

Endometriosis: ancient disease, ancient treatments

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Ever since Vincent Knapp published his 1999 article "How old is Endometriosis?" (1), there seems to have been renewed interest in identifying just when endometriosis was discovered as a distinct disease entity.

While the history of endometriosis subsequent to its 1860 microscopic unveiling by Karl von Rokitansky has been well-studied, its story leading up to that moment has remained largely unknown. The time seemed ripe to cast light on this chasm of history and give voice to the inaudible narratives of illness that have been lost in the margins of centuries. Inexact as the study of history may be, nevertheless clinical observations from the past may offer unique perspectives that would otherwise have been entirely overlooked.

Moreover, in surveying the historical development of scientific medicine, it is evident that nearly all of our current understandings of complex disease-states have resulted from the synthesis of centuries of observations. Even medical theories that ultimately proved to be exquisite fallacies have actually served as essential counterpoints throughout the ages, refining knowledge by producing the searing clarity that only unanticipated failures can yield; the sort of shock medicine sometimes needs to achieve transformative change. Viewed in this light, to exclude the formative years leading up to the microscopic discovery of endometriosis is to deprive our discipline of an invaluable reservoir of knowledge that may reveal

essential new insights about a disorder that continues to reign as one of gynecology's most perplexing diseases.

SOLVING THE MYSTERY OF HYSTERIA

Was Freud Wrong Yet Again?

With these ideas in mind, we applied a broader set of criteria in searching historical records for the earliest possible signs of endometriosis, taking care to include historical descriptions of clinical and macroscopic findings that corresponded to contemporary understandings. Historical perspectives on pelvic pain in women have also informed our analyses.

By applying this broader set of criteria we were able to uncover substantial, if not irrefutable, evidence that hysteria, the now discredited mystery disorder presumed for centuries to be psychological in origin, was most likely endometriosis in the majority of cases (Fig. 1). If so, then this would constitute one of the most colossal mass misdiagnoses in human history, one that over the centuries has subjected women to murder, madhouses, and lives of unremitting physical, social, and psychological pain. The number of lives that may have been affected by such centuries-long misdiagnoses is staggering to consider, likely involving figures in the multiple millions.

Methodologies

A broadly defined subject such as pelvic pain is naturally bound to yield results

mired in inescapable ambiguity, especially because conditions like appendicitis, nonendometriotic ovarian cysts, infections, and leiomyomas can produce similar gynecologic symptoms (2). However, after filtering all histories through the lens of modern understandings, we feel confident that the following analyses include only those patterns of illness that share significant correspondence to current clinical interpretations of endometriosis.

For our research methodology, we pursued several strategies, including traditional searches of the PubMed/Medline databases. Additionally, archival research was performed at several locations including the National Library of Medicine in Bethesda, Maryland; the Lane and Green libraries at Stanford University in California; and the medical history library of the University of California at San Francisco.

In some cases, it was necessary to translate primary sources that were available only in Latin. For this specialized task, we consulted with the Cambridge-educated Latin and Greek scholar, J. R. T. Holland of Quintus Latin Translation Service, whose expertise in translating medical texts from premodern eras proved especially crucial for demystifying several contested areas of the history of endometriosis.

Newly digitized medical literature made available by Google Books also proved to be a surprisingly useful new source. To achieve an interdisciplinary perspective, we also referenced a wide range of material from outside of medicine, drawing from the disciplines of psychology, literature, art history, and medical anthropology. Given the allegorical nature of many these alternative sources, they were not evaluated in the same manner as the medical literature intended to represent empirical

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FIGURE 1

Replica of Sigmund Freud's couch, where patients presenting with endometriosis-like symptoms were often diagnosed with hysteria. (Reproduced courtesy of Konstantin Binder, photograph from the Freud Museum in London.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

FIGURE 2

Experts on medieval medicine describe this late 13th-century image from a medical textbook as one depicting a case of uterine suffocation, a disease profile with many similarities to endometriosis. (Reproduced with permission of Oxford University, Bodleian Library, MS Ashmole 399, f. 33–34.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

experiences. Rather, their utility lies in their unique ability to convey otherwise nearly imperceptible cultural undertones, the prisms through which illnesses are invariably experienced and conceptualized.

With thousands of conceivable sources from which to choose, this brief survey should in no way be considered an exhaustive study. Nevertheless, we believe it fills a gap in the literature by providing a multidisciplinary historical analysis of endometriosis as it may have been conceptualized before its 1860 microscopic discovery by Rokitansky. We first presented the preliminary results of this research in March 2011, at the World Endometriosis Symposium held in Atlanta, Georgia.

The Search Begins

Historical representations of pelvic pain: Oxford's Bodleian Library MS Ashmole 399. We began our analysis by focusing first on the broadest category under consideration: historical representations of pelvic pain in women. As it turned out, this subject proved rather elusive, one curiously and consistently neglected in the archives of history. Detailed accounts of menstrual pain in particular were rarely if ever chronicled. Yet the hundreds of medicants for gynecologic ailments listed in the various *Materia Medicas* throughout the ages provide in themselves a strikingly different account, articulating by proxy stories of illness that belie those found in mainstream medical literature.

It was by tracing these nearly imperceptible leads that we eventually stumbled upon a late 13th-century medical manuscript, referred to as MS Ashmole 399 (folios 33–34) in which images of a woman apparently doubled over in pain can be found (3) (Fig. 2). Although there are no texts to accompany the original drawings, experts believe the imagery represents

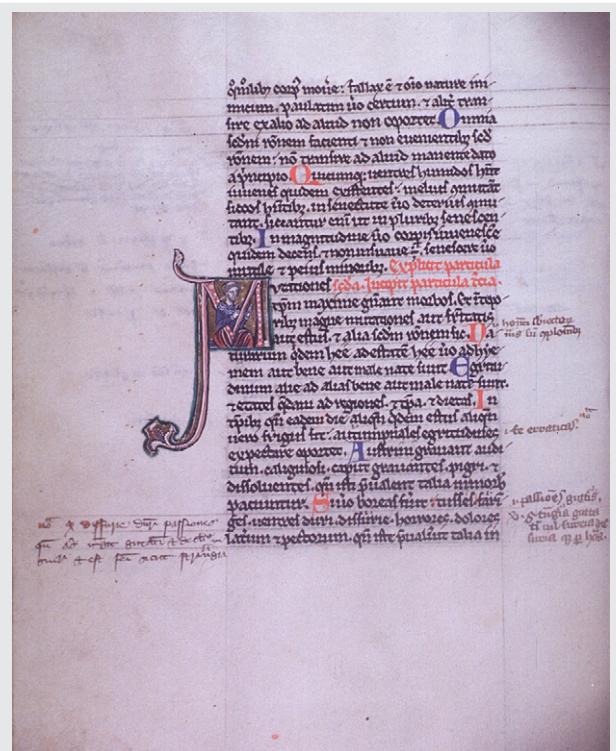
a woman suffering from what was usually called at the time “strangulation or suffocation of the womb.” The linguistic lineages of these terms are still contested, but many scholars believe their roots can be traced to the *hysterikos-hysterike pnix* family of disorders, loosely defined disease frameworks formulated by Hippocratic and other Greco-Roman authorities throughout Classical and Late Antiquity, and the original source of the word *hysteria* (4–7).

CLASSICAL AND LATE ANTIQUITY

The Animalistic Womb

Although strangulation or suffocation of the womb took on many contradictory meanings throughout history, their earliest antecedents may have stemmed from concepts first posited by the ancient Egyptians as long ago as 1855 BC. However, they were later popularized by the Hippocratic texts, Plato, and other Greco-Roman sources of Classical Antiquity (8) (Fig. 3). The basic concept underlying these disorders rested on the premise that the uterus was not actually a regular organ, but rather one more analogous to a live animal, hungry for motherhood.

FIGURE 3



In the Hippocratic Corpus several gynecological symptoms are mentioned, which bear striking similarity to those of endometriosis, including uterine ulcers, adhesions, and infertility. (Page of text in "Aphorismi" with an illuminated small "M," Record UI. 1014450-55, In: Hunayn ibn-Ishaq al-'Ibadi, Oxford, 13th century, I. 19v, Isagoge and other medical texts, Census 78. Reproduced courtesy of the U.S. National Library of Medicine.)

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Though a metaphorical rather than literal analogy may have been intended, the idea of the animalistic womb eventually began informing everyday practices. From this pretext emerged one of ancient medicine's most enduring dogmas, the idea that if a woman did not fulfill the socially proscribed roles of marriage and motherhood her uterus would be deprived of its intended purpose. From this presumed unnatural state, it was believed that the uterus would begin to wander about—the famous wandering womb—and thus contribute to the onset of all manner of illness (5, 7, 9–14). The notion of a wandering womb naturally strikes a modern audience as an anatomic impossibility. Yet it suggests a causal connection with pregnancy that is nearly identical to a modern assumption about endometriosis: the idea that pregnancy can temporarily suppress symptoms.

The Hippocratic Corpus

These theories inform many of the medical practices described in the Hippocratic corpus, a compilation of works written by various authors throughout the 5th through 4th centuries BC. The translations of these Hippocratic texts have been the subject of academic debate for centuries. However, after

consulting numerous sources, we identified several relatively unambiguous disease profiles that allude to the wandering womb and other symptoms suggestive of endometriosis. The correlations become particularly evident when we learn that the Hippocratics viewed the following four factors as highly predictive of gynecologic disease: [1] menstrual dysfunction is a cause of disease, [2] pregnancy is a possible cure, and [3–4] pain and infertility as potential outcomes if the woman is left untreated (7). Nearly 2500 years have passed since these observations were made, yet remarkably they correspond nearly seamlessly to the set of symptoms identified today as emblems of endometriosis. It is unfathomable that such uncanny correlations could remain suspended in a timeless stasis for so long. But what is even more incomprehensible is how such a uniquely patterned symptom profile could exist for ages without others realizing it was the hallmark of a distinct disease.

It was most likely the endless upheavals of medieval times that left such crucial Hippocratic insights buried in the debris of history. This is the most plausible explanation because, as we will see, these four core assumptions would inform essentially all Greco-Roman ideas of why gynecological disorders arise up until about the fifth century AD, the period many mark as the beginning of the European Middle Ages.

The Hippocratic texts provide many examples of how these four core concepts not only influenced ancient diagnostics and prognostics but also closely paralleled modern views. For example, in a near conceptual equivalent to the 20th-century notion of endometriosis as a “career woman’s disease,” the Hippocratics suggested that delaying motherhood could trigger disorders of the uterus, with painful menstruation cited as one such outcome.

Women who suffered from dysmenorrhea were therefore urged to marry and conceive as quickly as possible (15).

Other dire consequences were predicted for those who failed to partake in the pregnancy prescription. One Hippocratic author warned that “if they have never been pregnant, the deranged state of menstruation is more common and more dangerous than when they have borne children” (a paraphrase by the translator) and that she will be “release[d] from this disease, when she is pregnant” (4, 7).

Childlessness in older, married women (i.e., cases of presumed infertility) was recognized as another predisposing factor for gynecologic disorders (4). Drawing from the same pregnancy-as-therapy orthodoxy, another group believed to be particularly susceptible to gynecologic disorders were presumably fertile women who nevertheless remained childless; young widows and virgins who had already menstruated but remained unmarried typified this category of susceptible females (4, 16).

Detailed reports of menstrual disorders. Detailed accounts of other menstruation-related disorders were reported in a chapter titled “Aphorisms,” in which the Hippocratic author describes menorrhagia as a potential cause for pathology (16) and proclaims: “When the menses are excessive, diseases take place” (17). It was also observed that in some women their “floodings,” an archaic term for menstruation, were followed by “grumulous clots . . . accompanied with

FIGURE 4



Allegorical image of fumigation, as depicted in John Collier's painting "Priestess of Delphi," 1893. (Reproduced with permission of the Art Gallery of South Australia, Adelaide.)

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pain, inflammation of the uterus, [and] hysterical paroxysms." Additionally, in the Hippocratic chapter titled "Diseases of Young Girls" (translated less accurately today as "Virgins"), the authors observed that "the menses sometimes suddenly appear abundantly at the end of three months, in clots of black blood, resembling flesh; sometimes ulcers of the uterus ensue, requiring much attention" (16). The Hippocratic author goes on to report: "When in a diseased state, the menses are of a bilious character; they have a black and shining appearance . . . and are accompanied with an erratic fever, chills, nausea, and heartburn." Allusions to perhaps bowel or lung endometriosis are also evident in the observation that "sometimes the menses are vicariously discharged by vomiting or stool; more commonly is the case with virgins than with married women..."

Uterine adhesions and ulcers. In the chapter "On the Nature of Women," we learn that the Hippocratics were also familiar with uterine adhesions. As the translator of these texts explained, they advised that "in case of adhesions between the uterus and other parts, indurations, suppuration of the womb, and ulcers, sometimes arise, or discharges which prove fatal if not attended to; fomentations of urine are among the measures recommended. The usual effect of this state is said

FIGURE 5



Lytta vesicatoria, known in modern times as the aphrodisiac Spanish fly, was one of many pharmaceuticals prescribed in the Hippocratic Corpus for treating menstrual disorders and infertility. (Reproduced courtesy of Christophe Franco, <http://en.wikipedia.org/wiki/File:Lytta-vesicatoria.jpg>.)

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to be sterility" (16). Some of these translations are still the subject of heated academic debates, particularly the term "hysterical paroxysms." Yet based on the textual evidence in its entirety, it is at least reasonable to surmise that these Hippocratic physicians may have been encountering endometriosis.

Medical therapies. The types of therapeutic options available were generally ingestible concoctions, fumigants, or suppositories that contained such substances as the urine of men or bulls, tar water, chaste tree (*Vitis agnuscastus*), pomegranates, cantharides, or castor oil (Figs. 4–6). In analyzing the histories of these individual substances, we came across some surprising results. The medicinal usage of cantharides, for example, has an especially colorful history; although it is actually derived from dried beetles, throughout history it came to be known as the infamous aphrodisiac "Spanish fly."

Pomegranates and chaste tree also were deployed for centuries as contraceptives and treatments for menstrual disorders. Known as *shiliu* in Chinese, the pomegranate has been traditionally viewed in China as a source and symbol of fertility (18). Recent studies have even begun to analyze its purported antiproliferative and antiaromatase properties (19).

In contrast, the pine resin-derived nostrum known as tar water was practically incompatible with life (21). The same foul substance Charles Dickens's character Pip was forced to ingest as punishment, tar water was considered by the Hippocratics as so effective (or so odious) that women of antiquity were warned they would be "barren forever" if they ingested it (20, 21). Fragments of this belief appear to have been handed down over time because today some veterinarian studies have shown pine extracts to exert modest anti-fertility effects in animal models (22, 23).

FIGURE 6



Recent studies have begun to analyze the purported antiproliferative and antiaromatase properties of pomegranates, prescribed for fertility and menstrual disorders in both Hippocratic Medicine and ancient Chinese medicine. (Reproduced courtesy of Benjamin Trovato, <http://en.wikipedia.org/wiki/File:PomegranateChina.jpg>.)

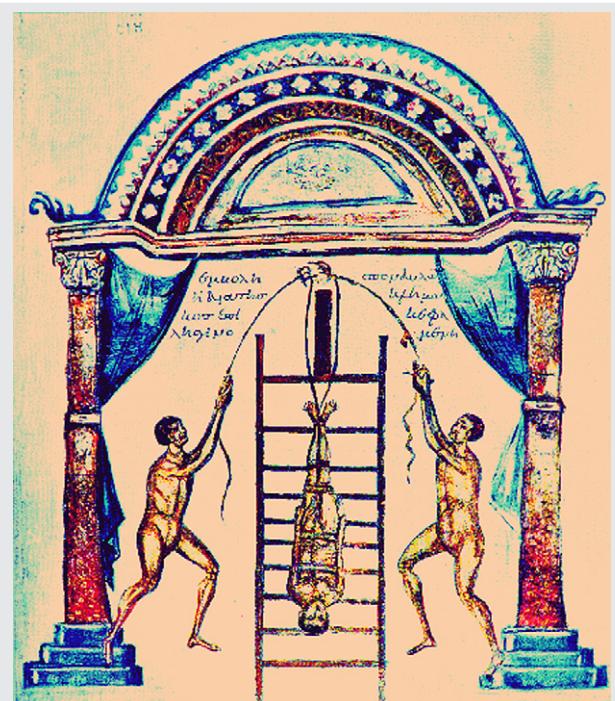
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As for the use of urine for medicinal purposes, in modern gynecology we are no doubt familiar with the use of pregnant mare urine extracts as Premarin's main ingredient. What is less clear is whether the ancients would have been capable of extracting similar hormone-disrupting constituents from the urine of bulls or men. The literature provides few examples of well-designed, peer-reviewed studies in humans, but several animal studies do suggest that bull urine can exert anti-estrogenic properties in mice (24).

Other more inventive therapies were explored as well. One of the most unusual therapies was the practice of succession. Designed as a mechanical means for repositioning the uterus, a session of succussion involved tying the patient to a ladder, which would then be turned upside down and shaken up and down until the womb returned to its rightful place (25) (Fig. 7). In this case, visibly prolapsed uteri were most likely the intended target, making the practice infinitely more comprehensible from a modern standpoint.

Admittedly our analyses of ancient pharmacology are speculative at best, given the absence of high-quality evidence to support these theories. As Renckens argues so effectively in his article about alternative treatments in reproductive medicine, much of the existing evidence appears to be

FIGURE 7



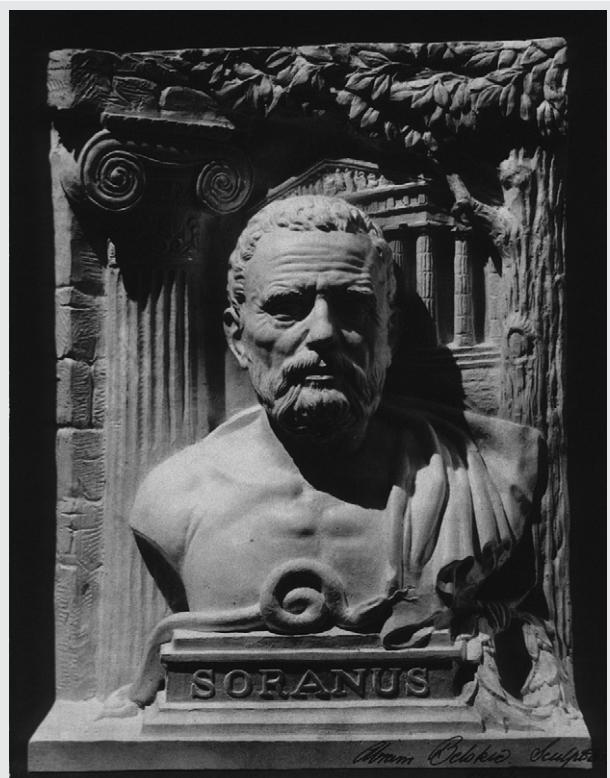
Uterine suffocation, vaginal prolapse, and other gynecologic conditions were sometimes treated with succussion, the ancient Greek practice in which patients are bound to a ladder, turned upside down, and shaken vigorously, with the idea being that the uterus would be shaken back into its proper position. (Reproduced courtesy of BioMed Central Ltd and SpringerImages. Scoliosis 2009;4:6. Image from the illustrated comments of Apollonius of Kitium on the Hippocratic treatise *On Articulations*. Bibliotheca Medica Laurenziana, Florence.)

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woefully inadequate (26). Even so, further investigations may be warranted. As reported in a recent editorial by endometriosis expert, Dr. Linda Giudice (2), preliminary studies suggest that: "Chinese herbal therapies have exhibited antiproliferative, antinociceptive, and prosedative properties, as well as anti-inflammatory actions, antioxidant characteristics, suppression of COX-2 and cytokines, and mechanisms involved in the cytokine response, such as inhibition of NF-KB" (19, 22–24, 27).

"Extremest anguish." Although we do not usually think of the acclaimed philosopher Plato (375 BC) as being involved in medicine, this did not stop him from expressing his own opinions about gynecologic disorders. In fact, Plato was actually among the first to mention the extreme pain that women suffered as a result *suffocation of the womb*. He explained that the disorder is triggered when "the womb remains barren too long after puberty, is distressed and sorely disturbed, and, straying about the body and cutting off the passages of breath, it impedes respiration and brings the sufferer into the extremest anguish and provokes all manner of illness besides" (28, 29).

By the time Roman scholar Pliny the Elder (23–79 AD) began reporting on suffocation of the womb, several new

FIGURE 8

Soranus of Ephesus (circa 98–138 AD) described many endometriosis-like symptoms, including menstrual disorders that led to infertility and cases of uterine suffocation that caused violent uterine contractions. (Reproduced courtesy of the U.S. National Library of Medicine; Portrait no. 6313-A.)

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observations had been added to the diagnostic profile. Included among these was an account of the disorder's peculiar ability to reduce women to some sort of semiconscious state, lying "as if dead for seven days" (7).

Soranus

Inflammation of the uterus. About a century later, Soranus (ca. 98–138 AD) reported similar findings, but offered critical new clinical insights when he explained that women were falling unconscious as a result of the disorder's characteristic violent uterine contractions, which Soranus observed could manifest in either chronic or acute forms (7) (Fig. 8). To explain these symptoms, Soranus departed from tradition by becoming the first to suggest inflammation of the uterus as part of his radical new theory about the origins of suffocation of the womb.

More than just an essential new theoretical framework, Soranus's detailed macroscopic knowledge of these and other uterine pathologies supports the idea that human autopsies may have informed his views. Although Soranus admitted to having performed autopsies, they would have been considered highly unorthodox and somewhat risky for the times. Indeed, unassuming as this revelation may seem, Soranus's

accurate anatomic descriptions of the uterus actually call into question other historical accounts that claim human dissections had been all but abandoned by that time.

As for those susceptible to uterine disorders, Soranus reports that the conventional views of his day were that "many women, menstruating with difficulty and pain because of a long widowhood, have menstruated freely after marrying again," with marriage implying that the conception curative would soon follow (15, 30). In another chapter Soranus revisits the topic from a different angle, explaining again that many physicians view pregnancy as healthful because it was believed that "some women, menstruating with difficulty and suffering uterine pressure, have been freed of their troubles after pregnancy" (15).

Other symptoms. Investigating the other symptoms ascribed over the years to suffocation of the womb is a complicated matter. Yet after careful evaluation of research by several scholars specializing in women's ancient medicine, we rounded up all the disparate descriptive evidence and found that convulsions, epileptic-like "fits," abdominal pain, nausea, vomiting, digestive disorders, gritting of the teeth, excessive perspiration, palpitations, ashen skin, and the appearance of lumps near the abdominal sidewalls were all among the most commonly cited symptoms (5, 9, 10, 12). The observation of lumps appearing to the side of the uterus was a symptom that piqued our interest considerably, but several insurmountable translational ambiguities made it quite difficult to extract any additional insight about this particular description.

Convulsive symptoms as part of gynecologic medicine represent another intriguing challenge to our modern conceptions of diagnostic criteria. As it turned out, the original meaning of hysterical convulsions during this era generally referred to women falling to the ground, doubled over into a fetal position. Such descriptions correspond well to the images found in the MS Ashmole 399 drawings, and they could very easily be describing a response to acute abdominal pain (5).

Celsus

Reports of women suffering from convulsions and/or epileptic-like symptoms in association with suffocation of the womb continued to be mentioned by the next generation of medical scientists. Roman scholar Celsus described women suffering from "violent" illness coming from the womb, who fall down as if suffering from epilepsy. However, "rather than exhibiting the normal signs associated with that disorder, such as foaming or eyes rolling back, instead [they] lie down as if in sleep" (Fig. 9).

Of particular note, Celsus reports that, in some cases, the disease returned frequently and that "some women suffer from this their entire lives" (4, 7, 29). This specific observation proves especially relevant in view of our current historical study of endometriosis, but it was Celsus's reports alluding to violent fits of the womb that seemed to attract the most attention throughout the ages. Some scholars even have suggested that Celsus's comment was the original source behind the term "hysteric fits."

Despite both the Hippocrates' and Celsus's unambiguous explications of a gynecologic disorder distinct from regular

FIGURE 9



Second-century Greek encyclopedist Celsus (circa 25 BC—circa 50), described cases of a violent uterine illness that caused women to fall to the ground, convulsing and fainting from attacks of acute pain. (Reproduced courtesy of the U.S. National Library of Medicine, Portrait No. B04927, titled "A. C. Celse" by Pierre Roch Vigneron, Paris, 1865.)

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epilepsy, over the years the boundaries separating the two disorders became more diffuse, leading to a continued conflation of epileptic fits with hysterical fits. This practice would later figure into a series of rather curious theories that developed about women and illness in subsequent eras (31).

Dioscorides

Just a few decades after Celsus, one of the most celebrated physicians of Late Antiquity emerged, the Greek physician Pedanius Dioscorides. His *De Materia Medica* (ca. 77 AD) stood for ages as one of the most influential ancient treatises in Western medicine, “the chief source for herbalists of all nations” and compulsory reading in medical education for more than 15 centuries (32, 33) (Fig. 10). Dioscorides’s text differs from others reviewed so far in that it is organized in an encyclopedic format. Enumerating nearly 1,000 pharmacologic compounds in a descriptive manner, though without commentary on presumed etiologies, the encyclopedic organization can be disorienting. However, it reflects the best pharmacologic science of the day, offering an informative narrative about 1st century medical practices and furnishing some insight into gynecologic disorders as they were understood and treated nearly 2000 years ago.

Pain and collapse. Though the theoretical continuity concerning uterine suffocation is clearly evident in *De Materia*

FIGURE 10



Simplicium vires obscura nocte reuelas,
Describis forma, quaque colore suo.
Afferis hanc partem diuinè, externaque vana
Ne nos decipient, te monitore, patent.

E 2

In Greek physician Pedanius Dioscorides’s acclaimed work, *De materia medica* (circa 77 AD), uterine suffocation is described as a menstrual disorder with many parallels to endometriosis. (Reproduced courtesy of the U.S. National Library of Medicine, Portrait No. 1550.3, anonymous work titled "Dioscorides Pedanius of Anazarbos".)

