat 2012 – Clinical descriptions suggesting the presence of endometriosis were found

in the oldest known medical text the Medical Papyrus (1825 BC) or Egyptian concepts (1855 BC). These are introduced in Redwine 2012 and Nezhat 2012.

139. Batt 2013, Laganà 2017 – Müllerianosis as an organoid remnant of Müllerian tissue in the native area of embryologic Müllerian development. Organoid remnants are not what is more commonly called endometriosis.
140. Batt 2013 – Hamartoma is a neoplastic Müllerian growth in the normal Müllerian area.
141. Brosens 2013 – Endometriosis is a progressive disease

142. Raposo 2013 – Extracellular vesicles involved in intercellular communication (signaling)
143. 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/
144. 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
145. Sugamata 2015 – Leukotriene receptor antagonist (LTR-A), an anti-

allergic drug, is associated with apoptotic fibroblasts and degeneration of collagen fibers and may this decrease the transition to deep infiltrating endometriotic disease. http://dx.doi.org/10.4236/ojog.2015.56045

146. Kobayashi 2014 – Infectious precursors or infectious induction of endometriosis.

147. Gargett et al. 2014, Brosens 2015 – Perinatal retrograde dissemination is like Sampson but suggests an earlier occurrence shortly after birth.

148. Forte 2014 – Chromosomal anomalies and instability can alter gene expression

149. Khan 2014 – Occult non-recognized endometriosis found in 15.2 % of women with visible endometriosis (15.2%) and 6.4% of controls (6.4%). There are thee patterns of occult microscopic endometriosis 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). Also see Martin 1989 for increase with awareness of subtle appearances, Khan 2010 for endotoxins, Hopton 2014 for “near-contact” laparoscopy, and Khan 2016 for cross-talk between inflammation and ovarian steroids or the stress reaction.

150. Hopton & Redwine 2014 – Khan (2014) confirms that most (84.8%) women with endometriosis do not have occult endometriosis.
151. Signorile 2014 – Anti-müllerian hormone (AMH) in the normal endometrium, acts in a paracrine fashion, negatively regulates cellular viability. Treatment of endometriosis with AMH decreased growth.
152. Abrão 2015 – In women with deep endometriosis, surgery is the therapy of choice for symptomatic patients when deep lesions do not improve with medical treatment.
153. Guo 2015 – Repeated tissue injury and repair (ReTIAR) due to cyclic bleeding in endometriosis.

154. Laux-Biehlmann 2015 – Pain due to activation of peripheral nerve endings in response to retrograde and extra-uterine menstruation
155. Canis 2016, Canis 2017 – The extent or the surgical phenotype of the disease may be related to the initial anatomic localization, type, and severity of the trauma. The local natural history of endometriotic lesions may depend on the tissue on which they have developed. If the trauma is stopped and the injured tissue is repaired, the severity will not increase significantly. True recurrences of the disease may be rare unless a new trauma induces further endometriotic lesions.
156. Koninckx 2016 – There are four phenotypic types of endometriosis:

subtle, typical, cystic ovarian, and deep infiltrating.

157. 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.

158. Khan 2016 – The bacterial contamination hypothesis reviews the lipopolysaccharide regulation of the pro-inflammatory response in the pelvis and growth of endometriosis via the LPS/TLR4 cascade. Menstrual blood was highly contaminated with Escherichia coli and the endometrial samples were colonized with other microbes. Cross-talk between inflammation and ovarian steroids or

the stress reaction was also observed in the pelvis. T GnRHa treatment may worsen intrauterine microbial colonization, with the consequent occurrence of endometritis in women with endometriosis.

159. Pavone 2016 – Retinoid analogs may induce apoptosis in endometriotic cells and tissues, thereby reducing disease burden. See Halme 1988.

160. Tiboni 2016 – Animal defects on therapeutic or lower levels doses of aromatase inhibitors include skeletal anomalies, abnormal head morphology, increased anogenital distance in female fetuses, urinary tract system anomalies, and placental enlargement.

161. 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.

162. 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 as important as

the genetic and epigenetic changes are associated with the specific phenotypes of endometriosis.

163. 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.

164. Makiyan 2017 – Congenital primordial germ cells remnants can be the source.

165. Anglesio 2017 – Cancer-associated driver mutations can be present in deep infiltrating endometriosis. See Guo 2018 and Lac 2019.

166. Aoyagi 2017– 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. Also, see Kistner 1958 & Klemmt 2006
167. Kohl Schwartz 2017 – Mild endometriosis, as in superficial lesions, is related to a great extent to an inflammatory disorder, possibly leading to defective folliculogenesis, fertilization, or implantation, presenting an increased risk of miscarriage.
168. Parasar 2017 – Mouse embryonic stem cells (mESCs) express both glandular (CD9) and stromal (CD13)

markers of human endometrium, suggestive of a novel endometrial precursor cell population. This model represents a potential key step in elucidating the mechanisms of ectopic endometrial tissue growth.

169. Vigano 2018 – Endometriosis should be defined as a fibrotic condition with endometrial stroma and epithelium. See Guo 2018.

170. Guo 2018 – The six driver genes reported to be mutated in endometriosis (the RP set) may play important roles in fibrogenesis but not necessarily malignant transformation.

171. 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/

172. Brosens 2018 – Progression requires active neo-angiogenesis.
173. Panir 2018 – Non-coding RNA is associated with endometriosis.
174. Foster 2018, Luo 2018, Matsuzaki 2018, Sui 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.

175. Matsuzaki 2018 – Using autophagy inhibition may decrease the chance of recurrence.

176. 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.