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Medica, Dioscorides still provides fresh new perspectives about menstrual dysfunction and a uterine disorder named “strangulation of the uterus,” which exhibits the same tendency as suffocation of the uterus to render women unconscious. Like his predecessors, Dioscorides describes a disorder that causes women to suddenly fall down, apparently hovering either in some sort of quasi-conscious state or in an otherwise diminished condition that renders them unable to raise themselves to a standing position. As noted before, many of these signs could signify responses to acute attacks of pain. That the afflicted women are lying down in some fashion can be established by a prescription for shellfish shells that is believed to help “rayse up such women as are troubled with strangulatus uteri, & such as have ye falling sicknesses” (32).

Medication. Views about menstrual disorders were surprisingly advanced, with Dioscorides clearly acknowledging menstrual pain as an organic, pathologic condition requiring medication, something that even some 21st-century physicians fail to recognize at times. As for medicinal substances, the inventory abounds with prescriptions for such items as

bed bugs, brains, human urine, and other decidedly indelectable morsels. We will spare the reader these details and offer instead excerpts of the least odious medical therapies, one of which is a dysmenorrhea treatment described as “the horne of an Hart being burnt & washt, if it be dranck the quantitie of twoe spoonfuls . . . It is good also for women troubled with ye flux (of ye wombe) being given with somme liquor fitting for that grief” (32).

As for Dioscorides’s references to “women troubled with ye flux”, naturally many so-called troubles aside from dysmenorrhea could be correlated with menstruation, such as amenorrhea, anemia, or menorrhagia. However, based on evidence derived from other passages, it appears that Dioscorides was likely referring specifically to menstrual pain and the other symptoms associated with strangulation of the uterus. Further evidence substantiating this view can be inferred by the fact that those other menstrual disorders were assigned their own distinctive remedies.

Menstruation suppression. Dioscorides’s work is remarkable for another reason, as it appears to be the first of its era to mention in unequivocal terms medications designed to suppress menstruation. Like the Hippocrates 500 years earlier, it demonstrates that Dioscorides recognized menorrhagia not only as a distinct menstrual variation but as a potentially pathologic disorder in need of medical intervention (32). For this ailment, Dioscorides suggested that the brain of a hare, “being dranck after three dayes after ye menstrual courses,” is reported to cause sterility; likewise, it stops the “flux of ye wombe and of the belly” (30, 32).

This was a particularly interesting discovery because many historians specializing in women’s medicine of antiquity have reported nearly exclusively on medicants prescribed for *inducing* menstruation, putatively for cases of amenorrhea but that many believe were actually intended as abortive agents. Without this critical insight offered by Dioscorides, the ancient world, as interpreted in modern times, would appear to be one either nearly devoid of any menstrual disorders other than amenorrhea or rife with epidemic abortive practices.

As mentioned before, naturally a retrospective evaluation of the efficacy of these substances is impossible. In any case, the majority of modern biochemical studies that attempted to measure the efficacy of ancient pharmacologic substances have proved inconclusive at best. However, a few studies using animal or *in vitro* models have pointed to possible minute traces of hormone-disrupting agents in medicants believed to have been used in antiquity (34–37).

Regarding Dioscorides’s prescription for the horn of a hart to treat menstrual ailments, our research found that “hart” was the British name for a male stag of the red deer species common throughout Europe and Asia Minor (38). In traditional Chinese medicine, red deer antler has been used to treat male impotence and gynecologic disorders in women (2). A recent animal study from an alternative medicine journal even suggests that some antler velvet products may “produce anti-inflammatory compounds that assist in the regulation of prostaglandins” (39).

Another modern study found that, of several medicinal herbs believed to have been used since antiquity, “20 showed strong and 10 weak anti-oestrogenic activity.” Among those found to have strong antiestrogenic activity was *prunella vulgaris* (commonly called Self-heal, or *Xiaoakuao* in Mandarin Chinese), an herb used in Hippocratic and traditional Chinese medicine for centuries to treat dysmenorrhea (34, 35). Whatever the case, it is clear many of these ancient beliefs survived the journey through time, as red deer antler and other products touting hormone-altering properties are still offered today in alternative medicine.

Galen

Violent uterine contractions and inflamed ligaments. Practicing medicine about a century or so after Dioscorides, Claudius Galen of Pergamon (129–216 AD) had at his disposal more than 500 years of medical heritage concerning suffocation of the womb, a disease entity with a symptom profile that had remained stable for centuries (7) (Fig. 11). Although convulsions and fits continued to be the headline symptoms, Galen offered fresh new insights, including one of the clearest descriptions of symptoms suggestive of adhesions and/or endometriosis-infiltrated ligaments.

Galen provided these new clinical symptoms as part of his proposed theory of pathogenesis, which suggested that suffocation of the womb was triggered when the membranes that anchor the uterus in place became engorged as the result of excessive menstrual blood. Galen believed that this excessive

FIGURE 11



9. GALEN—Experimenter in Compounding
(131–201 A.D.)

Claudius Galen of Pergamon (129–216 ACE), Roman physician of Greek heritage, described a gynecologic disorder that produced violent and painful uterine contractions and swollen and inflamed ligaments. (Reproduced courtesy of the U.S. National Library of Medicine, Call No. WZ 348 C25, no. 51 sol. Painting by Robert A. Thom [1952] titled “9. Galen—Experimenter in Compounding” [131–201 AD].)

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pressure on the ligaments caused the membranes to thicken and stretch with tension, which in turn pulled the uterus into contorted positions. In turn, Galen surmised that these contortions were causing the painful and violent uterine contractions, lacerations, and inflammation from the repeated physical friction (7).

Aretaeus concurrence. Aretaeus, a contemporary of Galen's, provided nearly identical descriptions, suggesting that the uterus's membranes underwent morphologic changes during menstruation, resulting in distending or contracting motions "like the sails of a ship" (7). Allusions to violent symptoms and instances of unexpected deaths were beginning to be mentioned with greater frequency by this time. Aretaeus went on to describe suffocation of the womb as a condition triggered "when [the] womb moves upwards" and "presses violently on intestines"; it causes "exhaustion, loss of control of the knees, dizziness, . . . her limbs are weakened," and "it resembles epilepsy" (30, 40). Expressing sentiments with uncanny parallels to modern concerns about productivity, Aretaeus even notes that, when the disorder is severe, there will be "hesitation in doing her tasks" (30, 40). For those attacks that have an acute onset, Aretaeus advised that it was essential for a physician to be summoned quickly to prevent death, an outcome that Aretaeus considered unexpected and difficult to believe as the woman just moments before had not appeared so gravely ill (29).

Psychological factors. In what may have been the first fateful moments when psychological elements began fusing more consistently with gynecology, Galen contributed another original if notorious observation. He made what appears to be one of the most explicit references associating uterine disorders with mental illness when he hypothesized that young widows, still viewed as particularly prone to uterine distress, could be "driven to madness as a result of their loss of sexual fulfillment" (41). Although there were somewhat similar allusions made in earlier works, including the Hippocratic texts, Galen elaborated on these notions with such authority that his work may have been the catalyzing force responsible for ushering in a disturbing new era in women's medicine, when gynecologic ailments first began to be conceptualized as psychological in nature. As subtle as this theoretical shift may at first appear, its repercussions would prove boundless, rippling through the very core of social and scientific beliefs for centuries.

Final Thoughts

With young girls who had begun menstruating considered particularly vulnerable to gynecologic dysfunctions and pregnancy considered a possible cure, Western medical authorities throughout Classical and Late Antiquity established the appropriate age of marriage as sometime within a year of menstruation, which was estimated to be approximately the ages of 14 to 15 during that period (4). Had some of these cases actually been early observations of endometriosis, conception as a potential cure would have appeared quite efficacious. After all, women during this era usually began conceiving in their teens and raised an average of five to six children, though probably experienced even more pregnancies due to

FIGURE 12



The reintroduction of supernatural disease etiologies in Western medicine occurred most dramatically during the Middle Ages, when pandemics like the plague wiped out an estimated 30% to 60% of Europe's population. It was during this time that uterine suffocation began to be misconstrued as the work of witchcraft or demonic possession. (Reproduced with permission of the British Library Board (C), Record Number: c6541-07, Shelfmark: Royal 6 E. VI; Page Folio Number: f.301: Plague victims etching by James le Palmer, titled "Omne Bonum.")

Nezhat. Endometriosis in history. Fertil Steril 2012.

the high rate of infant and child mortality. Meanwhile, with breastfeeding lasting up to the age of 2 years for each child, these culturally normative behaviors could have functioned as a natural suppressant of the disorder (if it was endometriosis). Therefore, many successive years of childbearing could have indeed made it appear to have been cured (4).

When one considers that suffocation/strangulation of the womb was also believed to be triggered by what was called "spoiled menstrual blood" or "spoiled seed"—in other words, another association with menstruation—then the notion that these ancient physicians may have been witnessing some cases of endometriosis is all the more plausible (5).

Translation ambiguity. Compelling though these historical vignettes may be, we are obliged to mention the many inevitable shortcomings of these investigations. To begin with, it is well known that analyzing ancient texts with the intention of importing meaning back into a modern context is an endeavor fraught with unavoidable translational and cultural misinterpretations. Thus, the resulting analyses may be more conjectural than conclusive. That most English translations available to us today have undergone a linguistic journey from Greek to Syriac to Arabic to Latin to English is just one example of how easily the original meanings could have been distorted. Complicating matters further is the fact that many of the ancient texts were derivative works, passed down as nearly verbatim transcriptions of previous publications. This means that one can never be entirely certain

whether ancient authors were reporting their own independently obtained observations or were simply presenting the clinical experiences of others as their own. Of course, today such practices are considered the ultimate in scientific sacrilege.

Naturally, the various symptoms described could also apply to dozens of other disorders. The contorting spasms, for example, could have been caused by tetanus, thought to have been somewhat prevalent in those time frames and geographies (30). As admitted from the outset, without histopathologic confirmations, concrete conclusions cannot be made. Yet when viewing the textual evidence in its totality, it is fair to assume that at least some of these cases could have been unwitting early descriptions of endometriosis, even despite some areas of ambiguity. Overall, the preponderance of evidence gives reason for pause. It is clear that the *hysterikos* family of disorders was to some degree a veritable diagnostic junk drawer. However, the continuity of core assumptions—such as viewing pregnancy as a potential cure for painful menstruation—which occurred in concert with the equally suggestive symptoms of vomiting, “violent pain coming from the womb,” and painful, blood-filled membranes serves as credible evidence that we are witnessing the formative outlines of a distinct disease paradigm edging into existence (7).

THE MIDDLE AGES

As epochs go, the European medieval era—the so-called Dark Ages—is often conceptualized as though it were one vast expanse of scientific and cultural stagnation. Considering that Europe was ravaged by a succession of falling empires,

wars, plagues, and pestilence, it is easy to see how such impressions were formed, especially when compared with the grand luminosity that had been Greco-Roman medicine and that was now evident in the scientific renaissances that were occurring in Asian centers (42) (Figs. 12 and 13). Indeed, progress in European medicine seemed to grind to a screeching halt. Some experts have characterized this stagnation as a period spanning 900 years, from about the 5th through 13th centuries.

Early Middle Ages (5th to 11th centuries AD)

Supernatural versus superscientific. In the apparent scientific void of the Middle Ages, theological and supernatural influences returned to the forefront of the popular imagination. Such beliefs competed alongside and at times edged out much of the hard-won scientific heritage that had been so meticulously synthesized throughout antiquity. It did not help that such revered scholars as Lactantius (4th AD) questioned the need for any further scientific inquiry, asking, “What purpose does knowledge serve . . . what blessing is there for me if I should know where the Nile rises, or whatever else under the heavens the ‘scientists’ rave about?” (42). In such an environment, miraculous cures and demonic possessions alike became plausible theories to explain health and sickness. As one historian described it, “illness metaphors were those of sin” or were invoked “as a salutary tool to scare people straight, with visions of hell dragged out for special effect” (42) (Fig. 14).

As we will see, these developments somehow insinuated themselves into the outer edges of women’s medicine, becoming the theoretical backdrop from which both social and

FIGURE 13



The widespread devastation caused by the plague was followed by unprecedented religious, social, and economic upheavals that profoundly affected the course of European history. (Reproduced courtesy of the U.S. National Library of Medicine, “Epidemics Die Pest, Plague scene” [Plague victims in city square], Call No. WA 100 C25 No. 6 box 12 sub.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

FIGURE 14



Throughout the Middle Ages many continued to view hysteria or other misunderstood disorders as signs of witchcraft or demonic possession, a charge that would have subjected women to a range of punishments and/or treatments, including executions, exile, or, as is depicted in this etching, exorcisms by a religious leader. (Reproduced courtesy of the U.S. National Library of Medicine. A priest healing a possessed woman, from *Histoire prodigieuse et memorables, extraictes de plusieurs fameux aureurs, Grecs, & Latins*, artist Pierre Boaistuau, ca. 1566. Paris: Gabriel Buon, 1598, p. 1272, Record UI No. 101435552.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

scientific views concerning women and illness were sometimes formed. These distinct ideologic shifts were exemplified well by the views of Greek physician Paul of Aegina (625–690 AD), who suggested that suffocation of the womb was an illness that usually afflicted “lascivious” women, or “those who use drugs to prevent conception” (7).

Almost as if in lockstep with the changing attitudes about sickness, treatments appeared to become noticeably harsher. For example, Oribasius (325–397 AD) suggested a shouting therapy as a means for reviving those who had passed out from suffocation of the womb (7). While the shouting treatment in itself is a powerful testament to the ideologic trends on the rise, it also demonstrates that uterine suffocation was still causing women to pass out, the same observation made by the Hippocrates nearly 900 years earlier.

Exotic notions such as shouting therapy and hungry lascivious wombs naturally have taken center stage in historical reviews, but it is important to note that medieval physicians did achieve several important clinical discoveries. For example, under the broad category of uterine suffocation or hysterical convulsions, Paul of Aegina did describe other potential symptoms such as abscesses or ulcers of the uterus that could burst open: “when the ulcer is spreading, the discharge is fetid, black, attended with great pains, and other symptoms of inflammation” (21).

Aëtius of Amida. Other achievements made it clear that all was not lost in terms of medical progress. In fact, two of the most crucial conceptual breakthroughs to date were achieved at this time by Aëtius of Amida (502–575 AD), who became one

of the first to suggest more explicitly that suffocation of the womb was predominantly triggered by menstruation. Similar to Galen, Aëtius surmised that the convulsive symptoms observed in those with suffocation of the womb were actually the result of painful uterine contractions. As for the root cause of such violent uterine contractions, Aëtius suggested they occurred as a result of the “cooling of the uterus during menstruation” (29).

Alas, such breathtaking breakthroughs were often followed by spectacular reversals. Within a few centuries of Aëtius, a most unfortunate addition to treatment practices was introduced: choking the necks of women suffering from uterine suffocation. This “therapy” was believed to induce the womb to return to its rightful place (7). Indeed, such discordant developments—characterized by soaring highs and perilous lows—would epitomize the next several hundred years of European medicine.

China and the Near East. While developmental dissonance ensued in Europe, Asian countries stood in contrast as flourishing centers of medical and scientific innovation. Many historians have described Babylon and China of the 9th century as leading the world intellectually. It was in these Asian centers that the hospital was invented, the concept of zero was refined, and *al-jabr*—algebra—was developed to exquisite perfection (42) (Figs. 15 and 16).

Arabic, Persian, and Muslim science. Arabic Medicine, which many believe is more correctly described as Muslim medicine, was especially progressive. Its cultural emphasis on scholarship meant that Muslim scholars were among the

FIGURE 15

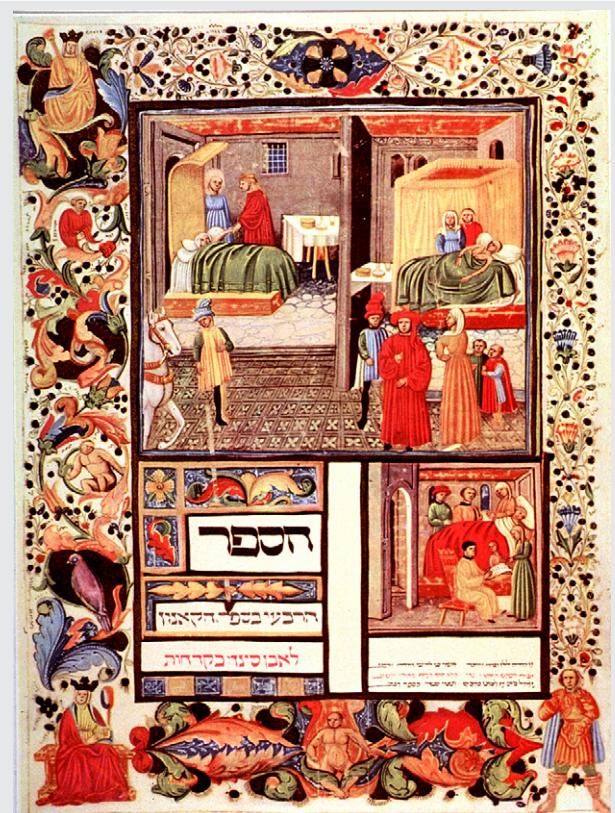


While European centers were descending into the so-called dark ages, Asian and Middle Eastern centers of science and medicine were on the ascent. (Reproduced with permission of the Wellcome Library, London. Image no. L0034735, Woodcut from *Tong ren shu xue zhen jiu tu jing* [Illustrated Manual of Acupoints on the Bronze Man] by Wang Weiyi, published in 1443; Illustrating methods of locating the *gaohuang* [vital region] point. Library of Zhongguo zhongyi yanjiu yuan [China Academy for Traditional Chinese Medicine].)

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first to rediscover and commission the translation of thousands of Greek and Roman medical texts (30), which would prove a crucial factor in the rebirth of scientific inquiry that later revolutionized European societies. Physicians played a vital role in these translational efforts, including three of the most esteemed of the era: Persian physicians Haly Abbas (?–994), Avicenna (980–1037), and Rhazes (865–925). As many of the medical theories arising out of this era shared a great deal in common with those promulgated by the Greco-Roman scholars of antiquity, few new insights into uterine suffocation were made. However, this new generation of medical scientists did isolate and discover dozens of new medicinals that were unknown to Europeans, including colchicum, camphor, senna, nutmeg, cloves, and alcohol-based concoctions, all of which would become essential new

FIGURE 16



Textbook pages from acclaimed third-century Persian physician, Ali al-Husayn ibn Sina, better known in the west as Avicenna (980–1037). (Reproduced courtesy of U.S. National Library of Medicine, call no. WZ 56 C24 no. 3-d box 21 sub.)

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pharmaceuticals in Western medicine throughout and beyond the Middle Ages (43).

Another achievement of note was made by Avicenna, who reconceptualized pain as a biologic condition that was completely at odds with nature and without any conceivable medical benefit (43). In the wake of these influential new ideas, many conventional views about pain were called into question, especially those that assumed it to be beneficial for hastening healing or worse, a karmic payback for past misdeeds. Although these theoretical musings about pain may seem peripheral to the story of endometriosis, such efforts to decode its biological basis would eventually prove to be of central importance. Overall, with their abiding commitment to scholarship and scientific investigation, Muslim medical practitioners proved to be the critical catalyst for reinvigorating medicine in Asian centers and eventually throughout Europe.

High Middle Ages (12th to 13th centuries AD)

12th century. One of the earliest European centers to symbolize this scientific reawakening was Salerno, Italy. It was from Salerno that one of the era's best-known medieval

gynecology manuals was published by the female physician Trotula (Fig. 17). Although the Trotulan text offers many unique insights into 12th century medicine, what is most impressive is that its portrayals of uterine suffocation continue to be essentially identical to those described by the Hippocratics nearly 15 centuries earlier. For example, as an extension perhaps to the Hippocratic experiments with bull urine, the Trotulan author mentions that an especially effective treatment for suffocation of the womb called for: “a powder be made of the testicles of a fox or a kid and that this be injected (into the vagina) by means of a tampon” (44).

As the renaissance spirit of Salerno suggested, the trend toward scientific medicine was clearly on the rise. Even so, saints, miraculous cures, and demonology continued to figure into the story of medicine. A curious amalgam of healing practices emerged, with the afflicted often seeking succor through traditional medical channels as well as through supplication to saints or designated temples of healing. It was within this milieu, when medicine reflected a peculiar mix of empirical, magical, and theologic elements, that the often bizarre pain behaviors of those seeking divine relief at public temples were sometimes construed as instances of demonic

possession. Outlandish as these superstitions seem to our modern sensibilities, they were surprisingly enduring, persisting for several centuries with devastating consequences for women in particular (43).

THE RENAISSANCE: 16TH CENTURY

While not the most conducive environment for scientific progress, nevertheless by the 16th century a new generation of medical pioneers achieved important milestones. Henri de Mondeville, called the Father of French surgery and surgeon to the king of France, challenged the long-standing belief that wounds needed to undergo suppuration in order to heal (43). And what would one day prove beneficial to the story of endometriosis especially, by about 1250 autopsies had been reintroduced as a regular part of medical education in many parts of Europe, particularly Italy, France, and Germany (30).

Challenging Ancient Anatomic Assumptions

Organized university medicine also returned to Europe, with Padua and Bologna now among the era's leading centers of science and medicine. Within a few hundred years, the results of these educational innovations were clearly evident during the golden era of anatomy, when such pioneering anatomists as Vesalius and Gabriele Falloppio finally began challenging the edifices of ancient anatomic assumptions. Crashing sounds of an empire falling must have been reverberating across Europe as Vesalius sent Galen's five-lobed, blood-making liver and seven-segment sternums back to the midden heap of history (Figs. 18 and 19). There is even evidence to suggest that Vesalius may have studied suffocation of the womb (by this time also called hysterical fits). As one storyteller recounted,

Vesalius, it is well known, had commenced dissecting a woman who had apparently died of an hysterical fit, when he perceived, on making the first incision, by her movements and cries, that she was still alive. The circumstance rendered him so odious in the sight of his fellow-countrymen, that he was forced to quit his native country and being shipwrecked on the coast of Spain, died of hunger (45).

Considering that many of Vesalius's own professors denounced him as “a madman whose pestilential teachings were poisoning Europe,” it is possible that this story is more apocryphal than credible (46). Of course, if true, it would surely have to count as one of the most spectacular misdiagnoses in history.

Medical bloodletting. Even with Vesalius's purported monumental misstep nearly stealing the scene, it could not be denied that the Renaissance had indeed arrived. Some of the most dramatic religious, social, and scientific reforms in history occurred during this time, when questioning orthodoxy became a nearly universal mandate. Even patients, those hitherto strangely anonymous and presumed passive receptors of medicine, began to call into question traditional medical practices. This trend can be observed through the laments of

FIGURE 17



A page from a 12th century work attributed to Trotula, one of the most celebrated female physicians of ancient times, whose prescriptions for uterine suffocation included vaginal suppositories composed of ground goat gonads, among other ingredients. (Reproduced with permission of Wellcome Library, London.)

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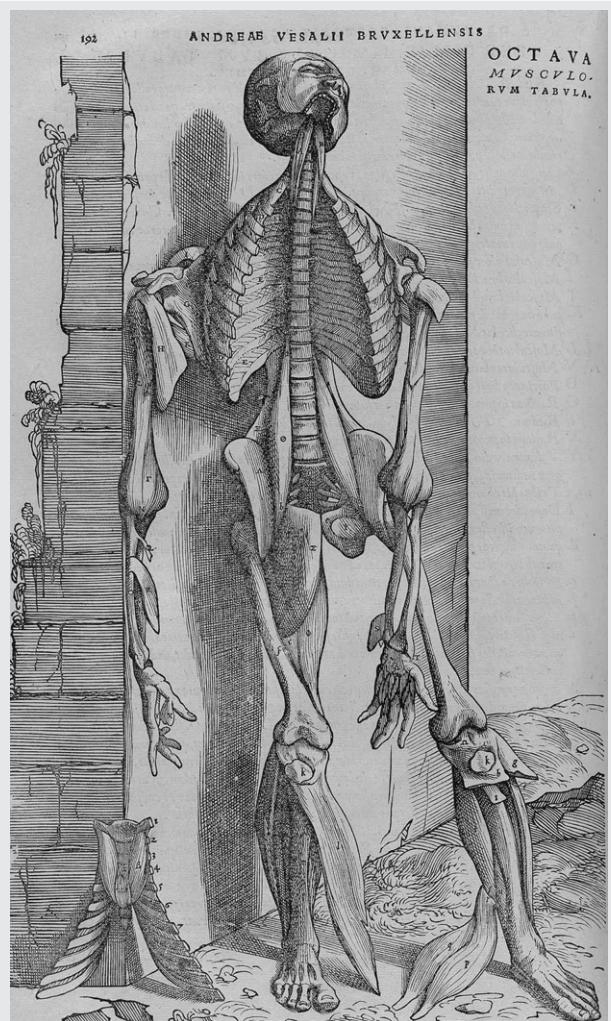
FIGURE 18

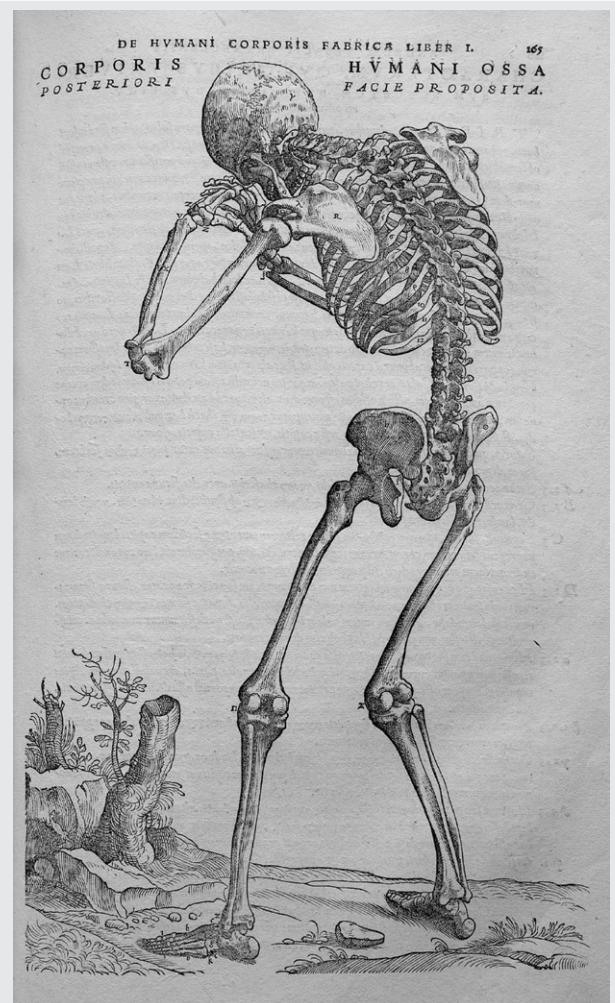
Image from Andreas Vesalius's groundbreaking anatomy work, *De Humani Corporis Fabrica* (1543), which shattered thousands of years of assumptions about human anatomy. (Reproduced courtesy of the U.S. National Library of Medicine. Woodcut by Stephen van Calcar and the Workshop of Titian, Basel, 1543.)

Nezhat. Endometriosis in history. *Fertil Steril* 2012.

one 16th-century physician, who wrote, “I am astonished by some, who will more willingly take twenty different drugs than endure one bloodletting that is necessary, given its great ease and simplicity. Drugs . . . [have] considerable drawbacks, not to mention the nausea, the upset stomach, and the severe intestinal cramps they usually bring about” (43).

Ambroise Paré

As for progress toward understanding suffocation of the womb, by the 16th century some of the era’s most renowned medical authorities, such as William Harvey, Paracelsus, and Ambroise Paré, were explaining women’s illnesses in etiologic terms that traced their heritage back to disease categories in existence for over 2,000 years. By this time,

FIGURE 19

Another image from Vesalius's *De Humani Corporis Fabrica*. (Reproduced courtesy of the U.S. National Library of Medicine; Call No. QS 11 C27 box 1 sub, Vesalius, Andreas, *De humani corporis fabrica*, p. 165 [Liber I], Basileae, Ex officina Joannis Oporini, 1543.) Nezhat. Endometriosis in history. *Fertil Steril* 2012.

suffocation/strangulation of the womb was also being referred to as hysteria, hysterik fits, or dysregulated vapors (vapours), which was a word used to connote menstruation.

In terms of women viewed as particularly susceptible to suffocation/strangulation of the womb, Ambroise Paré (1510–1590), France’s leading physician of the era and surgeon to four successive kings, offered essentially identical explanations to those found in the Hippocratic texts. However, Paré suggested that it was not just virgins and widows, but also married women who abstained from sexual relations who were most often afflicted with the disorder (5, 47, 48).

Like Aetius from several centuries earlier, Paré suggested that menstrual vapors caused strangulation of the womb. Describing the attendant symptoms of menstrual vapors, Paré observed that women suffer from “strangulation of the womb . . . swlon or puffed up by reason of access of gross vapors and humors,” leaving women “snatched as it were by

a convulsive smotherion” (5). The swollen uterus that Paré describes could correspond to general inflammation but also to symptoms of adenomyosis. Paré also noted that women suffering from suffocation/strangulation of the womb were in so much agony that they believed themselves to be “near death” (29).

Paré’s observation that menstruation triggered the disorder again demonstrates that for centuries physicians had consistently observed several of the signature markings of endometriosis. Like Galen and Celsus, Paré also introduced the critical observation that the uterine ligaments were somehow involved in the illness, noting that the uterine “vessels and ligaments [are] distended with fullness” (29).

17TH CENTURY

With medicine still hovering at the threshold between the old and the new, explanations of illness again reached an improbable apex. The pain symptoms associated with suffocation/strangulation of the womb began to be construed more frequently as a sign of demonic possession, madness, or witchcraft. However, illness depicted within a demonologic framework was not actually new. Ancient texts from various cultures had attributed demonic or otherwise supernatural causes to the condition of epilepsy especially (30). Additionally, the idea that pain could mimic signs of madness had been considered throughout the ages, with many allusions made in medieval times of people driven mad by pain. At one point, pain was even called the “originator of madness” (7).

Organic, Mental, or Supernatural?

Demonic possession. The convergence of these various theoretical elements found expression in Hendrick Hondius’s engraving from 1642 called “Pilgrimage of the Epileptics to the Church at Molenbeek” (sometimes thought to be a depiction of dancing mania) (Fig. 20). The engraving shows a pilgrimage of women suffering from hysteria-associated epileptic-like symptoms on their annual journey to the renowned healing shrine of St. Vitus, viewed since “pagan times” as a source of miraculous cures, particularly for epileptic disorders. Legend had it that if one were to jump over the bridge leading up to the shrine, the sufferer would be free of illness for 1 year. However, by the time of Hondius’s engraving, the hystericoepileptic systems of the female supplicants were occasionally construed as a sign of a mass outbreak of either dancing mania or demonic possession, which is why Hondius portrays the afflicted women being forcibly thrown off the bridge and into the river below—cold water being the only known cure for such conditions (5, 30, 49–52).

The symptoms of these pilgrim women were said to have been swelling of the abdomen, “pain and dejection, uncontrolled screaming, swooning, convulsive movements . . . after which the victims fell senseless to the ground.” As such, it was not much of a conceptual stretch for even casual observers to interpret these symptoms as related to suffocation/strangulation of the womb (5, 49). We should not be surprised that it was Paracelsus—the man who burned Avicenna’s books in a public bonfire and declared nature to be “the sole origin of diseases”—who raced to the rescue of science by

FIGURE 20



Engraving from 1642 representing folkloric conceptions of women’s illness, including hysteria and other disorders that may have been endometriosis or other gynecologic conditions. (Courtesy of the U.S. National Library of Medicine. Engraving by Hendrick Hondius, titled “Pilgrimage of the Epileptics to the Church at Molenbeek, 1642.”)

Nezhat. Endometriosis in history. *Fertil Steril* 2012.

vehemently rejecting the notion that demonic possession caused this or any other illness. Instead, Paracelsus hypothesized that hysterical convulsions could stem from three possible sources: [1] “imagination,” [2] “sensual desire,” or [3] “corporeal causes” (49).

Of the corporeal causes, Paracelsus insisted that the uterus’s “own elements” could “[turn] on itself,” thereby causing uterine contractions (29). Even though the evidence was scant, these accounts of hystericoepileptic pilgrims would find their way into the history of women’s medicine by way of Sydenham and Charcot, two 19th-century authorities on “hysteria,” who would later cite these stories as proof that the phenomenon of mass hysteria was possible, which in turn supported their hypothesis that hysteria was a psychological condition (49).

Illness as witchcraft. Situated in this peculiar new, culturally specific framework, we can see how vestiges of the original *hysterikos* concept were both transmitted and transformed through time, the subject of endless reinterpretation depending on prevailing cultural influences. Although the concept of demonically induced illness was deeply influenced by folkloric notions of illness, nevertheless popular beliefs do provide important insight into how societies as a whole may

FIGURE 21



Painting from 17th century depicting the devastating consequences of a plague outbreak in Naples, Italy. Allusions to supernatural forces as a causative factor are symbolized by the witches that can be seen flying in the air on brooms. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by D Gargiulio titled "Die Pest in Neapel 1656" [Plague scene in city], Call No. WA 100 C25, No. 4, box 12 sub.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

have viewed women who suffered from symptoms of pain. Considering that these events at St. Vitus's shrine occurred during an era when an estimated 20,000 to 40,000 people were burned alive at the stake for supposedly engaging in witchcraft, then it becomes clear that societal perceptions of illness could even have fatal consequences (Fig. 21).

Nothing exemplifies these shifting narratives of illness better than the unsettling accounts found in the court records of women being convicted for and sometimes tortured and executed as a consequence of their hysterical conditions, a fate permissible under the statutes from England's Witchcraft Act of 1604 (53–56). To trace this unfortunate departure from scientific medicine, the commentary provided by physicians of the era becomes key to understanding the controversies under consideration. At issue was whether hysteria was an organic uterine pathology, a form of mental illness, or the consequence of supernatural events.

The transcripts of a 17th-century witchcraft trial in which Dutch physician Johannes Weyer (also Weir) (1515–1588) was called in as an expert witness provide unique insight into these debates. Effecting tones of overt indignation, Weyer did his best to persuade the court that hysteria was unquestionably an organic condition, a “bodily disease like all other medical conditions” (7). Had there been doubt about whether persecutions figured into the history of women’s medicine, Weyer’s next statement shatters any lingering incertitude. Imploring the courts to end their practice of “torturing and killing women,” Weyer exclaimed, “Don’t

you know that these poor women have suffered enough? Can you think of a misery anywhere in the world that is worse than theirs? If they do seem to merit punishment, I assure you, their illness alone is enough” (29).

In another witchcraft trial of 1602, English physician Edward Jorden explicitly mentioned hysteria’s connection to menstruation when he was summoned to court as an expert witness. In this case the woman on trial was not the one suffering from hysteria. Rather she was accused of using witchcraft to cause the disorder in her neighbor’s teenage daughter. Defending the accused woman vigorously, Jorden asserted that all of the teenage girl’s presumed symptoms of possession actually pointed to hysteria, a condition he viewed as a uterine pathology triggered by menstrual irregularities (7). As for the erratic nature of the symptoms, the “tics, swoonings, [and] convulsions,” Jorden described these as simply signs of illness, which should not be “imputed to the Devil” but rather to “true natural causes” (7).

Few if any had advanced a plausible theory to explain the choking fits considered for centuries to be a common symptom of suffocation of the womb. Yet here again Jorden was at the forefront, countering claims of demonic possession by explaining that “another argument of theirs is the offence in eating, or drinking, as if the Devil meant to choke them therewith. But this Symptom is also ordinary in uterine affects” (57). Despite Jorden’s efforts, the defendant, Elizabeth Jackson, was sent “to the pillory” for punishment (29) (Fig. 22). Jorden was so disturbed by this outcome that he

FIGURE 22



A painting from 1892 depicting a woman convicted of witchcraft who has been sent to the pillory for punishment. (Reproduced courtesy of the U.S. Library of Congress. Painting by Geo H. Walker, titled "The Witch, No. 2" [1892].)

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published the monograph, *A Briefe Discourse of a Disease Called the Suffocation of the Mother*, with the hope that its edifying message would help spare other women the fate that Elizabeth Jackson endured. Historian William Coventry provided an insightful analysis of these unfortunate moments in history when he observed that: “the spectacle of young girls screaming, crying, choking, and convulsing in court as they accused innocent people of sending murderous specters to harm them created an enormously compelling scene” (53).

Nymphomania and Lovesickness

Although demonology would eventually be discredited by the 18th century, the physical-psychological etiologic divide, couched at times in accusatory undertones, would linger in the background of women’s medicine well into the 20th century. During this era of etiologic chaos, hysteria was sometimes diagnosed as nymphomania, also referred to as madness from the womb, womb-fury, and furor uterinus. Regardless of the name, all were undeniably suggestive of willful moral depravity, an “immoderate inclination to venery” as one 17th-century physician put it (58). Outbreaks were said to have even occurred in convents. Diagnosing the purportedly afflicted nuns with “hysteromania or . . . erotomania,” French physician Claude Quillet exclaimed, “These poor little devils of nuns, seeing themselves shut up within four walls, become madly in love, fall into a melancholic delirium, worked upon by the desires of the flesh, and in truth, what they need to be perfectly cured is a remedy of the flesh.” In the most “extreme cases” of nymphomania, some even recommended that afflicted women be strapped into straitjackets (59–61).

Two of history’s most prominent female figures, Marie Antoinette and Pauline Bonaparte, would become ensnared by this milieu of morally mediated disease constructs, as

both were eventually accused of nymphomania. In the case of Marie Antoinette, the gynecologic disorders that she suffered from most of her adult life were no doubt counted as evidence against her. Pauline Bonaparte, on the other hand, was given the diagnosis of nymphomania specifically after visiting her doctor for pelvic pain (62, 63) (Figs. 23 and 24).

Lovesickness, a decidedly more innocent version of nymphomania, also emerged as a folkloric explanation for women’s illness. It was rooted in concepts of not only *hysterikos* but also a type of melancholy madness that had been proposed by Galen and other ancient authorities (30, 64). Just as in ancient times, young women were viewed as especially susceptible to such disorders, as dozens of 17th-century paintings devoted to both nymphomania and lovesickness suggest (5, 7, 48, 64). Yet, it was not just popular culture that had been influenced; in university archives across Europe, hundreds of medical dissertations list furor uterinus or nymphomania as the thesis topic (Figs. 25 and 26).

Backward steps in women’s medicine. These new concepts of illness represented several backward steps in women’s medicine. First, disorders viewed as gynecologic for thousands of years were now being defined as *psychological in nature*. Far from being an innocuous shift, this change would end up negatively impacting women with endometriosis well into the 20th century. And these were not just theoretical musings—nymphomania was still listed as a disorder in the International Classification of Disease until 1992 (58).

Because certain illnesses were now perceived to be indicators of immorality, women were sometimes also blamed for their own illnesses (7). In this case, not only were images of mad, lascivious wombs influencing popular notions about

FIGURE 23



Having suffered from gynecologic disorders most of her life, Marie Antoinette was among countless women through the ages whose conditions were sometimes perceived to be signs of nymphomania. (Reproduced with permission of the Wellcome Library, London. Engraving by Jean Duplessis-Bertaux, image no. L0010596.)

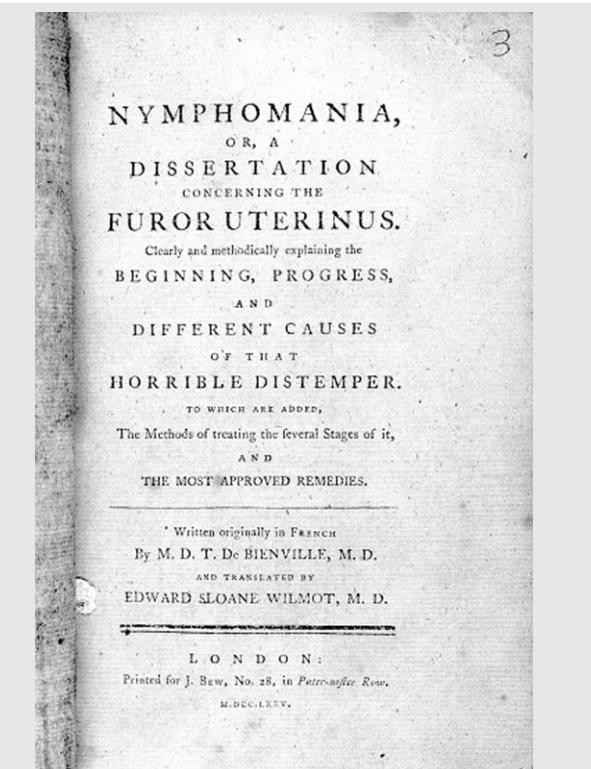
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women and illness, but now the derisive concept known as the “curse of eve” had also seized the popular imagination. Derived from a misinterpretation of the Biblical passage Genesis 3:16, the curse of eve concept originally suggested that women were cursed by God to endure painful childbirth labor, but it was later distorted even further to include painful menstruation (65–67).

Ridicule in literature. These sensationalized motifs of illness were especially popular sources of satire, and many were incorporated into popular literary works, including those of Shakespeare, in which female characters faked or otherwise wielded their hysterical condition to attract attention, manipulate men, or escape from domestic responsibilities (7, 29). For example, in the novel *The Life of Gargantua and of Pantagruel*, the 1534 satire by physician-author Rabelais, women with hysteria are clearly targets of satire.

Nevertheless, some of their portrayals actually offered some of the most insightful views to date about the physical

FIGURE 24



An 18th-century treatise by French physician T. D. de Bienville was highly influential in introducing the concept of nymphomania into the popular conscience. (Reproduced with permission of the Wellcome Library, London. Image no. L0026663; Title page of T. D. de Bienville's *Nymphomania, or, a dissertation concerning the furor uterinus, clearly and methodically explaining the beginning, progress and different causes of that horrible distemper*, English translation published in 1775.)

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symptoms of hysteria, with one character explaining that: “the movements [of the womb] sometimes [are] so violent that the woman is thereby deprived of all other senses and power of motion, as though she had suffered heart-failure, syncope, epilepsy, apoplexy, or something very like death” (29). Even though the uterus is clearly implicated as the source of the symptoms, those suffering from the condition are still viewed as socially and sexually deviant, as expressed by another character from the Rabalais novel, who explains that: “those virtuous women who have lived modestly and blamelessly, and who have had the courage to rein in that unbridled animal and to make it obedient to reason, are deserving of no small praise indeed . . . once this same animal is glutted, if glutted it can be . . . then all these specialized motions come to an end, all appetite is satiated, and all fury appeased” (29).

The Physical-Psychological Divide

Historical vignettes like these appear to evince an absence of scientific thought, but the story is far more complex. While the 17th century marked the time during which Galileo was

FIGURE 25



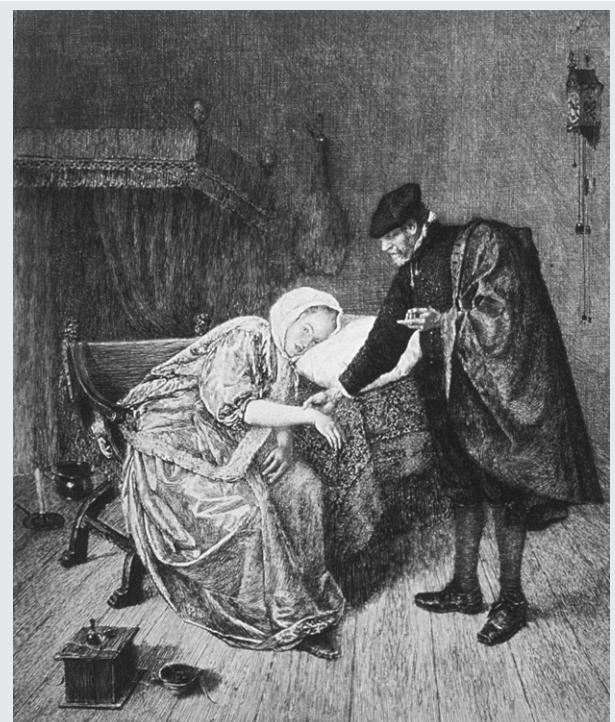
A 17th-century painting in which a young woman is shown being examined by a physician. The imagery alludes to the concept of lovesickness, with the orange, a symbol of fertility at the time, being held to the woman's pelvic area as just one image indicative of these ideas. (Reproduced with permission of the Wellcome Library, London. Image no. L0017889; oil painting after Richard Brakenburg [1650–1702], titled "A medical practitioner taking a girl's pulse and holding a flask of her urine, with four other figures on the left and a maid opening a door on the right.")

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on trial and the humoral framework of disease predominated, it was also an era in which some of history's most revolutionary discoveries were made, and was the same era in which (30) Bacon, Locke, Newton, Halley, Voltaire, and Rousseau all hailed. (30) (Fig. 27).

A similar duality continued to characterize the debates about hysteria, which remained divided along the physical-psychological etiologic fault line. However, biases in historical reporting have no doubt skewed our understanding of these academic disputes. For example, with countless caricatures of wild, hysterical women looming large in the popular imagination of the period, those fantastical images are bound to capture the attention of medical historians, who frequently then privilege these sensationalized accounts over the comparatively dry clinical realities portrayed in conventional medical texts. This tendency to prefer more exotic explanations of illness is exemplified by the sentiments of Peter Mitchell, a historian of 17th century medicine, who expressed dismay that the theory of hysteria as a psychological disease "fell on the deaf ears of a medical profession seemingly

FIGURE 26



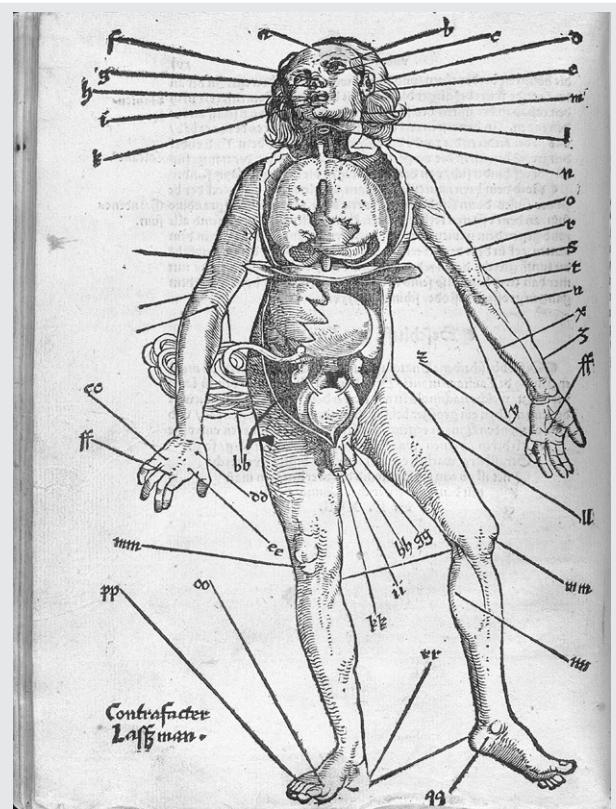
A satirical painting from 1663 in which a young woman presumed to be suffering from lovesickness is depicted being treated by a doctor. Scholars who have studied this painting suggest that the artist used the term lovesickness to euphemistically allude to the concept of a wandering womb, for which sexual activity was considered the only known cure. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Jan Steen, titled "The Doctor's Visit" [ca. 1663].)

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steeped in the utero-centric model of female physiology and pathology" (68).

Violent menstruation as a trigger in hysteria. When we factor into our analysis the biases of historical reporting, it becomes clear that scientific medicine was not only thriving, but had catalyzed an awakening interest in matching clinical results more carefully with the pathologic findings obtained by autopsy. In fact, the emerging discipline of pathologic anatomy ultimately helped rescue hysteria from falling further into etiologic wastelands. Even though some fringe groups still attempted to categorize hysteria as a psychological-neurologic disorder, the uterine-menstrual connection held strong as one of the most credible theories of pathogenesis. As a result, many physicians were acknowledging that hysteria was primarily the result of menarche "rampaging furiously throughout the body, causing violent paroxysms and anatomic upheaval," which "wreaked vast physiological damage" (7).

A synthesis of views. With our subject so inextricably linked to blood, it should come as no surprise that the great blood doctor himself, William Harvey, offered his own take on hysteria.

FIGURE 27

A 16th-century surgical textbook etching illustrating the best areas of the body in which to perform bloodletting. (Reproduced courtesy of the U.S. National Library of Medicine. Medical textbook published by Hans von Gersdorff [circa 1455–1529] from *Field Book of Surgery* [Strassburg 1519].)

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Remarkably, Harvey's belief that sexual abstinence or unhealthy menstrual blood (aka, spoiled menstrual blood) could cause hysteria was nearly identical to theories that had been postulated by the Hippocratic authors 2,000 years earlier. Explaining his views, Harvey observed "how many incurable diseases of the blood are brought about by unhealthy menstrual discharges . . . or from over-abstinence of sexual intercourse when the passions are strong" (5, 29). Harvey warned that if women "continue too long unwedded" they will be "seized with serious symptoms—hysterics, furor uterinus, or fall into a cachectic state, and distempers of various kinds" (7).

It seems clear that Harvey believed both the menstrual/uterine and hungry womb theories simultaneously; but ultimately science prevailed, and Harvey eventually favored an organic explanation. In fact, Harvey was one of the earliest in modern times to observe a connection between ulcers of the uterus and hysteria. While treating one of his patients for an ulcer of the uterus, he noted that, when he dilated the uterus, it contracted and made the woman suffer the same symptoms as those of hysteria. Harvey relied on this experience as definitive proof that hysteria was a uterine condition after all (29). Harvey's remarks also demonstrate that reputable

physicians from recent history had noted hysteria's unequivocal connection with menstruation (7).

Menstrual disorders and refluxed blood. Some of Harvey's contemporaries also made it clear that they were not completely sold on the psychological nature of hysteria. Rather, 17th-century practitioners continued to challenge this notion by repeatedly emphasizing the organic and menstrual connection. Like Harvey, English physician Thomas Willis (1622–1675), recognized today as the founder of neuroscience, presented a mixed picture of hysteria that sometimes referred to its perceived organic aspects while leaving room for the possibility of psychological elements. For example, Willis suggested that hysteria "most often happened to the Female Sex, in whom the menstrual flux and other accidents of the womb, do challenge a part in the morbid cause." Yet he began to depart from this view after performing autopsies on women diagnosed with hysteria, whose uteri appeared to be normal. This apparent absence of pathology helped convince Willis that other psychological-neurologic elements must be involved (29). Having the acclaimed nerve doctor himself allude to a neurologic etiology was enough to set off a whole new wave of speculation about hysteria's true nature. In the aftermath, the utero-centric edifice could be seen crumbling anew, leaving the door wide open for behavioral and psychological etiologies to continue festering in scientific medicine (Fig. 28).

Contrast these views to the work of renowned German anatomist Johannes Vesling, whose publication from 1647 introduced the idea that "extravasation of blood into the genital track" could cause uterine tumors (69). Vesling's original work is not available, but if we accept as accurate the 19th-century secondhand account of his work, Vesling's observations would be the earliest instance in modern times that a refluxed-blood theory had been introduced to explain the presence of pathologic uterine growths.

Thomas Sydenham

A disease of civilization. Despite the preponderance of evidence pointing to an organic condition specifically located in the uterus and associated with the onset of menstruation, hysteria was increasingly classified as a psychological-neurologic disorder. This convincing alternative was made all the more plausible when autopsies continued to reveal no identifiable pathology.

Of all the 17th-century practitioners to postulate an alternative to the uterine etiology, Oxford-educated physician Thomas Sydenham (1624–1689), known as the English Hippocrates, provided the most impetus to the growing popularity of the psychological-neurologic theory of origin (Fig. 29). This was surprising, because Sydenham embodied some of the best attributes of the new scientific era. He believed, for example, that experiments were useless unless they could be duplicated by others. It was even reported that Sydenham's legendary disdain for untested book learning was so excessive that, when a student asked which medical books should be studied, Sydenham replied "Read Don Quixote" (30). The story may be apocryphal, but it reflects the Enlightenment spirit of rigorous scientific investigation.