177. 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/

178. 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.

179. Christofolini 2018 – Differences in allelic genetic distribution between fertile women and women with endometriosis and infertility are seen in the KAZN gene for grades 1 and 2 and LAMA5 gene for grades 3 and 4. Infertility may be genetic.

180. Margatho 2018 – CA-125 decreases more on etonogestrel (ENG) implant than on levonorgestrel-releasing intrauterine system (LNG-IUS). However, the decrease in soluble CD23 and endometrial nerve fiber density were similar. CD23 and nerve fiber density may be a surrogate marker for response to hormonal suppression with implantable progestational devices. See Oosterlynck 1994 for CA-125 and natural killer activity response to excision.
181. Chen 2018 – Women affected by endometriosis have an independently elevated risk of placenta previa in pregnancy.
182. Sui 2018 –Autophagy-related proteins, microtubule-associated protein

light chain 3 (LC3) and Beclin1 were lower while matrix metalloproteinase-2 (MMP-2) was higher in women with endometriosis.

183. Nishihara 2018 – Oxidative stress in women with infertility is associated with endometriosis.

184. Jiang 2018 – IL-37 regulated the biological behavior of ectopic endometrial stromal cells through multiple signaling pathways such as β-catenin, p-p38, p-ERK1/2, and p-JNK, and this signaling was abolished by a Wnt/β-catenin inhibitor.

185. Rekker 2018– Cell-type-specific analysis revealed differences in miRNA expression patterns between stromal cells isolated from the endometrium and endometriomas. Two molecular

mechanisms are involved in endometriosis pathogenesis. First, HOXA9 and HOXA10 genes are regulated by miR-139-5p among other factors and are potentially involved in endometriosis-associated infertility. Second, the aberrant expression of miR-375 in ectopic stromal cells may contribute to higher levels of EDN1 in lesions, which can be associated with pain mechanisms or be involved in the regulation of invasive growth and cell proliferation in endometriosis development

186. Gibson 2018 – 'Intracrine' is a 1980s concept based on the ability of cells within non-gonadal tissues to both produce and respond to the same hormone. Intracrinology is the way that

tissue such as endometriosis can utilize inactive steroids present in the blood to respond to local physiological demands and ‘fine-tune’ the activation or inhibition of steroid hormone receptor-dependent processes.

187. Koninckx 2018 – The genetic/epigenetic theory is a theory of transition from endometrial or other stem cells to endometriosis. It is not dependent on the cell of origin or method of dissemination. The set of genetic and epigenetic incidents transmitted at birth are hereditary aspects that predispose to the endometriosis-associated changes in the endometrium, immunology, and placentation. However, to develop typical, cystic ovarian or deep

endometriosis lesions, a variable series of additional transmissible genetic and epigenetic incidents are required to occur in a precursor cell. Subtle lesions are viewed as endometrium in a different environment until additional incidents occur and can be called "endometriosis." After additional genetic and epigenetic incidents, those can transition into "endometriotic disease." Typical cystic ovarian or deep endometriosis lesions are heterogeneous and represent three different diseases.

188. Flores 2018 – Symptomatic response to progestin has been unpredictable. However, a progesterone receptor status can predict clinical response and, therefore, be useful in clinical management.

189. Arosh 2018 – Dual inhibition of ERK1/2 and AKT pathways, that regulate signaling proteins in human endometriotic cells in an epithelial cells and stromal cell specific pattern, can decrease the growth and survival of endometriotic lesions by decreasing proliferation and inducing apoptosis of epithelial cells and stromal cells of the endometriotic lesions
190. Lac 2019 – Incisional endometriosis can develop driver mutations like deep infiltrating endometriosis. See Anglesio 2017 and Guo 2018.
191. Ryu 2019 – Chrysin derived from honey, propolis (bee glue), or passion flowers has anti-inflammatory and anti-angiogenesis effects. Chrysin suppresses the proliferation of

endometriosis and induces programmed cell death by activating the endoplasmic reticulum stress response, inactivating the PI3K signaling pathways, increasing the cytosolic calcium level and generating of reactive oxygen species.

Subtle Inflammatory Lesions (Subtle Peritonitis)

Additional concerns are raised by inflammatory lesions suggestive of endometriosis in adolescents and children. (Marsh and Laufer 2005, Cabana et al. 2010) Endometrial or endometrioid stroma can be challenging to recognize in inflammation (Clement 2007), and the conclusions that these are endometriosis is reasonable. However, Marsh and Laufer (2005) and Cabana et

al. (2010) did not exclude infection, endotoxins, or other causes of inflammation (Khan 2014, Khan 2016, Canis 2018) as the source of the inflammation. If these are infectious, then antibiotics can treat active infection and potentially decrease long-term morbidity. Conversely, 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.

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

Khan KN, Kitajima M, Hiraki K, Yamaguchi N, Katamine S, Matsuyama T, Fujishita A, Nakashima M, Ishimaru T, Masuzaki H. Escherichia coli contamination of menstrual blood and effect of bacterial endotoxin on endometriosis. Fertil Steril 2010, 94:2860–2863.

Khan KN, Kitajima M, Fujishita A, Nakashima M, Masuzaki H, Kitawaki J. Role of bacterial contamination in endometriosis. J Endometriosis Pelvic Pain Disorders 2016, 8:2-7.

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 specific 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.

Patient's questions include:

- What do I have?
- How did I get it?
- What can we do about it?
- Will insurance cover it?

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 many, 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 (Malinak 1979, Martin 1989). Excision was successful in my practice (DCM), 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.

Reversal in 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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