FIGURE 28



While others were beginning to view hysteria as a neurologic-psychological condition, English anatomist Thomas Willis (1622–75) generally believed it had an organic etiology, suggesting that it would “most often happen to the Female Sex, in whom the menstrual flux and other accidents of the womb, do challenge a part in the morbid cause.” (Reproduced courtesy of the U.S. National Library of Medicine. Cover of Thomas Willis’s *Pathologiae Cerebri et Nervosi Generis Specimen* [1667], Call no. 7128.5.)

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A disease of frayed nerves. Enlightened or not, the precedent had been set by Willis and others for categorizing hysteria as a psychological-neurologic affliction. Perhaps it was because the mind represented the ultimate unknown in medicine that Sydenham found himself enthusiastically subscribing to the notion of hysteria as an exotic new disease construct, perhaps a “disease of civilization,” the consequence of “frayed nerves as a result of the growing industrial age” (7). In fact, Sydenham felt that hysteria was not only increasing in lockstep with the advancing industrial age, but that it was reaching epidemic proportions. And, as many others had suggested over the centuries, he also believed that it was particularly rampant among upper-class “leisured ladies” whose lives were often characterized by idleness and overindulgence, behavioral influences thought to be predisposing factors to hysteria (7).

“Cyclical” symptoms. However, despite his preconceptions, Sydenham described a diagnostic profile that bore a remarkable resemblance to our modern understanding of endometriosis. His recommended treatment was a “hysterical pill” containing predominantly opium for the cyclic and erratic pains. More-

FIGURE 29



Although English physician Thomas Sydenham noted many symptoms of hysteria with striking correlations to endometriosis, such as hysterical lumps, hysteria of the stomach, vomiting, diarrhea, and back pain, he still concluded that its etiology was psychological in nature, perhaps the consequence of “frayed nerves as a result of the growing industrial age.” (Reproduced with permission of the © National Portrait Gallery, London. Portrait by Mary Beale [1688].)

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over, he was aware that “cases where pain in the bladder and retention of urine occurred” were commonly misdiagnosed as calculus (7, 40).

Hysteria of the stomach. In connection with what was called “hysteria of the stomach,” Sydenham noted that continuous vomiting and diarrhea were common symptoms (29). Reports of mysterious lumps also returned to the diagnostic profile, with Sydenham reporting that “hysterical lumps” occurred throughout the body (40). Sydenham also viewed the back pain reported by hysterical women as the disorder’s most reliable diagnostic feature (29).

Far from being contemptuous of women with hysteria, Sydenham repeatedly demonstrated his profound empathy for those suffering from the disorder. His view was that the pain suffered by hysterical patients was more severe than that of other diseases, adding that, aside from fevers, “of all chronic diseases . . . hysteria is commonest” (7, 29).

Daniel Schrön

With their illness now situated within the context of psychological disorders, women experiencing unidentifiable

ailments were left especially vulnerable to misdiagnoses. Still, by the late 17th century, an era characterized by a growing interest in morbid pathology, a few physicians held a completely different point of view. They departed from the hysterical disease construct in favor of focusing nearly exclusively on the physical signs of uterine pathology.

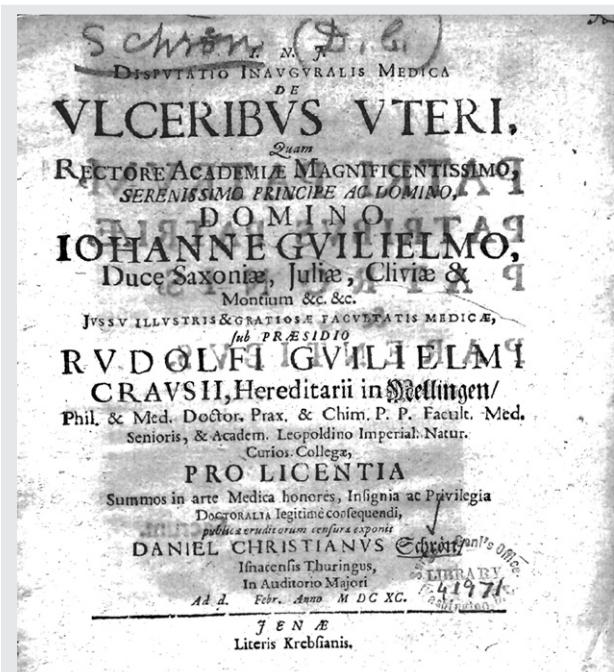
One such investigator was the German physician Daniel Schrön, identified by Vincent Knapp as one possible early pioneer. In Schrön's 1690 dissertation on ulcers of the uterus, several gynecologic symptoms were described that bear some similarity to those of endometriosis (30, 70) (Fig. 30). In view of the many outstanding ambiguities and controversies that have followed Knapp's interpretation of Schrön's work, we analyzed the original Latin language thesis ourselves and found credible evidence to support Knapp's conclusions. Though a certain margin of error is assumed in translating a 322-year-old medical document from Latin, we can confirm with a reasonable level of confidence that Schrön indeed may have been describing endometriosis in many cases.

Fibrous, glandular, and spongy membranous parts of the uterus. Schrön begins his thesis by delineating the multiple types of tissue that could be found in the uterus, such as fibrous, glandular, and "membranous" parts. In an age when few used the still-primitive microscope technologies available, Schrön's ability to report distinctions of such accuracy demonstrates a sophisticated anatomic knowledge that many medical historians assume had yet to be secured by that period. And, by paying homage to the many renowned anatomists of his era, such as Bartholin and de Graaf, Schrön establishes that even early 16th-century anatomists had a much more sophisticated understanding of different tissue types than has been commonly assumed in modern times.

To demonstrate this sophisticated knowledge, Schrön explains that "Bartholinus, that celebrated anatomist, considers that the membranous part in the substance of the uterus is the product of two sources, and . . . that one of these . . . is from the peritoneum, whilst the other is unique . . . which however one cannot differentiate, except in the case of ulcerated abscesses. We have seen that enclosed within these internal and external walls, there is a fleshy layer composed of flesh-like fibres, resembling those internal organs . . . [and] a spongy layer full of hollows, containing countless little tubes." Descriptions as remarkably accurate as these may seem unbelievable; however, even though the microscope was in its infancy at the time, anatomists of the era were able to observe such intricacies with the help of fairly powerful magnifying glasses (71).

Swelling "globules." Schrön goes on to provide another description that is remarkably similar to modern observations, stating that "the anatomists also describe a glandulous layer or, if you prefer, a layer full of little gland-like corpuscles" (70). It is these tissue elements, Schrön says, that can undergo ulceration and change shape; he explained that "when their action is disturbed, they become the agents of many kinds of fermentation . . . and develop into a new substance which is hard and much bigger, like the glandulous bodies, or if you prefer, little balls [globules] not dissimilar to the hardened yoke of an egg that Regner de Graef observed in his 'Treatise

FIGURE 30



Title page of 17th-century physician Daniel Schrön's dissertation, which contains descriptions of clinical and macroscopic signs and symptoms highly suggestive of endometriosis.

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on the Organs of Women' . . . from which the formation of a hard swelling develops" (70).

Deep ulcers "under the surface." As for the many types of ulcers observed, Schrön notes that, though "the eyesight of the surgeon cannot penetrate all ulcers," there are types that reside "deep under the surface" of the uterus (70). Remarkably, Schrön noticed that such ulcers appeared to have developed at different times, an observation with uncanny parallels to modern understandings of how older lesions can be distinguished from newly established ones. Expanding on these findings in more detail, Schrön states, "Some furthermore are recent, others well-established, others again dirty, of evil character, cavernous or filled with tubes, cancerous, etc." (70).

Nonsyphilitic lesions. While his descriptions could suggest many different types of ulcers, Schrön is careful to differentiate these lesions from other common conditions of his era, such as "sores, abscesses, small pox, scabies, etc." as well as pathologies he describes as "sexual" diseases, with syphilis mentioned specifically (70). As for those most susceptible to the disorder, Schrön observed, "It is when women are of a timely age to marry that they are particularly assailed by these ulcers" (70).

Descriptions of symptoms. Concerning the pain, he notes, "Once again, among the essentially inherent signs of uterine ulcers it is pain which forms the preeminent feature; when this is at its most intense, as Plater testifies in the cited

work, then, from the pain, or tearing and stinging sensation which acts in various ways, uterine ulcers are named as the problem” (70).

Preliminary refluxed blood theory. Schrön also suggests that bleeding (presumably menstrual, though this is not explicitly stated) may occur in other parts of the pelvic area besides the uterus. To address this potentiality, Schrön suggests that other areas of the pelvis outside of the uterus should be examined for signs of this ulceric condition, such as painful tenderness. He explains that these ulcers can arise outside of the uterus due to what he describes as the known ability of uterine blood to travel outside the uterus, causing the lesions. Explaining this observation in detail, Schrön reports:

For a flow of blood can also arise outside the sphere of the uterus, and for this reason, as it often deceives the doctor, the sense of touch must be invoked for assistance. If ulcers have a fixed location around the internal orifice or the exterior areas, then they can be investigated by touch on account of the extremely delicate sensitivity of the parts in the same area (70).

As for the collateral damage that uterine ulcers can cause, Schrön simply says, “The two possible outcomes are death or sterility” (70).

Stagnated blood origin. To further explain why “stagnation” of menstrual blood would give rise to lesions, Schoen brings us back to the same ancient idea of spoiled menstrual blood that had been propounded for centuries by that time. Schrön offers a variation of this theory:

There are various consequences of stagnation, including primarily inflammation. In addition all inflammation that is properly so-called afflicts the part with redness, heat, pain, and swelling, and, as the last and well-known characteristic, the power to suppurate. Having taken these facts as true, then tumors, abscesses, swellings, ulcers, etc. are readily allowed (70).

As for treatment options, in another uncannily modern view, Schrön concludes that “the principal remedy comes from surgery.”

Hereditary disposition. Concerning contributing factors, excessive menstrual bleeding is mentioned as a potentially predisposing factor (70). As to other proximate causes, it is interesting to note that Schrön is one of the few we have uncovered to offer heredity as one possibility among many. Although a few allusions to this theory were made by the ancient practitioners we have covered, Schrön provides the most explicit declaration on the subject: “Nor clearly should one reject an hereditary disposition, because Sennert, in his work *Surgery* (book 5, chapter 17, page 11) notes that there are certain families in whom ulcers erupt as though it were by hereditary right, and others also have observed the same phenomenon” (70).

Ambiguous aspects. As critics of Knapp’s research have pointed out, other characteristics mentioned by Schrön have

limited correspondence with endometriosis, such as descriptions of suppuration and pus. However, during that period, nearly every ailment was thought to stem from an inflammatory process, making it possible that Schrön’s observations of pus and other signs of suppuration were simply interpretations conforming to the established belief systems of the day. In other words, rather than being accurate representations of the facts, his analyses may have been reflecting culturally produced notions of disease states. In any case, even 20th-century investigators have detected elements that could be said to have pus-like coloring. In 1908, for example, endometriosis pioneer Thomas Cullen reported observing adenomyomas with “many . . . cyst-like spaces contain[ing] fresh blood or yellowish blood pigment” (72).

Moreover, it is not clear how many autopsies Schrön performed, or whether the conditions under which cadavers were kept contributed to the degradation of tissues. Given these many extenuating factors, the entirety of Schrön’s work should not be indicted merely for an observation of pus, which may, in any case, have been a forgivable misinterpretation of the tissue specimens under inspection.

The other ambiguous aspects of Schrön’s work relate to his statements concerning vaginal excretions. Before drawing any conclusions, it is helpful to consider the entire paragraph from which these statements about vaginal excretions were drawn:

Most of all the complaint is made manifest by excretions of various colors, such as bright yellow, dull yellow, green, dark purple, black, muddy, and stinking, which flow from the uterus and stain linen [underwear] with various colors, either at intervals or continually, in accordance of course with the manner in which the matter is flowing. Fernel agrees with these, and states that an aggregation of corrupt blood drips out; it is varying in quantity, substance, and color, sometimes stinking, but at other times lacking any smell, while at times the sort of matter emerges that can only with difficulty be differentiated from a normal flow.

The descriptions of “dark purple, black, muddy” excretions, and “an aggregation of corrupt blood” could point to endometriosis, but the other descriptions prove too ambiguous to be of any help. Schrön also viewed this wildly disparate clinical picture as confusing. In fact, to address the dilemma of trying to differentiate between these various discharges, particularly that of normal menstruation as opposed to menstruation accompanied by ulcers, Schrön resorts to invoking the tenants of the ancient master, Galen, advising that “as a result, Galen, *De Locis Affectis*, chapter 5, states that unmistakable visible signs of a menstrual flow must often be sought.”

These interpretations of Schrön’s work may still be viewed as inconclusive and contested, but after considering the textual evidence in its totality, we do not feel that two areas of ambiguity—pus and confusion over the nature of vaginal discharge—are sufficient grounds for summarily discrediting the idea that endometriosis could have been the disorder Schrön was observing. Overall, enough passages have

clear parallels to modern perspectives that it is entirely plausible that Schrön was indeed witnessing cases of endometriosis. Schrön provided remarkably accurate differential diagnoses, distinguishing the ulcers he observed from those deriving from syphilis, for example. Additionally, the clinical signs he reported correlate to the same cluster of symptoms and physical manifestations that had been consistently observed for more than 2,000 years. Among the most relevant of these were Schrön's descriptions of extreme pain, deeply embedded growths, swollen and painful globular-like nodules, old and new ulcers, and explicit associations with menstruation, particularly menorrhagia. By what appears to be a synthesis of centuries of observations—including those of Galen as well as his contemporaries such as Bartholinus, Regner de Graef, and Sennert—Schrön also achieved several breakthroughs, including the introduction of a rudimentary theory of retrograde menstruation and recognition that the disorder was potentially heritable.

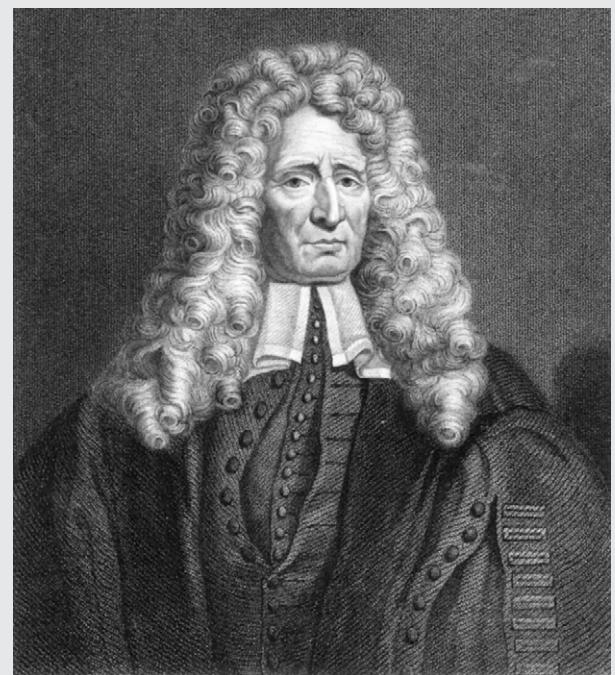
Frederik Ruysch

Another 17th-century investigator, the well-regarded Dutch anatomist Frederik Ruysch (1638–1731), also may have stumbled upon cases of endometriosis. Unlike Schrön, Ruysch was not identified by Knapp, but instead was repeatedly cited by several early to mid-19th-century physicians who had discovered for themselves a disorder that was most likely endometriosis (Figs. 31–34). Like Schrön, Ruysch advanced his own version of a reflux theory, suggesting that congenital malformations of the uterus obstructed menstrual blood, which caused the blood to back up and spill into the peritoneum, thereby causing pain, lesions, and inflammation [73]. However, Ruysch's theory departed from Schrön's in one crucial way: he believed the effusion of blood and subsequent formation of lesions occurred only when an obstruction to menstrual flow was present.

Ruysch reached his conclusions during an autopsy of a woman who had died of an unknown cause. During the postmortem analysis, Ruysch noticed two things that surprised him. First, he found that blood apparently deriving from the fallopian tubes had refluxed (referred to then as effused or extravasated) into the peritoneum. The theory that this could occur had been circulated for years (recall Vesling's observation in 1647), but it was apparently still believed to be an anatomic impossibility, improbable enough that it was treated as an important discovery over a century later. Second, Ruysch noted that where the blood had spilled lesions of some kind had developed. Running through the possible differential diagnoses, Ruysch apparently ruled out the possibility of an ectopic pregnancy. In the same medical textbook but under a different section, Ruysch also relates his clinical findings from a young girl who had presented with pelvic pain and other symptoms similar to those of the woman he had autopsied earlier. Upon examination, the girl was found to have a congenital obstruction to the flow of her menstrual blood [74, 75].

Based on his observations (and possibly on other works that have not been translated), Ruysch hypothesized that the refluxed blood found at autopsy and in the young woman

FIGURE 31



Portrait of Frederik Ruysch (1638–1731), acclaimed 17th-century Dutch physician and anatomist, whose works include descriptions of refluxed blood in the peritoneum and other clinical symptoms somewhat suggestive of endometriosis. (Reproduced courtesy of the U.S. National Library of Medicine. Engraving published by J. Wandelaar and J. Jenkins; Call no. 5890.3.)

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with the congenital obstruction was the cause of the symptoms of pain and pathologic growths:

In the anatomical observation of this corpse I also observed that the pelvis was full of the impure dregs of liquids, making very nearly two pints and a highly offensive smell, or possibly these liquids had been propelled from the uterus through tubes or egg-ducts into the pelvis, and I find this easy to believe because I have on a number of occasions discovered liquids in the pelvis resembling those which I found in the uterus (75, 76).

Regrettably, Ruysch's descriptions are exceedingly sparse, comprising only a few frustratingly obscure paragraphs. However, in one passage Ruysch mentions clinical symptoms somewhat suggestive of endometriosis, which he says can now be explained by his autopsy results. Concerning these symptoms, he notes that "this is very often the source of those tears and complaints about an intolerable pain and chill in the area below the stomach, and blockages, and indeed not infrequently a continual flow of menstrual blood" (74). From this condition, Ruysch explains, "there arise terrible fevers, agonies around the area below the stomach, loss of consciousness and similar ills, and death itself."

Schrön versus Ruysch. Although Ruysch's work was later cited by others, Schrön, who preceded him by a year, should be considered the first in modern times to offer a brief but

FIGURE 32

A painting from 1683 in which Ruysch is depicted performing an autopsy for his students. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Jan van Neck [1683], titled "The Anatomy Lesson of Professor Ruysch.")

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fairly clear reference to a reflux etiology. All the same, Ruysch's insights provide a crucial piece of evidence to support the notion that investigators were coming closer and closer to identifying what may have been endometriosis. In both Schrön's and Ruysch's works, the conceptual continuity with Sampson's theory of retrograde menstruation is remarkable. Given such similarities, it is all the more surprising that these ideas were apparently lost in history until Sampson resurrected them nearly two and a half centuries later. Ruysch's underlying obstruction theory is also nearly identical to modern theories about Mayer-Rokitansky-Küster-Hauser syndrome, which studies suggest increases the likelihood that endometriosis will develop.

18TH CENTURY

The works of Schrön and Ruysch serve as much needed counterpoints to the tales of madness, witchcraft, and demonology invading the sanctity of science. In contrast, their work clearly demonstrates many principles of scientific medicine were informing their analyses, especially the burgeoning field of pathologic anatomy, a discipline that appears to have been established long before its commonly assumed official founding by Giovanni Morgagni in the 18th century.

Eighteenth-century medical literature also continued to be loaded with descriptions of hysterical symptoms exhibiting striking parallels to endometriosis. One recent study analyzing admissions for the hysteria ward of an 18th-century Edinburgh infirmary found that most of the women diagnosed with hysteria had "loss of appetite or other digestive problems, menstrual difficulties, and fainting spells," symptoms suggestive of many organic diagnoses (7). Just as Schrön

had suggested in the previous century, the concept that hysteria could be inherited also continued to be advanced. In attempting to distinguish epilepsy from hysterical fits, a physician in 1702 observed that "Vapours as well as other Diseases [were] transmitted to us from our Fathers and Mothers," while apoplexies presumably were not (77).

Diary entries from women also serve as especially revealing sources for helping us understand hysteria's pain symptoms in particular. One undated entry from the diary of Lady Mary Montagu (1721–1751) was particularly haunting, she wrote, "I have seen so much of hysterical complaints, tho' Heaven be praised I never felt them, I know it is an obstinate and very uneasy distemper, tho' never fatal unless when Quacks undertake to cure it. I have even observed that those who are troubled with it commonly live to old age. Lady Stair is one instance; I remember her screaming and crying when Miss Primrose, my selfe, and other girls were dancing 2 rooms distant" (78).

Neuroses, Nymphomania, and Ovaries

Even with such an endless parade of physical symptoms and expressions of pain, the trend toward viewing hysteria as a nervous condition—or worse—seemed to march on unabated. Accusations of immorality or duplicity also remained in the background as explanatory factors, while others began viewing hysterical women as mentally deranged (7). In such cases, women with hysterical symptoms were in danger of being sent to madhouses such as Bedlam, a place people would visit for entertainment to "view the lunatics for a penny" (7). One of the era's most respected "nerve" doctors, English physician William Cullen, was particularly influential in keeping

FIGURE 33



Image of Ruysch's 17th-century textbook, title page, and frontispiece. (Reproduced courtesy of the U.S. National Library of Medicine.)

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alive the notion that hysteria was a psychological-neurologic disorder (Figs. 35 and 36).

Cullen's stance is all the more surprising upon discovering that he had observed hysteria to be connected to "menstrual difficulties," when too much blood in the uterus caused a "turgescence of blood" which in turn overloaded the body's vascular systems, including those of the brain. Of note, Cullen was even one of the first in our historical review to mention that the ovaries were somehow involved in hysteria, explaining that they were particular painful in hysterical women [29]. Remarkably, Cullen was able to deftly explain away all of these undisputed gynecologic symptoms by reframing them as part of his neurologic theory of origin, asserting that the vascular overloads caused by menstruation were triggering systemwide neural dysregulation [29]. Worse still, Cullen went on to implicate behavioral or psychological factors as the true causes, blaming the condition on "young widowhood, and to passions of a sensitive mind" and claiming that "females liable to nymphomania" were especially prone to the disorder.

As one can imagine, physicians themselves noticed that patients revolted against a diagnosis of hysteria. It was observed that women were thoroughly "unwilling to own a disease that [would] expose them to dishonour and reproach" [7]. Upon being diagnosed with hysteria, Queen Anne promptly

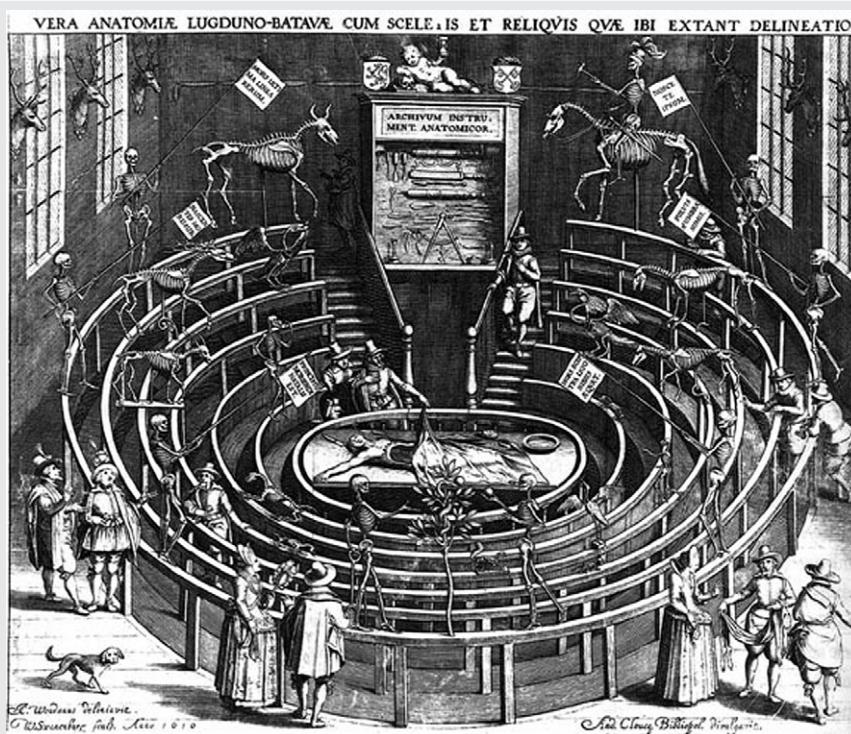
fired her personal physician, indignant at the suggestion that she was mad, immoral, or imagining it all [7].

Arthur Duff

Although the voluminous chronicles of hysteria have attracted considerable attention from medical historians, in the background an endless stream of investigators had been studying the less dramatic but equally enigmatic disorder of inflammation of the uterus (endometritis or metritis), a condition that could also have been endometriosis in many cases. In fact, Arthur Duff, the Scottish physician identified by Knapp, dedicated his entire 1769 master's dissertation, "Dissertatio Inauguralis Medica de Metritide," to the subject of inflammation of the uterus (Fig. 37). With Duff's descriptions of metritis sufferers as experiencing intense and violent pain, vomiting, uterine contractions, and bowel symptoms, an image of a disorder with remarkable similarities to endometriosis begins to emerge [79]. Duff began his dissertation by explaining that metritis had recently been the subject of great "fixation" by pathologists, but that physicians were falling considerably short of uncovering its causes and true nature [79].

Description of symptoms. As for the terrible pain associated with inflammation of the uterus, just as the ancients had

FIGURE 34



As portrayed in this etching from 1610, the University of Leiden where Frederick Ruysch taught was especially progressive in the anatomical sciences for which the performance of autopsies played a central role. (Reproduced with permission of the Trustees of the British Museum. Etching by Willem van Swanenburg [1610], titled "Views of the University of Leiden; Plate 1.")

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Duff describes women lying prostrate for days with nausea, vomiting, shivering, strangulation of the uterus, uterine contractions, convulsions, bowel and bladder symptoms, interrupted pulse, delirium, back pain, and “an unquiet mind.” Duff notes that death is a possible outcome, explaining that “the patient is snatched away, though she deserves a - better fate” (79). Although Duff alludes to ulcers or lesions only briefly, he does mention that, upon the touch, the inflamed areas of the pelvic region are very painful for the patients (79).

Menstruation and refluxed blood. As for etiologic understandings, Duff reviews the prevailing theories of the era and eventually concurs that a menstrual disorder is at play, explaining that “it is clear that the proximate cause of metritis is provided by the vital movements of the arteries of the uterus, when they violently malfunction and are more forceful than natural movements, with the result that a significant quantity of blood is forced into this organ with an impetus that is greater than normal” (79).

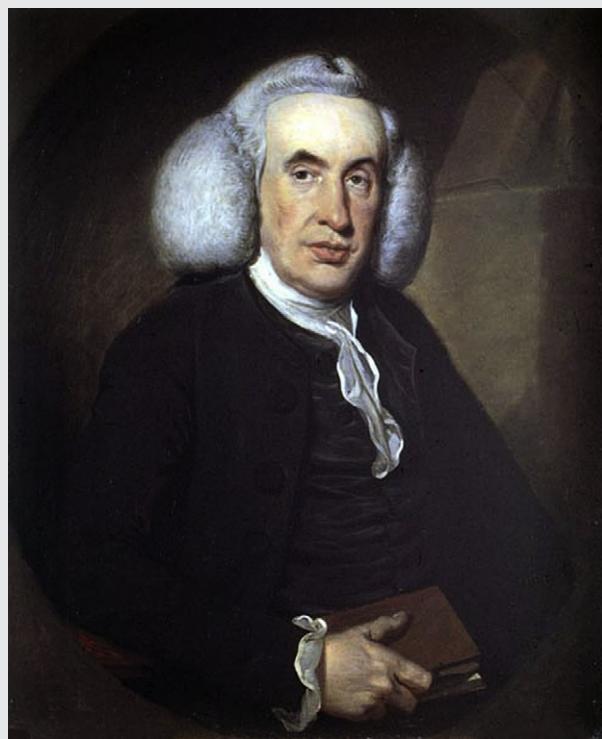
Duff’s circuitous manner of explaining things makes it difficult to discern his intended meaning. Based on other passages, it becomes clear that Duff is referring to the monthly engorgement of the uterus that occurs during menstruation. Adding to his hypothesis of a menstruation-related etiology, Duff further explains that “substances which have been forced back supply the irritant of a small amount of salt which

would normally pass through like sweat, as a result of which the quantity of matter that is driven back increases.”

Although it has languished in historical obscurity, Duff’s hypothesis that menstruation could trigger metritis was actually an unrecognized conceptual breakthrough. One reason Duff’s insights should be considered exceptional is because our research indicates that throughout history endometriosis may have been mistaken for metritis in many cases. This hypothesis is plausible when one considers that 19th-century investigators expanded the disease profile of metritis to include chronic, hemorrhagic, and exfoliating metritis, variations with nearly identical symptoms as endometriosis and which are described as occurring with menstruation (30).

19TH CENTURY

As exceptional as these 18th-century achievements were, studies on gynecologic disorders still seemed comparatively limited relative to other disciplines of medicine. As a result, for the next 200 years, our journey toward a long-sought, definitive understanding of endometriosis continued to be rife with uncomfortable uncertainty. But we have reached the 19th century, arguably one of the most spectacular centuries that medicine had ever witnessed, when some of the greatest milestones in women’s surgery were achieved, including developments that would eventually prove beneficial for women with endometriosis.

FIGURE 35

Even though 18th-century English physician William Cullen noted hysteria's many physical symptoms, including its connection to "menstrual difficulties," he implicated both neurologic and behavioral factors, noting that "females liable to nymphomania" were especially prone to the disorder. (Reproduced courtesy of the Hunterian Library, University of Glasgow. Portrait by unknown artist.)

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One of the most triumphal moments of the new century occurred in 1809, when Ephraim McDowell of Kentucky performed the first successful abdominal oophorectomy, during which a 22-pound ovarian tumor was removed from Mrs. Jane Crawford, who, in that preanesthetic era, sang herself through the surgery and went on to live another 33 years (Fig. 38). A few years later, in 1815, the first planned vaginal hysterectomy on a patient who survived was performed by German surgeon Konrad Langenbeck. And by mid-century improvements to the surgical sciences made it possible for Walter Burnham of Lowell, Massachusetts, to perform the first abdominal hysterectomy with a survivor in 1853.

However, as the surgical sciences began to flourish, a strange predicament arose. The growing need to supply medical students with corpses for autopsies gave rise to ghoulish tales of body snatching (Fig. 39). Equally strange relationships flourished. For example, the Barber-Surgery Company of London, the guild that regulated surgeons, actually sent Christmas gifts to executioners each year so that they would be guaranteed a steady supply of corpses. Poor families would be unduly burdened when in 1832 the Anatomy Act was passed in Britain, making it lawful to use the corpses of "unclaimed bodies," such as people who had died in factories or poor houses with no apparent family or those from families who could not afford

FIGURE 36

Those with mental disorders, including women diagnosed with hysteria, were often imprisoned in mental institutes such as St. Bethlehem Hospital (colloquially known as Bedlam), where patients were physically restrained in prison cells with chains and strait jackets. (Reproduced with permission of the Wellcome Library, London. Engraving by Ambroise Tardieu from *Des maladies mentales*, by J.E.D. Esquirol; published by Bailliere, Paris, 1838 plate XXV.)

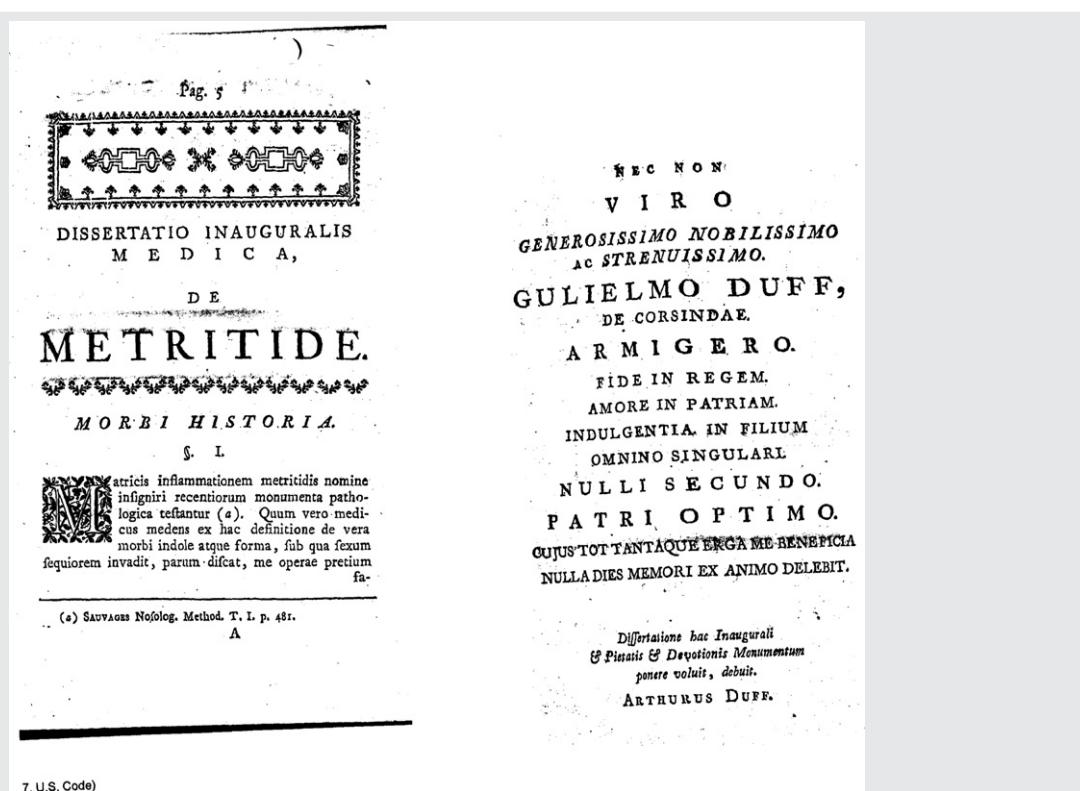
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burial expenses (30). In France, cadavers were even more freely obtained; one medical student from 1835 noted in his diary that they were easily procured for just "half a franc" (30).

Pioneering French Pathologists

The era's lively interest in the internal mysteries of corpses spearheaded the tremendous progress in the still-burgeoning field of morbid pathology, which would later play a decisive role in the eventual microscopic discovery of endometriosis. The discipline of morbid pathology was characterized by its emphasis on matching clinical observations to localized disease. In other words, the "symptoms had to correlate with any lesions or signs of disease in the tissue" obtained during autopsies (30). By mid-century critical discoveries such as William Jenner's 1849 differentiation of typhus from typhoid were achieved as a direct result of postmortem investigations (30). However, it was the French who were recognized as the leading pioneers in this new field of postmortem studies.

FIGURE 37



In Arthur Duff's 17th-century dissertation on metritis, he mentions several symptoms highly suggestive of endometriosis, including intense and violent pain that caused patients to lie prostrate for days with nausea, vomiting, strangulation of the uterus, uterine contractions, convulsions, back pain, and bowel and bladder symptoms. (Reproduced courtesy of the U.S. National Library of Medicine. Title page of Arthur Duff's dissertation titled *Dissertatio inauguralis medica de metritide* [1769]. Publisher Lugduni Batavorum, Apud Theodorum Haak, Call No. W4 L68 1769 D.1.)

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As one medical historian put it, “lesions were prized by Paris medicine as key to pathology” (30). This new emphasis on conducting postmortem analyses was clearly evident in the works of Marie Francois Xavier Bichat, the French pathologist of tissue-specificity fame and the father of histology (Fig. 40). Exemplifying this new age of empirical medicine, Bichat proclaimed, “You may take notes for twenty years from morning to night at the bedside of the sick, and all will be to you only a confusion of symptoms . . . a train of incoherent phenomena.” Instead, Bichat proclaimed, the moment one starts to perform autopsies “this obscurity will soon disappear” (30).

Bichat and others still relied on magnifying glasses—with the exception of John Bennett, who discovered leukemia using a microscope (80)—but there was a greater understanding that disease was actually specific to different tissues. That is, glandular and mucosal tissues rather than the organs themselves were considered important, and pathologic lesions were recognized to arise anywhere in the body that similar tissues were located. These revelations would one day play a key role in the eventual microscopic discovery of endometriosis (30).

Macroscopic discovery of endometriosis. Given the clear lead of French pathologists in the postmortem sciences, it is

not surprising that they were among the first in the 19th century to macroscopically distinguish what were in all likelihood cases of endometriosis. Their descriptions of a menstruation-triggered disorder were astonishingly identical to endometriosis, bearing all the characteristic clinical symptoms as well as macroscopic findings (30, 81). As we have seen, countless references to dysmenorrhea and other menstruation-related disorders had been noted throughout the history of medicine, but what made the observations by this group of French investigators unique was that they finally were able to correlate clinical symptoms to the postmortem findings that revealed corresponding pathologies.

In this way, this group of French pioneers was finally able to sufficiently narrow the symptom profile, allowing for a distinct disease entity with distinct symptoms to finally emerge. Even though microscopic confirmations were not made at this time, the signs and symptoms were essentially unmistakable. Because a consensus on nomenclature had yet to be achieved, the disorder was still called by many different names. Rather than attempting to reconcile this philologic confusion, for the sake of simplicity we will use the term “catamenial hematocoeles.”

Menstruation and lesions at autopsy. One of the crucial breakthroughs by this group of French investigators was their

FIGURE 38

American surgeon Ephraim McDowell performed the first successful abdominal oophorectomy in 1809, removing a 22-pound ovarian tumor from Mrs. Jane Crawford, who, in this preanesthetic era, sang herself hymns throughout the surgery and lived another 33 years. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Davenport titled *Ephraim McDowell* [November 11, 1771–June 25, 1830].)

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confirmation of what had been suggested for centuries: monthly menstruation was unequivocally the direct triggering event that led to the onset of an endometriosis-like disorder, with all the attendant symptoms including severe pain and internal growths. In contrast to practitioners from prior centuries, these scientists made observations for the most part without reference to hysteria, and they clearly considered it a purely organic pathology.

Catamenial hematoceles, pelvic sanguineous tumors, and rectouterine sanguineous cysts. These initial discoveries were made by a group of French investigators performing autopsies on women who had died from severe and sudden pain during menstruation (what appeared to be cases of ruptured ovarian cysts). After they noted the presence of blood throughout the peritoneum as well as the presence of pathologic growths, it became clear that a previously unknown disease was involved (69, 73).

Although the discoveries made by Vesling, Ruysch, and de Haen in the previous centuries were freely acknowledged by this group of French physicians, disputes over priority were rife in their own time, which makes it difficult to discern just who discovered what and when. Complicating matters was the fact that not everyone called the disorder catamenial hematoceles; others referred to the disorder as metrorrhagic hematoceles, retro-uterine hematoceles, pelvic sanguineous

tumors, blood tumors, rectouterine sanguineous cysts, and extra-peritoneal cysts to name but a few. All the same, the story appears to begin with Jacques Delpech, Joseph Recamier (75), Alfred Velpeau (69), Hippolyte Bourdon, Armand Trouseau, and Gustave Bernutz, all of whom were among the most commonly cited by their contemporaries as the first 19th-century investigators to report on catamenial hematoceles or their equivalent (69, 73, 76, 82, 83).

In 1830, Delpech noted a case similar to Ruysch's, in which a young woman diagnosed with menstrual retention presented with pain and some form of uterine lesions or tumors. She was found to have a vaginal obstruction disorder, leading Delpech to conclude, just as Ruysch had, that it was the extravasation of menstrual blood, in this case the result of an obstruction that had caused pain and lesions (82). Two years later, Recamier made similar discoveries and expressed surprise when "on making an incision to the posterior wall of the vagina for the purpose of evacuation of the contents of a supposed abscess discovered that instead of pus a copious discharge of black disorganized blood followed" (75) (Fig. 41).

Meanwhile, from Velpeau's 1833 atlas of surgical anatomy, the postmortems of patients described as having hysteria, suffocation of the womb, dysmenorrhea, or who "had long been subject to abundant menorrhagia" revealed macroscopic similarities to endometriosis and/or adenomyosis (72, 84) (Fig. 42). Included among these various postmortem reports were cases of obliterated tubes, ovarian cysts containing "blackish vesicles, with a mucous tissue of the same colour," and uteri double the normal size and riddled with nodules (84).

Gustave Bernutz

The investigator who deserves a goodly portion of plaudits for ensuring that the menstrual connection was vigorously emphasized was Gustave Bernutz, whose groundbreaking 1848 treatise on this newly discovered disorder described nearly all the clinical and macroscopic symptoms associated with endometriosis, including the specific link with the onset of "violent" pain symptoms at menstruation as well as the appearance and disappearance of nodules in relation to the cyclic pattern of menstruation. In his excellent summary of his 1848 article (published in 1866), Bernutz wrote about "the long explanations entered into for the purpose of showing the relation that exists between that form of intra-pelvic hemorrhage and menstruation" (73). In a seemingly exasperated tone, Bernutz attempts to defend his (and Ruysch's) priority in discovering the disorder, explaining that "the trouble I have taken to prove that certain pelvic tumours originate in a disturbance of the catamenial function, and are the remains of former menstrual extravasations, I might certainly have constituted a prior claim to the merit of having discovered haematoceles. But in reality I make no pretension to that discovery, the merit of which, as I stated in 1848, belongs entirely to Ruysch" (73).

John Hughes Bennett and Antoine Viguès

At about the same time as Bernutz, the eminent physician and pathologist from Edinburgh John Hughes Bennett, who is

FIGURE 39

Nineteenth-century satirical etching of bodysnatching in progress, which the artist has titled "A night watchman disturbs a body-snatcher who has dropped the stolen corpse he had been carrying in a hamper, while the anatomist, William Hunter (1718–1783), runs away." (Reproduced with permission from the Wellcome Library, London. Engraving by William Austin [1773], No. 25668i, L0001663 [also described as "The anatomist overtaken by the watch carrying off Miss W-ts in a hamper."])

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better known as the first to describe leukemia in 1847, also reported on what he considered peculiar cases of metritis that arose at the onset of menstruation and produced swellings, globular tumors, interference with bowel and urinary functions, and what he believed to be pelvic peritonitis (81, 85). At about the same time, Antoine Viguès, who was cited as among the most influential investigators, wrote an 1850 article "Des tumeurs sanguines de l'excavation pelvienne, chez la femme" that was recognized even by Bernutz as exceptional and highly influential in bringing the subject of catamenial hematocles to the forefront of study (86).

Armand Trousseau

To some degree, the nosologic debates were resolved when Armand Trousseau renamed the disorder "catamenial haematoceles" in 1858, after he had observed nodules and other symptoms that appeared and disappeared in conjunction with menstruation (76) (Fig. 43). Alluding to the extravasation of blood hypothesis, Trousseau reported that the disorder often "occurs in excessive menorrhagia or when there exists an accidental or congenital obstacle to the natural exit of blood from the uterus into the vagina" (76).

The *British Medical Journal* praised Trousseau's work not only for his new terminology, which more accurately described the condition, but also for his discussion of differential diagnoses, clearly distinguishing other varieties of lesions that formed as a result of injury or vascular aneurism (76). In summarizing Trousseau's work, his British reviewer provides one of the clearest explanations of what amounted to fresh insights at the time, and also provides

a rare firsthand account of just how little was apparently understood about menstruation:

To explain the occurrence of catamenial haematoceles, M. Trousseau calls to mind the phenomena which occur in the uterine system during ovulation. Under the influence of the menstrual act, the whole uterus is in a state of congestion that may be seen by the speculum. The neck of the uterus is swollen; the vagina, the labia majora and minora, are all in an evident state of erethism; and at the same time there is pain along the broad ligaments—a feeling of weight produced by the turgescence of the haemorrhoidal vessels. This great flow of blood to the uterus is followed every month by a haemorrhage. What is the seat of this? In general, Trousseau observes, the seat of haemorrhage (at least in disease as distinguished from injury), is the mucous membrane. It is not probable that the blood descends each month with the ovum along the Fallopian tubes; for the disruption of the ovum is a process of enucleation, and cannot produce haemorrhage; uterine haemorrhage occurs either from the internal surface of the uterus, or from the interior of the Fallopian tubes. It now becomes very easy to understand the formation of catamenial haematocele.

It is from the upper part of the Fallopian tube that M. Trousseau believes the blood in such cases to be derived. He does not think it possible, from the rapid coagulation of the blood in the vagina, that the fluid

FIGURE 40



Portrait of Marie François Xavier Bichat, renowned French anatomist, physiologist, and surgeon, known today as the father of modern histology and pathology. Bichat's contributions include advancing the notion that autopsies were essential to understanding diseases and that diseases attacked specific types of tissues rather than organs. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by Godefroy Engelmann [1788–1839] after Pierre-Roch Vigneron [1789–1872].)

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poured into the peritoneum can have passed upwards through the uterus and the tubes.

This theory perfectly accounts for the monthly relapses to which women who have once had catamenial hæmatocoele are subject. An excessive flow of blood to the uterine region and a special predisposition are sufficient to produce catamenial hæmatoceles at definite periods for an indefinite time" (87).

The summary of Trousseau's specific cases provides an excellent enumeration of all the symptoms, which were now recognized as part of this specific new disease category. One woman's case held particular interest:

Between two and three years ago, she had retrouterine hæmatocoele each month, for four months. During two years, her catamenia were regular; but on March 14th last, she was admitted into hospital with an enormous hæmatocoele, which disappeared, and appeared again at the monthly periods in April and May.

When once the blood is poured into the peritoneum, it follows hydrostatic laws. The patient is obliged to lie down to relieve the pain which she feels; and the fluid gravitates to the lower and back part of the pelvis. It accumulates in the recto-vaginal *cul-de-sac*; then it

FIGURE 41



RECAMIER (JOSEPH-CLAUDE-ANTHELME)
Né en 1774

Highly regarded French physician Joseph Recamier was one of the earliest in the 19th century to clinically and macroscopically describe cases with significant correspondence to endometriosis. (Reproduced with permission of the Wellcome Library, London. Portrait of J.C.A. Recamier by Auguste Corlieu, Centenaire de la Faculté de médecine de Paris: [1794–1894], published by Imprimerie Nationale, Paris, 1896, Image no. L0009737.)

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passes beyond the ligaments into the iliac fossae; thence it ascends, and submerges the uterus. In M. Trousseau's patient, the effusion reached the umbilicus. This female presented also with a peculiarity which obscured the diagnosis: the hæmatocoele was accompanied by a menorrhagia with retention, so that the uterus was excessively distended, and a round hard body was felt above the pubes, which M. Langier at first imagined to be a polypus. But, examining by the rectum, this surgeon (who had long known the patient) ascertained, as he had done before, the existence of an immense mass enveloping the uterus (87).

Trousseau also proffered treatment options:

The affection then demands the ordinary treatment of menorrhagia; and, of all remedies employed in this malady, M. Trousseau confides in none so much as in cinchona . . . If the hæmatocoele had reappeared, the patient would take dilute sulphuric acid and rhatany . . . The pain, in M. Trousseau's [patient's] case, was relieved by hemlock poultices, moistened with a mixture of belladonna and opium. This mixture consists of two parts of alcoholic extract of belladonna, and one part gummy extract of opium, with sufficient water to form a syrupy mixture . . . The [additional] treatment

had consisted in taking a drachm of calisaya bark every third day, and a preparation of steel daily (87).

The reviewer also helpfully distilled Trousseau's diagnostic recommendations into one simple sentence: "Whenever a woman, at the monthly periods, complains of pain in the hypogastric region, and suddenly loses colour, catamenial haematocele may be diagnosed" (87).

Edward Tilt

Another British literature review published by physician Edward Tilt provided one of the most comprehensive overviews on the subject of catamenial hematoceles. Most importantly, Tilt's exhaustive enumerations establish that by the time of his work's publication in 1852 nearly all the symptoms and macroscopic findings we understand today to represent endometriosis had been identified and officially ascribed to one disorder. Tilt noted, for example, that catamenial hematoceles were known to be accompanied by painful bowel movements, bowel constrictions, and excessive bleeding (81). As well, upon vaginal examination, the blood-filled nodules were

FIGURE 42

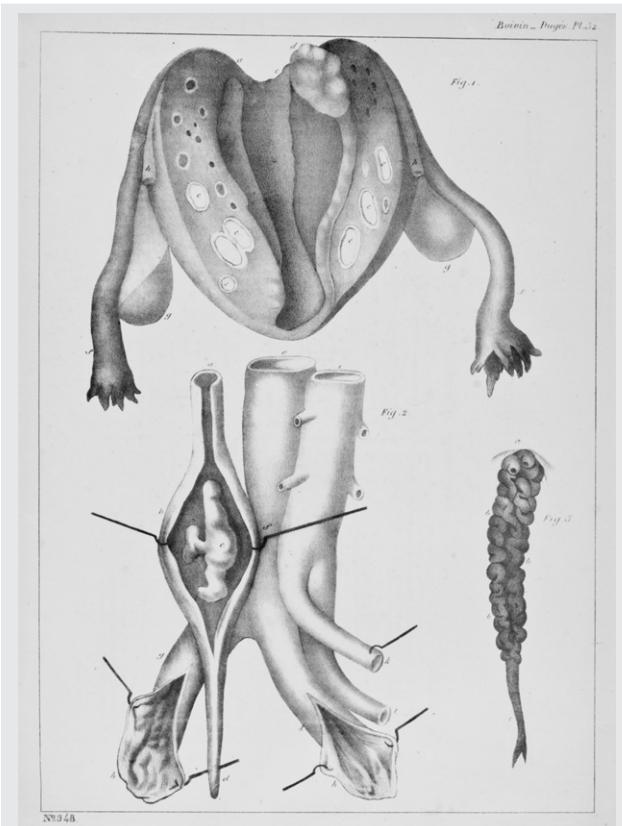
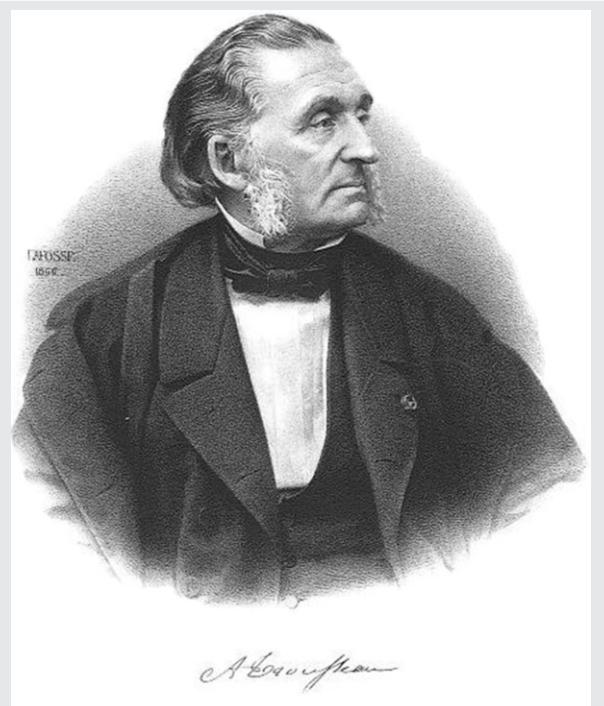


Image taken from Armand Velpeau's 1833 atlas on surgical and pathological anatomy. Based on the textual and visual evidence, this image may represent a case of adenomyosis. (Reproduced with permission from Lane Library, Stanford University. A. Velpeau, *Illustrations of All the Most Celebrated Medical and Surgical Works: Comprising a Complete System of Morbid and Descriptive Anatomy.*) Nezhat. Endometriosis in history. Fertil Steril 2012.

FIGURE 43



Portrait of French physician Armand Trousseau, who coined the term "catamenial haematoceles" and was one of the earliest in the 19th century to clinically and macroscopically describe cases with significant correspondence to endometriosis. (Reproduced courtesy of British Medical Journal Publishing Group, Ltd. Archives of Disease in Childhood Fetal Neonatal, 1999; 80[2].)

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found to be very painful when touched, and often appeared and disappeared in concert with menstruation, forming adhesions wherever they occurred that eventually would fuse the various pelvic structures together in a tangle of adhesions: in other words, frozen pelvis (69). It also appears that a nearly universal agreement had been reached that the disorder's most salient features were its menstrual connection, painful symptoms, and production of globular, fluctuating nodules.

Dysmenorrhea. Most impressively, Tilt relates that it was already common knowledge that patients usually had a history of experiencing both menorrhagia and dysmenorrhea. It was noted, for example, that "in the majority of cases the patients had suffered from pain with period" so often that he considered it "one of the most important symptoms to look for" (69).

Advances in Diagnosing Clinical Symptoms

With microscopy still a fledgling new field, careful clinical observations continued to be of critical importance. In this regard, the French were again pioneers. For example, French patient histories were exceptionally thorough, which helped them realize that women with catamenial hematoceles were often returning to the hospital at each menstrual cycle. At these monthly visits to the hospital, the women presented

with the same pain symptoms each time, which were described as “violent cramp-like pains in the lower belly” (69). Some of these women were said to be in such agonizing pain that they would be bedridden and vomiting for several days; others would drag themselves to the hospital each month, believing that they were dying. Nélaton, another French physician who was involved in these early discoveries, also found that his patients experienced similar episodes of incapacitating pain, reporting, for example, that one of his patients, “had been suffering for 4 years; nothing had given her any relief; she was forced to remain in bed all the time, and yet she had the appearance of perfect health” (88).

Rectovaginal cul-de-sac, iliac fossae, ovaries, fallopian tubes, bowel. Two subsequent literature reviews, one by John Byrne (75) and another by Alfred M’Clintock (69), noted additional symptoms, including painful intercourse. As for the various locations at which the lesions could occur, it was observed that “the effusion generally appears in the rectovaginal cul-de-sac, whence it may extend into the iliac fossae” (76, 89). However, it was also known that the lesions could present throughout the pelvic region, including inside the uterine wall itself, the ovaries, throughout the peritoneum, and on the bowel and bladder.

The disease’s ability to mimic ectopic pregnancies by invading the fallopian tubes was also recognized. In an effort to help others distinguish between these two conditions, Trouseau described cases studies in which deaths from fallopian blood bursting into the peritoneal cavity had occurred “in two young women without any relation to conception or attempted abortion; death took place in both so rapidly that suspicions of poisoning arose, and led to judicial inquiries, in which there was not elicited any other cause of death except that which I have stated” (76).

Chronic and acute forms. Three different forms of the disorder were noted: acute onset, intense, and chronic. In cases of acute onset, women died from what appeared to be burst ovarian endometriomas, as indicated by the dozens of descriptions that these early investigators reported from postmortem examinations.

Differential diagnoses. Armed with this impressive array of credible new data, many began to question the countless disease categories that conspicuously resembled catamenial hematoceles. Every day, it seemed dozens of disorders were being added to the growing list of differential diagnoses.

Tilt noted, for example, that the nodules could sometimes be distinguished from regular fibroids by their softer feel, the common presence of a retroverted uterus due to adhesions, and the absence of encapsulation, which was noted to make their removal much more difficult (81). Despite Tilt’s accurate advice, misdiagnoses were said to occur frequently, even by those familiar with the disorder (69, 89). One practitioner described the diagnostic difficulties, writing that it was “difficult to distinguish them from pelvic abscesses, especially when the broad ligaments are implicated” (89). To help distinguish between pelvic abscesses and catamenial hematoceles, one physician suggested that the difference was the catamenial hematoceles’ production of sudden

epigastric pain at menstruation which would not last as long as an abscess, nor would fevers ensue as normally occurred with abscesses (69, 81).

Ever frustrated at the chronic state of diagnostic disorganization, Bernutz continued to chastise those who made the “irrational” mistake of lumping into the category he had so painstakingly cleaned up disorders “so dissimilar as “extra-uterine pregnancies,” “congenital imperforations,” “menorrhagias,” “ruptures of aneurisms,” and “thrombus” (73). By the 1860s, this list had grown to include hemorrhagic pleurisy (69), syphilis, ovarian dropsy, chronic metritis, and hemorrhagic ovarian cysts (81, 90).

Chronic metritis versus catamenial hematoceles. The induction of chronic metritis into the list of differential diagnoses was an extraordinary advance, representing an overturn of thousands of years of thought. In fact, it was among the most significant discoveries of the pre-Rokitansky era, though medical historians have never identified it as such. As mentioned earlier, we deem this discovery significant because our research indicates that chronic metritis was among the most common disease categories, along with hysteria, that endometriosis had been lumped into for most of modern history.

Serving for centuries as a convenient diagnostic junk drawer for just about any elusive gynecologic disorder, metritis was indeed the same “inflammation of the uterus” that Soranus had written of 2,000 years earlier as responsible for all the symptoms of suffocation of the womb, including dysmenorrhea, sudden onset of violent uterine contractions, vomiting, fainting from pain, and sterility. And, recall that Soranus’s reports were nearly identical to those of Duff, who also described metritis as triggered by menstruation and causing violent pain, vomiting, uterine contractions, bowel and bladder symptoms, back pain, and prostration for days. Descriptions of chronic metritis from 19th-century sources were just as revealing (91). One medical encyclopedia from 1855, for example, reported: “In most cases, indeed, of chronic metritis there is much suffering attendant on menstruation” (92). However, the most substantial revelation gleaned from these historical texts was that one form of metritis would later be recognized as diffuse adenoma—and diffuse adenoma was the same disorder that Rokitansky microscopically discovered in 1860, which was later renamed *endometriosis* (93).

Hemorrhagic ovarian cysts. As mentioned, others in this pre-Rokitansky era also suggested that catamenial hematoceles were the same as “hemorrhagic ovarian cysts,” but this idea was somehow lost to ensuing generations. Karl Rokitansky’s 1860–1861 microscopic findings finally confirmed the connection. Later, the father of endometriosis himself John Sampson also came to this conclusion, noting in his 1921 article that adenomyosis (i.e., endometriosis) and certain hemorrhagic cysts were in fact the same disorder, only manifesting in different areas.

Proposed pathogenesis and competing theories. By this time, a variation of Ruysch’s reflux theory as one cause of catamenial hematoceles was viewed as common knowledge. For example, Byrne in 1862 noted that “the escape of blood

into the recto-uterine cul-de-sac of the peritoneum is a fact that has been so long and often clearly demonstrated as to leave no room for doubt” (75). One crucial distinction was made: in contrast to Ruysch, many by now believed that menstrual blood could reflux into the peritoneum, even when there was no known vaginal obstruction. However, like Ruysch, they believed that the blood itself was the predominant irritant that caused the lesions, inflammation, and what they believed was peritonitis.

However, several other competing and equally compelling theories of causality were circulating alongside the reflux theory. Ultimately, this etiologic chaos contributed to the somewhat contradictory diagnostic profile that began to emerge. At the root of this confusion was the reflux model’s inability to explain the disorder in its entirety; a vexing dilemma even today.

Vigorous sexual relations. One of the most common alternative theories was that blood could enter the pelvis by other means, including via external injuries to the abdomen (81). Other proposed theories would be considered quite peculiar by today’s standards; for example, some believed the lesions arose as a result of sexual activity or that engaging in intercourse during menstruation could trigger the reflux of blood. Vestiges of the nymphomania concept were also still influencing beliefs as others suggested that the lesions could arise from “violent bodily efforts, intense mental emotion, over-fatigue” and “excessive or rude coition” (69).

Clinical observations: final thoughts. All told, by the mid-19th century there were, as Byrne noted, “too many articles on the subject to even be able to mention (75). Although most credit Rokitansky as the first to identify endometriosis, our research indicates that these French physicians from the early to middle 19th century were in fact the first to do so in modern times. Even more crucially, they achieved a broader understanding than even their late 19th-century counterparts, by establishing nearly consistent nomenclature and offering a sufficiently narrow set of symptoms that were identical to modern findings, including accurate differential diagnoses.

Other 19th century investigators. It is interesting to contrast these discoveries with the research that was still underway into the condition of hysteria. Had a comparative analysis been made, the similarities between catamenial hematoceles and hysteria would have been evident. At any rate, while the proposed etiologies continued to reflect a wide array of theoretic moorings, the clinical profile of hysteria remained remarkably stable, with multiple parallels to endometriosis. For example, Baron Ernst von Feuchtersleben of Austria, a contemporary of Rokitansky, spoke of transient swellings throughout the body that occurred with hysterical outbursts (29).

However, German physician Wilhelm Griesinger (1816–1868) provided one of the most comprehensive pictures of hysteria as a disorder with nearly all the symptoms and signs of endometriosis. After years of study, he concluded that hysteria was aggravated by the onset of menstrual periods and that menstrual disorders were prevalent. Griesinger went on to state that pelvic disease was the most “exclusive cause of

hysteria,” and that local disease of the “genitals”—the ovaries and vagina—“were of the greatest importance in regard to prognosis and treatment” (29). Thus, Griesinger advised that all hysterical patients undergo pelvic exams (29). Like Schrön and a handful of others from prior centuries, Griesinger also noted an apparent hereditary propensity for hysteria (29). As for other symptoms indicative of endometriosis, Griesinger observed constipation, indigestion, and diarrhea. Similarly, the well-regarded German gynecologist Alfred Hегар (1830–1914) demonstrated his clear understanding that hysteria was an organic dysfunction and became one of the earliest to perform ovariectomies “in cases of intractable hysteria” (94).

Meanwhile, the foremost French psychiatrist Philippe Pinel, who would later be credited with laying the groundwork for Charcot and Freud, explained that the “violent” hysterical outbursts would start when a girl reached puberty; with each monthly menstruation, she would have hysterical outbursts along with “bowel and urination problems,” with symptoms persisting for “3 or 4 days,” after which the patient would return to normal. The same symptoms repeated at the next menstruation, during which time “the attacks renewed themselves with the same violence” (29).

Jean-Martin Charcot

Knowing that Pinel had identified menstruation as the triggering event of hysteria makes it all the more baffling that his contemporaries returned to the teeming quagmire of psychological explanations in search of exotic new clues. Yet this is exactly where we find the preeminent French psychiatrist Jean-Martin Charcot, who preceded and paved the way for Freud (Fig. 44).

Charcot’s first exposure to hysteria is said to have been in 1862 when he visited the Salpêtrière, the infamous insane asylum outside of Paris (Figs. 45 and 46). There, “sandwiched in between the ward for incurables and the ward for epileptics,” Charcot found an area reserved especially for women suffering from “hystero-epilepsy.” As one historian described the scene, some of these women had been viewed as “problematical young females,” who had been dumped at the Salpêtrière “by their exhausted families” (72). Others described the patients in the hysteroepilepsy ward as “among the saddest at the Salpêtrière” and that “Dante’s phrase ‘Abandon hope all ye who enter here’ might well have been written above the door” (77).

After studying these patients for some time, Charcot eventually began postulating his own theories, finding in particular that ovarian pain typified the hysterical experience. To address this particular symptom, Charcot even devised a contraption called an “ovary compressor” designed to ease the pain (29). Yet, even with all of the evidence pointing to a gynecologic cause, Charcot still concluded that hysteria was a psychological disorder. Before long, all the incriminating theories of the past were dredged up again, and women were accused anew of being mentally unstable, histrionic, and neurotically anxious. These theories continued to be accepted as valid partly because few could find any organic smoking gun (7).

FIGURE 44

A 19th-century painting depicting the renowned French psychiatrist Jean-Martin Charcot with one of his patients, a supposedly hysterical woman who has been put on trial for insanity. A diagnosis of hysteria could have led to ruinous consequences at the time, such as excommunication from family and community and involuntary imprisonment in a mental institute. (Reproduced courtesy of the U.S. National Library of Medicine. Painting by André Brouillet, titled "A clinical lesion at the Salpêtrière," *Une leçon clinique à la Salpêtrière* [1887].)

Nezhat. Endometriosis in history. Fertil Steril 2012.

Still, these fanciful ideas were not enough to stop the onward march of scientific medicine. The orthodoxies of old began to fall by the wayside, edging endometriosis toward its decisive moment of microscopic confirmation. Even the entrenched practice of bloodletting was finally being called into question (30). Another pivotal event was the introduction of a microscope that actually worked. When key improvements were made to the microscope around 1826 by Joseph Jackson Lister, it was finally welcomed into the armamentarium of medicine. Meanwhile, the first tentative steps into endocrinology were also under way, with Bernard leading the way with his astonishing discovery in 1855 that the liver excreted sugar on its own (30).

Rudolf Virchow

The degeneration theory. In such a context Rudolf Virchow, the renowned German pathologist recognized as the father of microscopic pathology, almost seems inevitable to the story of endometriosis (Fig. 47). As one medical historian put it, the conception of disease had once centered on Morgagni's organ, then on Bichat's tissue; and now, at last, we had Virchow situating disease in the essentially irreducible cell (30). Indeed, by approximately 1855, Virchow apparently had discovered the same catamenial hematoceles as the French group, but unfortunately no one made this connection. Thus, Virchow and other German and Austrian investigators described conditions similar to catamenial hematoceles that were instead referred to as cystic adenomyomas, soft myxo-myomatous cysts, or soft adenomatous myomas or cysts (95).

In explaining the softer forms of myxo-myomas, Virchow suggested that these cysts developed from the ade-noid tissue of the endometrium. In what would prove to be a powerfully influential idea, Virchow also asserted that these growths were examples of his widely accepted degeneration theory, which stated that regular fibroids could degenerate into multiple forms, including into these cystic types and sarcomas as well (95–97). As it would turn out, Virchow's soft myxo-myomatous cysts would also be eventually identified as adenomatous myomas—which were later renamed endometriosis.

Karl von Rokitansky

Microscopic discovery of endometriosis. When Austrian pathologist Karl von Rokitansky became the first to microscopically discover endometriosis in 1860, it was an exquisite synthesis of some of medicine's most salient developments: clinical pathology, microscopy, Bernard's endocrinology, Bichat's histology, Virchow's cell, de Graaf's ovary, Müller's reproductive tract, and Wolff's mesonephric ducts (Figs. 48 and 49). The newly improved microscopic histopathology technologies that had recently become available also helped Rokitansky realize that the endometrial-like glands and stroma he unexpectedly found in several tissue samples were aberrant growths and therefore constituted a previously unnamed pathology (Figs. 48 and 49).

Of course, other pathologists had access to microscopes and advanced histopathologic techniques. However, as endometriosis expert and historian Ron Batt noted, Rokitansky was

FIGURE 45



A rare image of a 19th-century vaginal hysterectomy being performed at the Salpêtrière hospital, the renowned French institute for psychological disorders where women diagnosed with hysteria were commonly sent for treatment. (Reproduced with permission of the Wellcome Library, London. Painting by G. Villanova, "Operation for vaginal hysterectomy by Professor Segond at the Salpêtrière Hospital, Paris, 1881." Image no. L0011589.)

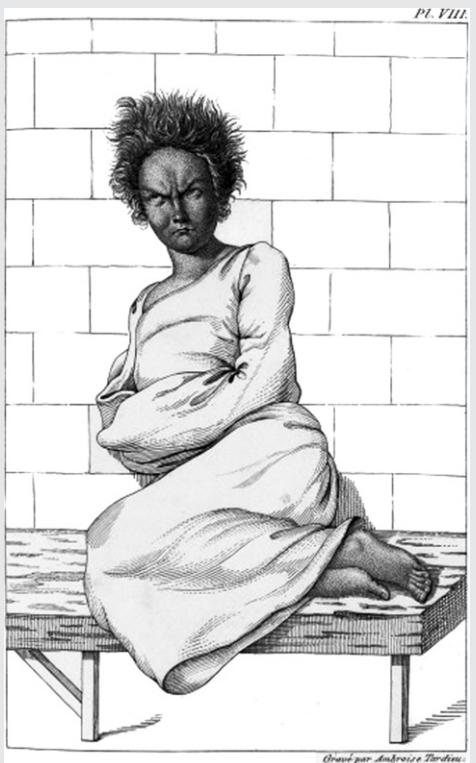
Nezhat. Endometriosis in history. *Fertil Steril* 2012.

"the age's champion dissector", and was therefore uniquely prepared for this moment by having performed at least 20,000 autopsies by Batt's estimate (30, 47). Such extensive experience proved pivotal: after Rokitansky thoroughly examined a recently excised uterine polyp, a "fresh specimen from a live patient", as Batt described it, as well as several other tissue samples stored from previous autopsies, he was able to perceive that "Some fibrous tumors of the uterus contain gland-like structures that resemble endometrial glands"(99). It is this discovery of Rokitansky's that is now viewed as perhaps the most pivotal moment in the history of endometriosis. That year Rokitansky published his findings in an article titled "On Neoplasias of the Uterine Glands in Uterine and Ovarian Sarcomas [Uterusdrusen-Neubildungen in Uterus und Ovarial-Sarcomen]" (47, 98, 99).

By 1861, Rokitansky had identified even more phenotypes, such as benign, solid, and cystic intramural uterine "adenoids," benign solid polyps that invaded the endometrial cavity, and a third benign type that invaded the ovaries (47). As for the ovarian type, he noted that "uterine-gland-containing sarcomas were also present in ovarian tissue sometimes leading to the formation of cysts," an observation that places Rokitansky as the first to microscopically detect that the two conditions derived from the same endometrial gland origin (99). Despite Rokitansky's priority in this area, today most attribute the microscopic discovery of endometriosis of the ovary to either Russell in 1899 or Sampson in 1921.

Cystosarcomas. Unfortunately, Rokitansky decided to use the rather misleading name "cystosarcoma" for the uterine polyps he had discovered, even though he knew the condition was benign (47). As Batt's research uncovered Rokitansky chose the term "sarcoma" to designate the benign growths, not because of any especial analogy with muscle-flesh, but in order to fix and define a name familiarized by long usage" (47). Some have discounted Rokitansky's work for using the term cystosarcoma. However, given the influence of Virchow's degeneration theory, it was an understandable decision. Moreover, even the early 20th century endometriosis pioneer, Cuthbert Locker, admitted that certain forms of endometriosis and other uterine growths undergoing "degeneration" were sometimes difficult to distinguish from sarcomas (100). And, even today growths are sometimes referred to as benign neoplasia.

It is curious to note that even with the prodigious number of autopsies Rokitansky performed, he did not appear to recognize that the disease he was examining was already being referred to by dozens of other names. For this reason in particular, his work proved unexpectedly inadequate for reducing the nosologic confusion. Also, because Rokitansky worked exclusively as a pathologist, few clinical symptoms were mentioned in connection with his microscopic findings. This may have contributed to the difficulty others had in connecting Rokitansky's discoveries to their own clinical experiences. Indeed, with the exception of von Recklinghausen, who

FIGURE 46

A fictionalized image of a female patient in a straitjacket from Salpetriere hospital. (Reproduced with permission of the Wellcome Library, London. Engraving by Ambroise Tardieu described as "Insane patient in a strait-waistcoat," from the novel *Les maladies mentales* by Jean Etienne Dominique Esquirol, Paris, 1838. Image no. L0011302.)

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referenced Rokitansky's work (47), it appears that other investigators continued to report on sanguineous cysts, catamenial hematoceles, ovarian hematoceles, soft myomas, and fibrocystic myomas with little mention of Rokitansky's cystosarcomas.

After Rokitansky

In addition to the terms already mentioned, lesions by dozens of other names that were described with similar endometriosis-like features continued to be referenced throughout the late 19th and early 20th centuries, including intrapelvic blood tumors (84), hemorrhagic endometritis hemorrhagic periperitonitis, "continuous growth" polyps of adenomatous uterine polyps, hemorrhagic ovarian cysts, hemorrhagic pleurisy (69), peritoneal ovaritis, subperitoneal sanguineous effusions (101), ovarian cystomata (102), hysteritis, abdominal aneurisms (103), ruptures of Graafian vesicles (104), ovarian cysts of abdominal wall, hematic cysts, internal menorrhagia, hemorrhages of ovarian vesicles, peritoneal polypi, fibrous polypi associated with internal hemorrhoids, pelvic cellulitis (105), cystofibromata (106), polypoidal submucous growths, and polypoid cystic adenomyosis of the uterus. Based

on our investigations of each of these disease classifications, they all shared significant similarities with endometriosis.

As for the French group's breakthrough research on catamenial hematoceles from earlier in the century, by the late 19th century interest in the subject seemed to fade considerably. This may have been a result of the influential views of the renowned London physician Robert Lawson Tait, whose 1888 discussion of catamenial hematoceles categorically debunked the earlier ideas, claiming that all cases of intraperitoneal hematoceles were merely the vestiges of ruptured ectopic pregnancies (103).

It was this supremely disheveled scene that the pioneers who followed Rokitansky were forced to disentangle. Among the first to follow Rokitansky and enter this chaotic fray was Waldeyer who suggested in 1870 that ovarian "cystomata" could trace their pathologic origins to an invasion of displaced epithelium stroma (102). In 1882 Babes from Budapest reported microscopic findings that described the presence of ectopic endometrial tissue in a specimen of uterine myoma (100, 107). Remarkably, Babes also described the presence of one of these "uterus myotum" in a 91-year-old woman, one of the oldest patients with endometriosis to have been reported in the literature. In 1883, Diesterweg described blood-filled cystic tumors lined with ciliated epithelium, and Austrian gynecologist Breus described a 7-liter cystic uterine myoma also lined with ciliated epithelium (47). In 1887, Johann Chiari became one of the first to report on the presence of microscopically confirmed endometrial tissue in the fallopian tubes, a disorder he called "endosalpingiosis" (100).

C. Schroeder

By at least the 1880s, if not earlier, some progress was made toward a consensus in nomenclature when Schroeder introduced the term "adenoma uteri diffusum." It was from this term that the acclaimed endometriosis pioneer Thomas Cullen and others in the 20th century would derive the modern term "diffuse adenomyoma," which Sampson in turn renamed endometriosis (93). Schroeder's work also figured into the crucial reexamination of metritis, for the second time in the century. Specifically, in 1888 Schroeder proposed that some forms of metritis were not separate disease entities at all, but were in fact the same condition as "adenoma uteri diffusum" (i.e., endometriosis). In other words, Schroeder recognized that certain phenotypes of metritis were actually most likely endometriosis (93). This critical breakthrough prompted others to reevaluate metritis in an entirely new light as well.

By the late 1880s, other diseases were added to the differential diagnostic profile of diffuse adenomyomas. During these investigations, poignant reports of the severe pain systems were recorded. In one article, for example, a woman diagnosed with diffuse adenomyomas was described as enduring pain symptoms that were "most severe during the first few days of the flow, but lasted through the whole time," and that "when the pain began she tossed about, groaning in agony, and often threw herself... on to the floor, where she rolled about in a most helpless state; she had twice threatened to take her own life in the despair of looking forward to the next menstruation" (108). Many patients

FIGURE 47

Renowned pathologist Rudolf Virchow proposed his highly influential degeneration theory in reference to gynecologic pathologies with many similarities to endometriosis and/or adenomyosis, referred to then as cystic adenomyomas, myxo-myomas, or soft adenomatous cysts. (Reproduced courtesy of the U.S. National Library of Medicine, Call no. Portrait no. 21.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

with endometriosis would probably agree that these descriptions come closer to capturing their experience of pain than the term “dysmenorrhea” ever could. Several authors now even admitted that some of their patients with diffuse adenomyomas were reporting that they had been experiencing “agonizing pain” with menstruation since their teenage years (109).

Franz Winckel

In 1887, Franz Winckel became one of the first to note that women with endometriotic nodules that were small enough to escape notice were more likely to be classified as hysterical. Specifically, he observed that: [these women are] “simply called ‘hysterical’ because the tumors are still too small to be recognized by palpation, and the uterus may neither be enlarged, displaced, nor otherwise affected” (110). He also indicated that the women’s outward appearance of health was a problem, reporting that: “While at the same time, the patients are apparently strong and vigorous, it is one of their greatest sorrows that their friends seem unable to comprehend why they should complain.”

Friedrich von Recklinghausen

These discoveries were certainly crucial contributions, but it was Friedrich von Recklinghausen who garnered considerable worldwide attention for his groundbreaking publications in 1893 and 1896 (Fig. 50). The latter monograph was particularly influential—or, as Cullen referred to it, “epoch-making” (72). Von Recklinghausen’s work stood out in part because he was among the first at the time to advance a sufficiently plau-

sible theory to explain the origin of these unusual growths. Moreover, von Recklinghausen’s new wolffian theory, named after the preeminent embryologist, Casper Wolf, represented an intriguing (if not entirely accurate) departure from traditional views about how pathologies arise. The tired, old ideas of yesteryear, implicating infection and inflammation, were retired from their service as explanatory precepts. Instead von Recklinghausen proposed that these growths derived from misplaced embryonic mesonephric ducts; in other words, they were practically preordained (47).

Although von Recklinghausen was not the first to advance an embryonic theory of pathogenesis (Breus had proposed his own a year earlier) and even though his theory would not pass scrutiny by later investigators, its introduction at this time served as a much needed catalyst for reawakening interest in the subject. His work also aided in the consolidation of nomenclature, as investigators around the world almost immediately abandoned their own terminology in favor of von Recklinghausen’s newly coined term “adenomyomata” (a term used to describe various forms of endometriosis at the time).

Von Recklinghausen controversies. One of the most acclaimed of von Recklinghausen’s contributions was his new, if somewhat disputed, insights into the glandular elements found in endometriotic growths. As Cullen explained in 1908, “Glandular elements have from time to time been noted in myomata and, according to Breus, Schroeder, Herr and Grosskopf were able to collect a total of 100 cases up to 1884. But not until the masterly work of von Recklinghausen, published in 1896, had this subject received much attention” (72).

FIGURE 48

Portrait of Austrian pathologist, Karl von Rokitansky, recognized as the first to microscopically discover endometriosis when he observed the presence of endometrial glands and stroma in pathologic lesions of the reproductive tract. (Reproduced courtesy of the U.S. National Library of Medicine.)

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Perhaps not surprisingly, it is this same crucial aspect of von Recklinghausen's research that has remained the subject of confusion, with some aspects still shrouded in ambiguity. In some histories, for example, it is suggested that von Recklinghausen completely failed to detect the glandular elements in the first place, or even if he did observe them failed to realize they were of endometrial origin, which is one of the most significant histopathologic features of endometriosis. Our review of the various sources reveals that although von Recklinghausen did observe glands and stroma in both intrauterine and extrauterine specimens, he assigned them to different origins depending on where the growths had arisen in the genital tract.

To understand how he derived this conclusion, we must reexamine the central tenets of the wolffian theory. First, it should be mentioned that the obsession with distinguishing between müllerian and wolffian tissue may well be a product of von Recklinghausen's era. During that time, embryonic studies were one of the most popular topics among pathologists; only within the previous hundred years had the different embryonic ducts from which the female organs differentiate been discovered, and they were the focus of many debates. It had already been established that the ovaries differentiate from the embryonic wolffian ducts, while the uterus, vagina, and fallopian tubes derive from the müllerian ducts. Because of these separate embryonic origins, von Recklinghausen concluded that endometriotic growths that occur in or near the

uterus, vagina, or fallopian tubes are of müllerian origin, and that, therefore, the glands and stroma observed in these areas derive from an endometrial (uterine) origin. Because the ovaries trace their lineage to the wolffian ducts, he insisted that the glands observed in growths in or nearby the ovaries were separate entities, not of endometrial origin.

Von Recklinghausen clung to his theory in almost heroic defiance against the empirical evidence. This peculiar system explains many of the confusing contradictions that characterize von Recklinghausen's work, such as how he became one of the earliest (after Chiari) to microscopically confirm endometriosis of the fallopian tubes. He made this discovery while proposing that another disorder, salpingitis nodoso, was in fact simply another manifestation of müllerian-derived extrauterine adenomyomata, and thus with glands and stroma of endometrial origin (100). Over the years much has been made of this material misstep by von Recklinghausen. In the final analysis, however, it should be viewed as an entirely excusable lapse. This becomes especially apparent when one considers that his error was discovered by Cullen and others who had access to more advanced microscopy and histopathology technologies. Years later, Cullen made an effort to point out these extenuating factors. Cullen also made it clear that even with newer technologies it was still difficult to distinguish between various tissues, noting that: "Sometimes the mucous membrane origin was easily proved, but in many cases not only were numerous sections necessary but in some instances a clear idea of the condition was obtainable only after an examination of very large sections embracing the entire uterine wall" (72).

After von Recklinghausen

Unlike Rokitansky's discoveries, which were offered without a compelling theoretical framework in which to make sense of his findings, von Recklinghausen's wolffian theory initially attracted some supporters, many of whom were his students. This may explain the increased enthusiasm for studying adenomyomata that occurred at the time. One preeminent endometriosis pioneer later even remarked that, despite the substantial flaw in von Recklinghausen's working model, he considered von Recklinghausen's work the critical contribution that placed diffuse adenomyoma on the map as a "real pathology" (100).

As endometriosis historian Batt has noted, it was also a time of "intense pathologic competition, with pathologists striving to have pathologic conditions named after them," which was perhaps another factor contributing to the flurry of research activity (99). Duly inspired, dozens of new investigators headed straight for the fray of analysis, with many eventually offering their own theories of pathogenesis. For example, in 1895 the dystopic theory was introduced by Orloff, who described "glandular spaces under the serosa covering uterine myomata," which he considered to arise from "embryonic cells" (111). Breus also advanced an embryonic cell theory of his own in 1894, one year ahead of von Recklinghausen's more well-known wolffian hypothesis (112, 113). In 1897, Kossmann "demonstrated that the tube could supply gland elements and found that tubal adenomyoma

FIGURE 49

Rokitansky with his fellow professors at the Vienna General Hospital. (Reproduced with permission of the Wellcome Library, London. Lithograph by J. Stadler, 1855, after A. Prinzhofer [1853], titled "Medical professors at the University of Vienna." Image no. V0006770.)

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was from accessory tubes," which advanced the theory that these growths arose from accessory müllerian ducts (114). Russian physician N. S. Iwanoff proposed his own coelomic metaplasia theory in 1898, and one year later Russell suggested that endometriosis "arose from Müllerian (paramesonephric) tissue" (112, 115, 116).

In 1896 German gynecologist William Freund of Strassburg contributed substantially to the much-needed clarification concerning the clinical symptomology by describing the physical symptoms most commonly reported by his patients. That same year, Pick reported that he had encountered endometrial tissue inside of the ovaries of one of his patients (117). Similarly, in 1897 Ries described endometrial tissue found in the lymphatic system. One year later, Russell reported being "astonished to find areas which were an exact prototype of the uterine glands and interglandular connective tissue" (116). By 1898, adenomyoma of the round ligaments had been reported by Bluhm (118). Other investigators of this era included Babe, Ruge, Ribbert, Schottlander, Hauser, Strauss, Ricker, Martin (119), Orthmann, Baraban, Schroder, Werth, and Pilliet (100, 120).

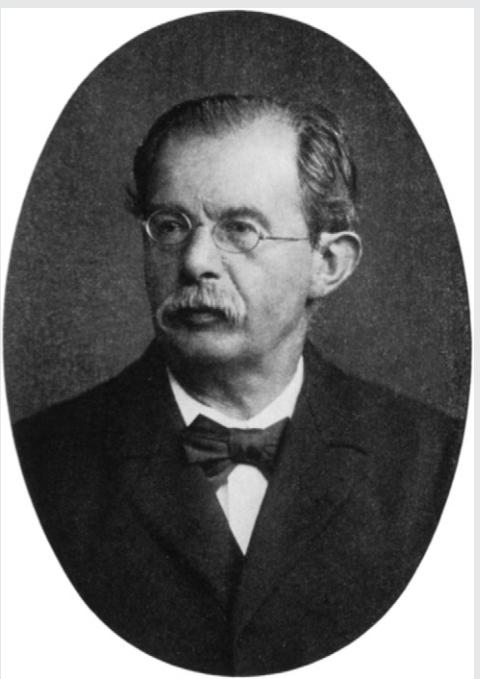
Thomas Cullen

Of all the late 19th-century practitioners, it was Canadian-born, Baltimore-based Thomas Cullen who would achieve some of the era's most critical new insights. One of the earliest

Americans to specialize in endometriosis and also well-regarded for helping establish the first gynecologic pathology laboratory at Johns Hopkins Hospital, Cullen holds a unique place in the pantheon of endometriosis pioneers for bringing all the disparate pieces together and formulating an exceptionally comprehensive clinical and histopathological picture of endometriosis (still called diffuse adenomyomas at this time) (121) (Fig. 51).

Cullen developed an interest in the disorder from the moment he microscopically observed his first case in 1882 (122). However, the catalyzing moment for Cullen was when he realized that the world-famous von Recklinghausen had made an astonishing error by identifying some growths as having wolffian rather than endometrial (müllerian) origins. Only then did Cullen understand the significance of his own observations. Within 3 years of von Recklinghausen's initial article, Cullen published his own first article on the subject, which distinctly contradicted von Recklinghausen by emphasizing the disorder's mucosal origin (99). Because Cullen could demonstrate that uterine adenomyosis "always could be traced to uterine endometrium," this meant that the wolffian theory was "impossible" (114).

Though the bulk of Cullen's work would occur in the 20th century, by the end of the 19th century he had already made significant contributions in understanding the debilitating pain that accompanied the disorder, describing patients as undergoing "severe pain in the lower part of the abdomen" and "painful and profuse menstruation" (99).

FIGURE 50

Portrait of renowned German pathologist Friedrich Daniel von Recklinghausen (1833–1910), who published highly influential works on endometriosis and advanced the Wolffian theory of pathogenesis. (Image courtesy of the U.S. National Library of Medicine. Published by J. F. Lehmann, Munich, Call no. Portrait no. 5608A.)

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Treatment Options in the 19th Century

As in previous centuries, cultural norms continued to shape medical beliefs, and therefore treatment options followed the prevailing trends of the period. For example, in the so-called Victorian era of the 19th century, women were viewed as unusually delicate; thus, even well-regarded physicians like Lawson Tait suggested that young women with menstrual cramps should refrain from reading novels or listening to music as these hobbies were thought to cause overexcitement of their sensitive emotions and thereby worsen their illness. Other cultural influences were not so harmless: for a brief time, clitoridectomies became a popular treatment for supposed cases of nymphomania (Fig. 52).

These of course are drastic examples of therapeutic extremes. However more scientific treatment options were pursued as well. Approximately eight distinct patterns of care were promoted during the 19th century when endometriosis was either strongly suspected or (after 1860) confirmed through microscopic investigations:

1. No surgical intervention (remedies such as leeches, caustics, tincture of iodine, hot douches, sponge tents, ovary compressors, manual adjustments to the uterus, morphine, enemas, and/or orally ingested opiates, herbal medicants, or alcohol)

2. The twist-and-tear-off method
3. Puncturing/“tapping” growths
4. The “clawing out” method
5. Electrocautery
6. Dilation and curettage (D&C)
7. Oophorectomy, subtotal hysterectomy (abdominal and vaginal)
8. Partial excisions

No surgical intervention. From the early to middle 19th century, before anesthesia and aseptic techniques were available, most physicians refrained from treating endometriotic surgically. However, this moratorium on surgery did not stop the development of invasive or painful treatments. In fact, aside from the milder prescribed therapies such as hot douches and morphine for pain, more invasive techniques such as bloodletting or the application of leeches to the cervix were practiced, some of which continued to be used up to the 1880s (Fig. 53). Indeed dozens of mainstream journal articles by well-regarded physicians demonstrate that leeches were considered a mainstay in treating any condition associated with menstruation (Fig. 54). To some extent, this form of treatment reflected that the spoiled menstrual blood theories, first proposed in Hippocrates’ time, still held sway (108).

In one unsettling account, a practitioner advised others to be sure to count their leeches, as they had been known to occasionally wind up lost inside the uterus, a dreaded event by both patient and physician. Surely, anyone with a healthy imagination would conclude that losing one’s leeches inside a patient’s uterus was definitely not a good thing to do. Even so, the author felt compelled to clarify that a lost leech would cause not only considerable physical pain but undue mental distress for the patient (123). Some attempts were made to discourage the use of leeches; Rousseau noted that leeches applied to the genitals led to “local disturbances” such as boils, and that healing leech bites became itchy, which could “lead to bad habits” (76). So central were leeches to 19th-century medical care that one medical historian found that they represented 4% of one London hospital’s budget; Meanwhile, France was, at one point, purportedly importing 33 million leeches each year (30, 123, 124).

A variety of concoctions for ingestion, often of unknown or questionable ingredients, also continued to be popular. Pinkham’s Vegetable Compound, one of the most successful of these patent medicines, even had its own catchy tune: “Elsie W. had no children | There was nothing in her blouse | So she took some Vegetable Compound, | Now they milk her with the cows” (Fig. 55). Even medicinal marijuana found its way into the story of endometriosis: Queen Victoria’s doctor, Sir John Russell Reynolds, was said to have prescribed her “monthly doses of Cannabis” throughout her adult life.

Other nonsurgical but nevertheless invasive techniques included the internal and external application of caustic stypics. These substances consisted of materials such as perchloride of iron, nitrate, or mercury-based compounds, which were applied directly onto the inner surface of the uterus or anywhere else that lesions could be felt (69). Sponge tents

FIGURE 51

Thomas Stephen Cullen

Portrait of Thomas Cullen, America's first and most influential endometriosis specialist. (Reproduced with permission of Oxford Journals. *Human Reproduction*, 2004;19[4]:760–768.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

designed as cervical dilators to relieve severe menstrual cramping were also in fashion for much of the 19th century. However, many practitioners complained of their popularity because of the serious uterine infections caused, all without any clear benefit.

One of the more peculiar (though decidedly more innocuous) treatments was the practice of repositioning uteri, which were thought to have become displaced. Many patients would present to their doctors with pain symptoms they believed to be from a displaced uterus. Patients commonly believed that uterine displacement could be caused by a strong jolt during a carriage ride on a bumpy road or from rough horseback riding. In one such case, the patient presented to her doctor after a riding accident in which she believed her uterus had become misplaced; the doctor said that the patient reported all of her symptoms vanished after he had manually repositioned her uterus. Of course, it is quite possible that healthy retroverted uteri were also treated in this manner and blamed as the cause of many uterine disorders.

The practice of repositioning inspired other unfortunate variations. The least invasive and presumably least painful was the method in which the physician would manipulate the uterus manually by actually “pulling and tugging” on it in an attempt to move it to a presumed normal position. Other methods involved specially devised instruments such as the intrauterine repository, which was worn by a patient to pull her uterus out of its backward sliding ways and restore it to its presumed correct position. As with the sponge tents,

because these intrauterine devices often caused severe infections, they were abandoned as soon as the surgical arts became safer in the late 19th century.

Humoral-based ideas still influenced treatment options as well, as can be inferred by the many purging emetics and enemas still being lavishly prescribed. Physicians were aware that many of these medicines were all but unbearable for their patients. One doctor recommended “a mixture of dilute sulphuric acid and turpentine”, but discovered that “the women that can bear to take this atrocious compound are few and far between.”

For milder cases, traditional palliative care was recommended, often in the form of alcohol, opium, or morphine for the pain. Outside mainstream medicine, folk remedies continued to be peddled, which comprised dubious ingredients with even murkier side effects. One such famous remedy prescribed specifically for hysterical women was Hoffmann’s soothing liquor—its main ingredient was ether, which no doubt must have led to disastrous consequences at times (40).

Twist and tear off. For any growth that protruded enough to be ligated, the twist-and-tear-off procedure could be employed. However, this method was also known for its high mortality rate.

Tapping and puncturing

The introduction of anesthesia by the mid-century made attempts to puncture the nodules feasible, through either vaginal or abdominal approaches. The mortality rates, however, were reportedly as high as 70%. After one member of that early group of French investigators lost a patient by this method, he strongly urged others to attempt puncture techniques only in cases when the lesions interfered with bowel function (81). The introduction of trocars as a safer means for puncturing was also suggested; one source noted that “puncture with a trocar” was preferred to the “incision with a bistoury.” However, even this safer method had its pitfalls. A surgeon named M. Monad attempted this procedure for what he thought was a simple case of a displaced uterus. It was too late when Monad realized that the patient actually had “peri-uterine sanguineous tumors (i.e. most probably endometriosis).” When he punctured this growth with the trocar, it caused an “effusion of blood into the utero-recto pouch” and the patient died of peritonitis (69).

Clawing out. From about the 1850s to 1870s, some dug out the nodules with blunt scissors or even with their own fingernails. To control the hemorrhaging that invariably ensued, packing and draining were attempted. However, these efforts usually proved useless and many died from blood loss or infection. In 1874, the renowned gynecologist James Marion Sims used this fingernail-clawing technique on an infertile patient with severe menstrual pain who subsequently died. Sims believed this outcome occurred because he misdiagnosed the patient with regular fibroids, a condition that he had successfully surgically treated numerous times. It turned out, however, that the patient had cystic myomas, the same growths that Rokitansky had identified as endometriosis. Unbeknownst to Sims, endometriosis was infinitely more

FIGURE 52

Image of an operating room from the late 19th century. (Reproduced courtesy of the U.S. National Library of Medicine. Described as "Instruction in Surgery. Scene in the Operating Room Amphitheater of the Massachusetts General Hospital, Boston Administering Ether to a Patient, 1888." Call no. WX 2 AM4 B7M4 No. 11 box 4 ins ovr.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

difficult to surgically excise than regular fibroids. As a result of this completely unexpected outcome, Sims emphatically warned that attempting to surgically excise endometriotic nodules was too dangerous unless severe hemorrhaging was occurring. This is one of the earliest detailed accounts we have found of a patient with endometriosis dying as a result of surgical intervention (125).

Electricity. Applying electrocautery directly onto the lesions was also used briefly in the late 19th century. By mid-century, after galvanization techniques were introduced into medicine, electric shock treatment was also used on women diagnosed with hysteria (40).

Dilation and curettage. Blindly applied dilation and curettage methods were deployed routinely soon after Recamier introduced an improved instrument and method for this purpose (126, 127). Recamier himself used this technique on the catamenial hematoceles he came across, incising through the posterior cul-de-sac.

Oophorectomy. After the success of McDowell's ovariotomies became known in medical circles throughout the world, many brave pioneers—both patients and physicians—began tentatively experimenting with this procedure for severe cases (those thought to be ovarian cancer for example). One medical historian estimated that at least 200 ovariotomies were performed in England between the years 1838 through 1855, before the widespread use of anesthesia and before the introduction of aseptic techniques (30). However, although McDowell reported only a 38% mortality for his own career total of 13 procedures, estimates from other sources indicate that mortality rates were as high as 75% for the average 19th-century physician (128).

Abdominal hysterectomy partial myomectomy. With the introduction of aseptic techniques, surgery came to be seen as one of the most promising forms of treatment for women's disorders. This was especially true after the 1880s: when aseptic techniques had finally been universally embraced, death rates were reduced to more acceptable levels. Within this surgical milieu, hysterectomies and myomectomies became preferred treatments. In fact, in 1883 Diesterweg became one of the earliest to suggest total hysterectomy for patients with endometriosis (129).

Attempts to remove nodules via procedures similar to a myomectomy were already understood to be highly risky and ineffective in the case of fibrocytic myomas (as mentioned, now identified microscopically as endometriosis). As one physician warned, "the termination of the cystic fibrocytic myoma is widely different from that of the simple [fibroid and leads] . . . to the destruction, sooner or later, of the life of the patient." In any case, it was eventually realized that simply excising the nodules or removing the ovaries was not enough to prevent the disorder from returning. Therefore, physicians began recommending hysterectomies.

Given the dangers of surgical interventions, it is not clear why doctors or patients took on these risks. One explanation might be the widespread belief in Virchow's degeneration theory: that is, these risky surgeries were performed not only by the woman's request to relieve pain and preserve her reproductive function but also because it was generally assumed that these growths would eventually degenerate into cancer. One physician of the era expressed precisely this sentiment when he recounted trying to remove nodules in the belief that they might turn cancerous, and lost his patient as a result. Hence, physicians began demanding that a common nomenclature be established because each type of growth called for

FIGURE 53



For centuries, bloodletting was routinely practiced and was among the most common treatments prescribed throughout the ages for women with endometriosis-like symptoms. (Reproduced courtesy of the U.S. National Library of Medicine, "La Tout Par Precaution/N. Guerard inv et fecit." Call no. WZ 336 G92 no. 1 sol.)

Nezhat. Endometriosis in history. *Fertil Steril* 2012.

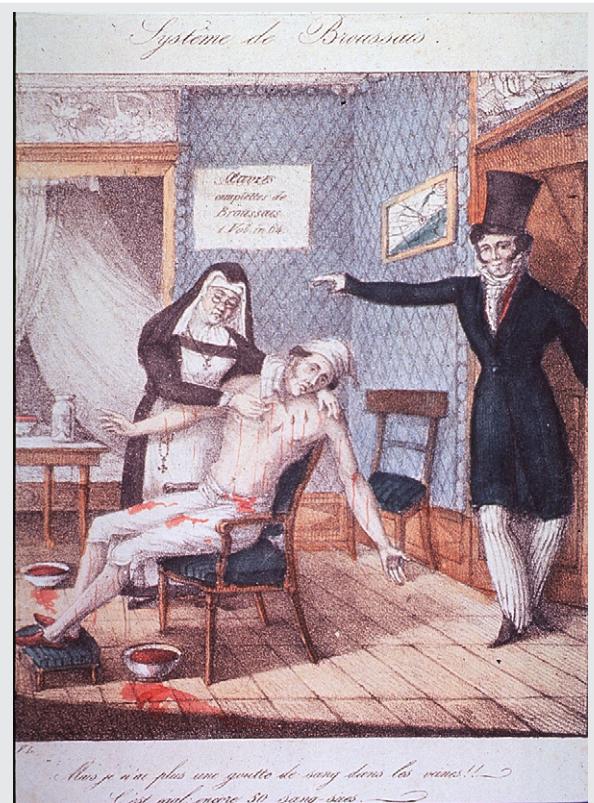
distinct surgical strategies: the right approach applied to the wrong lesion was potentially disastrous.

Surgeons versus Traditional Physicians (Internists)

The astonishingly high number of surgery-related deaths did not go unnoticed by nonsurgeons. Indeed, some of the most heated debates in medicine arose during this era as medicine transitioned from strategies of expectant treatment to those of aggressive surgical intervention. One internist author lamented the growing disuse of conservative methods in favor of surgical interventions, derisively remarking that such conservative approaches had "once more been forgotten by those modern surgeons who deem knife using surgical science" (130).

By the mid-century mark, when death rates for most gynecologic surgeries were still as high as 50% to 70%, skepticism was certainly understandable. Some even went so far as to refer to the newly introduced "ovariotomies" as akin to murder (128, 131). The methods surgeons used to reduce infections must have also been viewed as shocking departures from traditional medical care. For example, in these preantibiotic days, when aseptic techniques were still not entirely perfected, regulated, or accepted, it was

FIGURE 54



Until the late 19th century, the insertion of leeches inside of a woman's vagina and uterus was routinely prescribed for patients with endometriosis-like symptoms. (Reproduced courtesy of the U.S. National Library of Medicine. Call no. WZ 336 Z55 no. 42.)

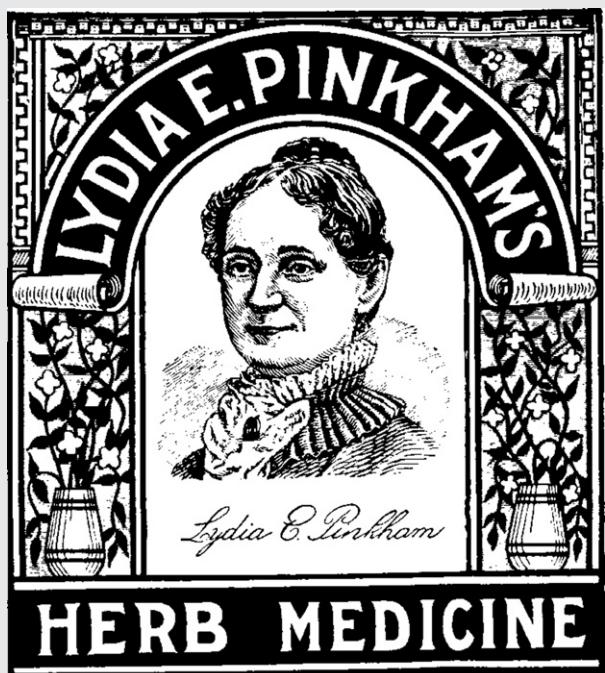
Nezhat. Endometriosis in history. *Fertil Steril* 2012.

a common practice for surgeons to pour hot distilled water into the abdominal cavity as a means for preventing septic peritonitis.

Methods that appeared to be even remotely invasive were also hotly contested. Even the newly introduced custom of routinely performing vaginal inspections with a speculum was debated. This practice, first initiated by French physicians, caused great outrage in British and American medical circles. In fact, for most of the 19th century, few physicians in Britain and America performed vaginal examinations of any sort, as they believed it to be too much of a violation of decorum (30, 124). These specula wars led one British physician to go so far as to suggest that French women were practically lining up to receive what he perversely imagined were gratifying speculum inspections. As he stated in 1838, "Our notions of modesty may be . . . out of date. Yet I trust . . . that some time will elapse before OUR wives and daughters will distinguish themselves in this free and easy style" (124).

Conservative and minimally invasive approaches. Dodging salacious accusations has never been fun, but the real vexing issue that surgeons and patients faced was the fact that mortality rates were still very high by modern standards,

FIGURE 55



Mrs. Lydia Pinkham's Vegetable Compound, a popular alternative medicine used by women throughout the late 19th and early 20th centuries for gynecologic and other conditions. (Reproduced courtesy of Wikipedia, http://en.wikipedia.org/wiki/File:Lydia_Pinkham.png.)

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"regularly exceeding 70%, even in the hands of the most eminent surgeons. The mortality rates for hysterectomies in particular were so high that the procedure was formally condemned by the Academy of Medicine in Paris in 1872.

Mortality rates. Even though by the latter half of the 19th century, mortality rates had improved from the mid-century highs of 75%, the incidence of mortality was still disturbingly high, leaving room for different approaches to be considered. For example, early attempts at partial excisions were being performed at least by 1852, though even in these more conservative cases recovery was not guaranteed. In an example offered by Tilt, a misdiagnosis similar to the one made by Marion Sims proved similarly disastrous for one Parisian surgeon, who "opened up the womb thinking to get out a fibrous uterine tumor" but instead found a catamenial haematocele, which again was known to be difficult to excise. As Tilt goes on to explain, the patient bled to death "because the artery was cut" (81).

With such consequences looming in the background, surgeons were desperate to find safer alternatives. By the 1880s, modest improvements to excisional techniques were made. For example, in 1888, Byrne describes his partial excision technique as a "case of pelvic haematocele cured by operation" (101). By the 1890s, Cullen was performing similar procedures in which only certain portions of the endometriosis would be excised from the uterus through an abdominal incision (132). From these examples we can see that 19th-century

practitioners were clearly interested in performing surgeries in the most minimally invasive way possible, a hundred-year head start on those of us who thought we were the ones to initiate this revolution.

Vaginal hysterectomies. With the pressure mounting to reduce mortality rates, vaginal hysterectomies were reintroduced as a presumed safer alternative to abdominal surgery. Osiander of Germany had already achieved the first modern-day vaginal hysterectomy by 1801. Langenbeck and others, especially French physicians, soon followed suit. Yet the method fell out of favor again, most probably as a result of its difficulty but also because new technologies and techniques were introduced that made abdominal surgeries somewhat safer.

Just as has been the case in modern times, the two approaches competed for attention. Despite its recognized difficulty to perform, the vaginal method was appreciated for its considerably lower risks. It was known to be associated with lower mortality, with some surgeons reporting rates as low as 15% in 1886, and somewhere between 2% and 10% by the late 19th century. It was also touted for its fewer post-operative adhesions and complications, and faster patient recovery.

Patient preferences. During this time of immense upheaval in medicine, an important trend could be seen emerging: the hitherto nearly soundless, formless beings known as patients began asking questions - and demanding answers. An article from 1896 provided the first hints that this trend was on the ascendant. The central issue addressed in the article concerned the dilemma that one doctor faced in deciding how to perform hysterectomies. He admitted that his own preference was for the abdominal route. However, his patients were so keen to avoid that method's large abdominal incision that they were pressuring him to perform the more demanding vaginal procedure, an approach that he admitted being ill-prepared to pursue. What a familiar dilemma this was; indeed, it what a startling reminder of history's recursive nature to see that the same sorts of dialogues that arose after videolaparoscopy was introduced had occurred a hundred years before.

Even though minimally invasive techniques were finally becoming available again, this did not exactly catalyze a wholesale departure from the older methods. One report from 1893 demonstrates that tapping was still being deployed: the surgeon explained that the untappable type of nodule, fibrocystic myoma (i.e., endometriosis), was "tapped by mistake" and that "the patient died of septicaemia from suppuration of the tumour" (133).

Final reflection on the 19th century. In other disciplines of medicine, endoscopic techniques figured prominently in the treatment of some of history's most well-known figures. In one famous instance of endoscopy going awry, the technique was even implicated in the downfall of an empire, the one that Napoleon Bonaparte's nephew was trying to rebuild. Yet among the hundreds of articles reviewed for this historical overview, other than a brief, vague account mentioning Howard Kelly's use of air cystoscopy in 1896, we found no evidence in the English language literature of the 19th century to suggest that endoscopic techniques were being applied to diagnose or treat any gynecologic conditions.

20TH CENTURY

By the opening hours of the 20th century, advances in multiple scientific arenas had already been achieved that would eventually figure prominently in the story of endometriosis. For example, the field of gynecologic laparoscopy was burgeoning, with Kelly, Ott, Bernheim, Orndoff, Short (134), Case, Hope, Fervers, Boesch, Anderson, and Benedict among the earliest to perform minor therapeutic and diagnostic laparoscopies. On the endocrinologic front, by 1895 Robert Morris had performed the first successful ovarian transplantation in a rodent, which helped bring the elusive workings of reproductive endocrinology into sharper relief (135). Meanwhile, the new discipline of histology was on its way to becoming an indispensable diagnostic tool, especially after the introduction of modern specimen-slicing technologies which transformed it almost overnight into an infinitely more accurate methodology.

Mental Illness

There was just one small problem, however: these fancy advances availed surgeons nothing in the face of a seemingly invisible pathology. Indeed, it would be an abiding irony of modern medicine that all the advanced technologies in the world—the exquisitely calibrated microscopes, the penetrating eyes of x-rays, lasers, loops, logarithms, longer and better incisions—would all prove powerless against the supreme inscrutability of invisible lesions governed by an unfathomable array of molecular mechanisms. Yet modern medicine was expected to outwit disease states; when no lesions were found at surgery, practitioners shifted their focus back to the patient's mental status; four thousand years of science and searching, only to arrive back to this.

It was the unseen saboteur of the century. By the early 20th century, significant milestones had been achieved nevertheless. After having captured the attention of such widely respected authorities as Rokitansky, von Recklinghausen, and Cullen, the signature symptoms of endometriosis (still known most commonly as adenomyosis or diffuse adenomyosis) had apparently become fairly well-known, at least in English-language and German medical publications. In a rush of optimism, endometriosis specialist W. P. Graves reported in 1906 that so much awareness had been raised about the disorder that “even hospital attendants” were suggesting it to doctors as a possible diagnosis (120, 126). Meanwhile, a new generation of investigators hastened the search for answers, such as Robert Meyer, who uncovered crucial new evidence in support of Iwanoff's coelomic metaplasia theory. In 1907 Meyer would also become the first to perform a bowel reanastomosis for the treatment of endometriosis (126), all without the benefit of antibiotics or other modern conveniences. Other early 20th-century endometriosis researchers of note were Hirst (136), von Franque (137), Pick, de Jong, Mahle (114), MacCarty, and Graves (138).

Atypical Clinical Experiences

It was already known that endometriosis could arise in different regions of the pelvis, but researchers were only now real-

izing that symptoms could also manifest in vastly atypical ways. Jasche was one of the earliest to describe these anomalies, reporting in 1909 that some cases involved uncommon symptoms such as “no sterility, no peritonitis, no pain, no dysuria, and no local pain” (100). Additionally, in 1918 English endometriosis pioneer Cuthbert Lockyer published his well-respected, widely referenced textbook “Fibroids and Allied Tumors.” Along with Meyer and Cullen, Lockyer was among the earliest to perform bowel resections on a patient whose bowel lesions were deeply infiltrating into the mucosa, which had been causing “diarrhea, defecation very painful, constipation and obstruction up to 3 weeks” (100). This form of extensive bowel endometriosis had rarely been seen, and both Lockyer and later Cullen incorrectly believed theirs were the first cases in which endometriosis had invaded the mucosa of the rectum.

Thomas Cullen

As advanced as both Meyer's and Lockyer's accomplishments were, it was the work of Thomas Cullen that continues to stand out throughout the 1900s. Having observed his first case of endometriosis in 1882, by the beginning of the new century Cullen had the advantage of 20 years' worth of experience on which to draw. After publishing on 22 cases of endometriosis in 1903, Cullen found his interest still piqued: “Since then I have paid especial attention to these growths and have been astonished at the striking frequency with which they occur” (72). Indeed, Cullen became a fount of new insights; he was the first, for example, to recognize the need to remove the appendix as a prophylactic treatment for endometriosis patients. Cullen's years of experience in the laboratory where he obtained extensive knowledge of histology and pathologic anatomy also paid off, helping him become the first to realize that endometriosis could invade pelvic nerves, a process causing patients “excruciating pain when the pelvic nerves are invaded and then menses comes” (47). One such patient of Cullen's experienced such severe menstrual pain that he felt “it was necessary to keep her under the influence of chloroform” (72).

Cullen's meticulous microscopic investigations were arguably the most crucial of the era for reducing the confusion concerning the histopathological features of endometriosis. To address any lingering doubts, Cullen made it clear that the defining microscopic features of endometriosis were the presence of glands that were “invariably surrounded by the normal stroma of the mucosa.” But, in a conspicuous departure from von Recklinghausen's theory, he asserted that these glands always derived from an endometrial origin. Without these crucial clarifications, it would have been difficult to re-establish a stable definition of endometriosis given the growing theoretical discord that had ensued since the introduction of the müllerian and wolffian theories in particular (72).

Kidney damage. Cullen was among the first to report the severe kidney damage caused by endometriosis encircling the ureters. Just as some other pioneers from the previous century had suspected, Cullen recognized early that even total hysterectomy did not ensure the disease would be cured. Cullen also provided some of the best descriptions of the disorder's ability

to render the anatomy into frozen pelvises, which he said appeared as if all the organs had been sealed into one solid mass by the powers of some biologic glue (126).

Demonstrating his gifted surgical skills, Cullen was again one of the earliest, after Meyer, to perform bowel resections and to advocate surgical intervention for bowel endometriosis, warning of the great danger it posed if left untreated. He pointed out that endometriosis-induced intestinal obstruction could cause some patients to become chronic invalids, and in some cases would “undoubtedly lead to her death” (Fig. 56).

Morbidity and mortality. Even after experiencing devastating surgical losses, Cullen continued to believe that the potential for intestinal obstruction was the far greater risk if it was left untreated. Bowel resections were known to be one of surgery’s most difficult operations and were associated with high mortality rates, so Cullen’s continued advocacy was viewed by his contemporaries as highly controversial. Even so, he remained a vocal proponent of the procedure’s use in serious cases. He was, however, quick to acknowledge the difficulty of these surgeries, stating that “without equivocation bowel surgery is infinitely more difficult than [even] hysterectomies for carcinoma” (126).

Predictably, most of Cullen’s patients died from these surgeries. In some cases, he was forced to perform back-to-back laparotomies because, as he explained, his patients did “worse and worse” after surgery. Other adverse outcomes would ensue months later. In one unusually delayed reaction, 5 months after the first bowel surgery his patient returned presenting with abdominal pain and vomiting. Cullen would later report that “they couldn’t figure it out until it was too late.” No blood had been coming from her stool, so they reasoned that it was probably nothing too serious. Therefore, an expectant approach was taken. She was recovering in the hospital from these symptoms after having received opiates for the pain, when, without warning, the “patient fell over, gasped a few times and died.” It was only at autopsy that Cullen uncovered the reason: adhesions had encapsulated her bowel into loops of unrecognizable strangulated sections.

Ever alert for other disorders that endometriosis may have been mimicking, Cullen also offered crucial insights concerning differential diagnoses. He was one of the earliest, for example, to directly suggest that presumed cases of pelvic inflammatory disease were in fact endometriosis, stating in 1918 that “when early operation is performed in these cases, a certain number of our ‘mild pelvic inflammatory cases’ that heretofore have gone from bad to worse will be cured” (126).

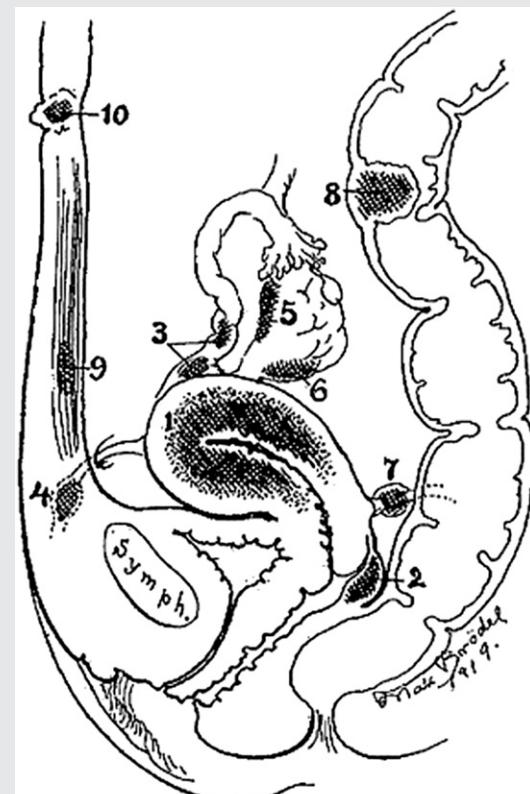
Evolution of surgical approaches. In the face of such unpredictable outcomes, Cullen’s treatment approaches clearly went through stages of evolution as his understanding of the disorder’s complexity grew over time. For milder cases, he recognized that a minimally invasive approach involving localized excisional techniques was sufficient. For those cases that had progressed beyond the stage where selective removal was effective, Cullen recommended subtotal abdominal hysterectomy with bilateral oophorectomy, stating that “for the diffuse variety, nothing but total hysterectomy should be performed.”

As for techniques, Cullen suggests abdominal entries for severe cases, owing to the fact that the vaginal route is often impassable and riskier when the uterus is completely fixed to other organs or when the adnexa are inflamed. In all, Cullen’s contributions profoundly impacted the course of events in the history of endometriosis. His publications were particularly influential, especially his 1908 masterpiece, “Adenomyomas of the Uterus,” which Sampson acknowledged as a crucial factor in catalyzing his interest in endometriosis.

After Cullen, before Sampson. Despite Cullen’s breakthrough discoveries, and although there were now many new investigators in endometriosis research, the disorder still generated a great deal of confusion, and dozens of names were applied to the same condition because sustained, widespread interest in the subject of endometriosis had failed to fully materialize. Many misconceptions were being circulated at this time, even though hints as to their inaccuracy were showing up in the literature. For example, despite dozens of case studies in which patients clearly explained that their symptoms had existed since their teenage years, there were still reports suggesting that the average age of onset was age 41.

Disappointment over the limited number of efficacious treatment options was also already evident as early as 1918,

FIGURE 56



An image of endometriosis of the bowel from Thomas Cullen’s 1920 article. *The distribution of adenomyomas containing uterine mucosa.* (Reproduced with permission of Oxford Journals. *Human Reproduction*, 2004;19[4]:760–8.)

Nezhat. Endometriosis in history. *Fertil Steril* 2012.

when even Lockyer remarked that “there is no doubt that cutting and medical treatment make matters worse.” Another physician from 1918 expressed dismay at the difficulty of definitively diagnosing the disorder, lamenting “how is a clinician to decide what can only be found out by the knife and anatomy?”

John Sampson

Even with the tremendous insights gained over the last few decades, the fact remained that the state of knowledge concerning endometriosis amounted to no more than a speck of dust when compared with the vast universe of lingering unknowns. The void was waiting to be filled. This is why the searing lucidity that characterized John Sampson’s works was greeted with such an effusion of enthusiasm from all around the world; his research filled the void by offering fresh new insights and the promise of more to come (Figs. 57 and 58). Known today as the “father of endometriosis,” Sampson was, in many ways, a very peculiar and exceedingly private man. His contemporaries recognized him as a gifted and meticulous surgeon, but others saw him as more of a “severe task master.” Whatever the case, it is evident now that Sampson’s uncompromising ways and exhaustive precision figured into his research papers, which were densely packed with exceedingly intricate descriptions and averaged 79 pages long.

Sampson’s article from 1927 is the most well-known, but his publications from 1921 and 1922 contain equally important discoveries, including allusions to his retrograde menstruation theory as well as important insights concerning endometriosis of the bowel (139). Another important detail Sampson mentioned in his 1921 article was his belief that hemorrhagic ovarian cysts were in fact the same disorder as endometriosis, a conclusion he based on exhaustive microscopic analyses. As mentioned before, this was a crucial insight in the story of endometriosis, because it correlated with the same conclusion made by the 19th-century French group who suspected hemorrhagic ovarian cysts to be the same as catamenial hematoceles. In this way, albeit somewhat indirectly, the historical linkages between catamenial hematoceles and endometriosis can again be discerned.

However, Sampson’s article from 1927, in which the term “endometriosis” was first proposed, proved to be one of the most influential publications in the history of endometriosis. It was in this work that Sampson introduced his retrograde menstruation theory (or we might say his reintroduction of Schrön’s and Ruysch’s reflux theories from more than two centuries before) as his working hypothesis to explain the presence of “heterotopic or misplaced endometrial tissue” (140). Sampson also reported on his continued efforts to search for miscategorized diseases that might be endometriosis. With his microscope serving as the final arbiter, Sampson continued to uncover even more diseases that were microscopically confirmed to be endometriosis. Sampson’s many distinct surgical philosophies were also evident in this and other articles. In contrast to Cullen, for instance, Sampson advised against surgical intervention for bowel lesions,

suggesting instead total hysterectomy with bilateral salpingo-oophorectomy (141).

After Sampson. Though the amount of research conducted before Sampson was not insubstantial, it was nothing compared with the thousands of articles written after Sampson’s pivotal research reached the international airwaves. The much-needed consensus in taxonomy had finally been achieved, and eventually it was clear that the term “endometriosis” had been accepted into the fold of taxonomic convention. Within 20 years of Sampson’s 1927 publications, endometriosis was found throughout the body and in teenage girls as well. Moreover, at least six theories of pathogenesis were advanced. Meanwhile, in 1925, the French gynecologist Cotte performed the first presacral nerve resection, a procedure that would one day be offered to endometriosis patients.

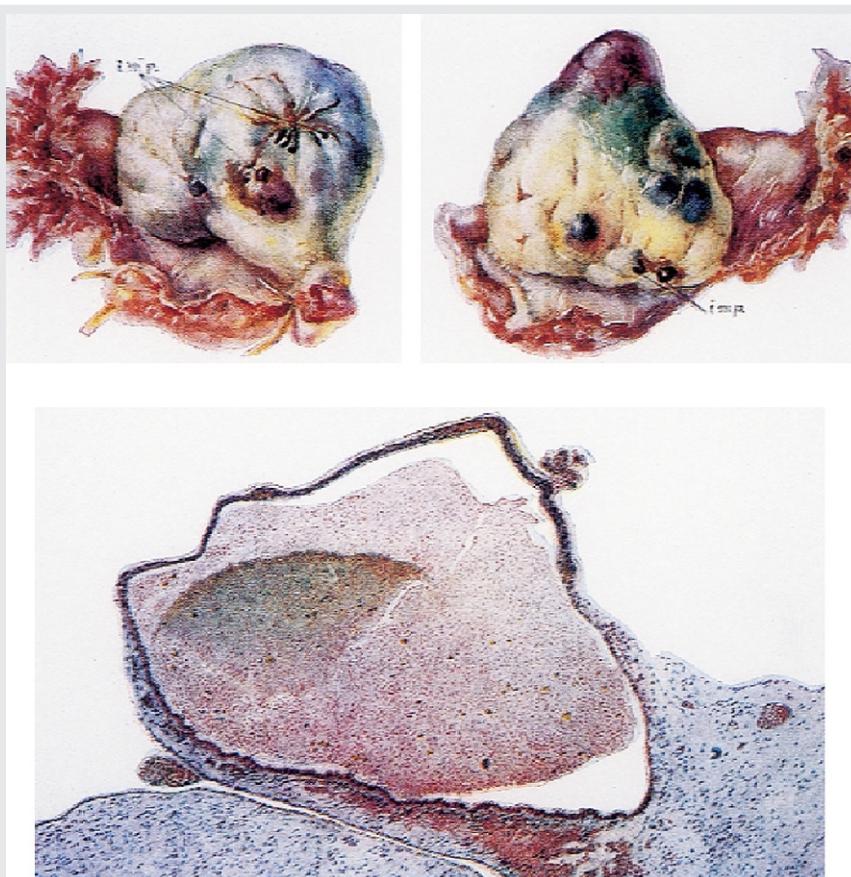
Before the end of the 1920s, reports of postoperative iatrogenic deposits in laparotomy scars had been reported (142), and important debates were under way about managing endometriosis as conservatively as possible. For example, in 1929, Lawrence R. Wharton published a seminal report about the use of conservative surgery for the removal of endometriotic lesions. Although others had suggested similar approaches, Wharton’s work was especially influential given its arrival when the heady days of multiple laparotomies were in full throttle. Atypical experiences continued to be noted as well, with studies demonstrating that even patients as old as age 85 could present with symptoms that required surgical intervention. The mystery of pathogenesis also continued to be a topic of great interest, and Halban conducted some of the best research on the subject (143).

1930s–1940s

By the end of the 1930s, endometriosis of the lungs, large bowel, colon, rectum, bladder, lymph nodes, cervix, and round ligaments had been reported (144–148). More cases in teenagers were discovered, which launched a brief period of active research on the subject (149). An article published in 1946 by Fallon was especially influential and brought this segment of the population into sharp relief (150).

Naturally, speculation about the etiology of endometriosis continued, with some reporting that endometriosis was probably of tubal origin, while others reevaluated the theories of the late 19th century (151). Some reports were beginning to emerge that suggested endometriosis was not as rare as had been believed. Animal studies with endometriosis implants were also in progress (152, 153).

12th-century androgenic treatments revisited. Early in the decade of the 1940s, important advances in endocrinology were made by Fuller Albright, the father of modern endocrinology, which had far-reaching, positive consequences for endometriosis research. For example, testosterone and progesterone, first isolated and synthesized in the 1930s, had by now entered into the repertoire of therapies for endometriosis. The first English language article on the subject was published in 1941 by Geist and Salmon, who suggested using androgens as a potential treatment for endometriosis (122).

FIGURE 57

Drawings of endometriosis specimens from John Sampson's seminal works of the 1920s. (Reproduced with permission of Wolters Kluwer Health. *International Journal of Gynecological Pathology*, 2001; 20[10].)

Nezhat. Endometriosis in history. Fertil Steril 2012.

Of course, this was not the first time in history that prescriptions for hormone-disrupting substances were suggested for

gynecologic disorders; recall that the Hippocratics had prescribed bull urine and practitioners from the early 12th century had suggested ground-up goat testicles as a treatment option.

Clinical trials. The 1940s represented an era when endometriosis research clearly intensified. By the end of the decade, dozens of surveys and clinical trials had been published, with Keene and Kimbrough, Counseller, Payne, Fallas and Rosenblum, Holmes, Hayden, Sanders, Fallon, and Meigs cited as among the most notable investigators.

Understanding of the different types of lesions had also considerably advanced, which in turn led to the introduction of more nuanced surgical approaches. Some of the most important refinements in surgical techniques included the renewed interest in conservative approaches, particularly directed toward avoiding the removal of ovaries, a subject, which like today, was the focus of many heated debates. Meanwhile, after being effectively abandoned for nearly two decades, interest in laparoscopy began to reemerge as a viable diagnostic modality. Many attribute this change to the influence of legendary French gynecologist Raoul Palmer, whose innovations made the technique considerably safer and more reliable (Fig. 59).

FIGURE 58

Drawings of endometriosis specimens from John Sampson's seminal works of the 1920s. (Reproduced with permission of Wolters Kluwer Health. *International Journal of Gynecological Pathology*, 2001; 20[10].)

Nezhat. Endometriosis in history. Fertil Steril 2012.

Misdiagnoses and misconceptions. As encouraging as this precipitous uptick in endometriosis research was, it did not completely curtail the vast array of spectacular misconceptions about women and pelvic pain that lingered in the popular imagination, some of which had been circulating since at least the late Iron Age. For instance, in a throwback to antiquity, 20th-century physicians began urging women to get married and have children as soon as possible, the result of growing awareness about endometriosis' potential impact on fertility. Suggestions that endometriosis only afflicted certain social classes also continued to be made; one investigator from 1949 asked, "Is endometriosis principally a disease of the higher social and economic levels of society?" And, despite the groundswell of interest that Sampson had so decisively launched, many articles lamented the fact that endometriosis continued to be misdiagnosed.

1950s–1970s

The 1950s was a decade characterized by both controversial and pivotal developments. Routine pelvic exams became much more common in the United States as a result of growing awareness about cervical cancer in the wake of Papanicolaou's research and his development of the Pap smear as an effective predictive technology. Driven by concerns about cervical cancer, surgical standards were also transforming: by the 1950s, the preferred form of hysterectomy in the United States had changed from supracervical to total abdominal hysterectomy.

It was during this time as well that one of the most pivotal breakthroughs in reproductive medicine was achieved by the legendary John Rock, who in association with George Pinkus developed a hormonal contraceptive, initially introduced in 1957 for the treatment of menstrual disorders. Among the first to be treated with this early version of the pill were women with endometriosis (154) (Fig. 60). However, given the limited understanding at the time about the pill's long-term effects, the initial prototypes were composed of such high doses of estrogen that many patients suffered considerable side effects. Some studies have suggested that higher incidences of cancers and other fatal complications later ensued among this early treatment population. Other promising new medical interventions were also introduced during this period, including Danazol, which arrived in the late 1970s via research by Greenblatt and Dmowski.

Even with this groundswell of novel treatment options, the overwhelming majority of studies indicated that endometriosis continued to be substantially misdiagnosed, with some reports suggesting that as many as 70% of cases during the 1970s went undetected (155). These diagnostic delays were disappointing, but advances in research progressed at a rapid clip. Research into the theories of pathogenesis continued throughout this period, with Ferguson publishing some of the most important works in this area in 1969 (156). Donald Chatman overturned long-standing myths concerning endometriosis, pelvic pain, and peritoneal pockets when he became one of the first to demonstrate that as many as 68% of peritoneal pockets were infiltrated with endometriosis, a figure that

jumped to 79% just a few years later after he had conducted even larger studies.

In terms of surgical options for women with endometriosis, multiple laparotomies and hysterectomies remained the standard surgical interventions of the day. However, laparoscopy continued to demonstrate its diagnostic prowess, the first step toward ending the practice of relying on exploratory laparotomies as a diagnostic modality. By 1955, Palmer had made headlines with his debut of the first color film of a live laparoscopy; a few years later, Hans Frangenheim of Germany would produce his famous 1958 color film of a laparoscopically captured ovulation in progress, a feat that would reverberate throughout the world of gynecologic laparoscopists for years to come (157). By the end of the 1960s, Melvin Cohen and Alvin Siegler were treating tubal disease laparoscopically, one of the first truly minimally invasive surgical options of the 20th century to have been offered to patients with endometriosis of the tubes.

Throughout the 1970s Batt, Brosens, Bruhat, Buttram, Clarke, Darai, DeCherney, Franklin, Gomel, Hasson, Levinson, Manhes, Rioux, Rock and many others achieved similarly significant advances in microsurgical techniques and other minimally invasive methods. Gomel, for example, reported improved fertility outcomes after applying his meticulous

FIGURE 59



One of the most pivotal breakthroughs in reproductive medicine was achieved by legendary pioneer, John Rock, in association with George Pinkus, who developed a hormonal contraceptive, first introduced in 1957. Among the first to be treated with this early version of the pill were women with endometriosis. (Reproduced with permission of Getty Images, photography by Lew Robertson.)

Nezhat. Endometriosis in history. *Fertil Steril* 2012.

FIGURE 60

Raoul Palmer, pioneer of gynecologic laparoscopy. (Reproduced with permission of Journal of Society of Laparoendoscopic Surgeons, 1997;1[30]:289–92.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

microsurgical techniques (158, 159). Other surgical advances involved new technologies or techniques, such as bipolar devices that were developed and adapted for use with laparoscopic surgery in 1973 by five independent sources; Cloutier, Corson, Hirsh, Kleppinger, and Rioux (160–162). Hasson's 1971 introduction of "open laparoscopy" allowed for direct visualization during trocar placement (163). Clarke's laparoscopic suturing innovations were especially crucial for enabling progress toward operative laparoscopy (164, 165). Meanwhile, in 1979, the team of Bruhat, Mage, and Manhes, became one of the first to apply a CO₂ laser in laparoscopic procedures, while Yona Tadir of Israel independently accomplished the same a few months later (166). Bellina, Donnez, Diamond, Martin, Sutton, and Tulandi were also among the earliest to incorporate the laser into their gynecologic surgery practices. By 1974, Kurt Semm had expanded laparoscopy into therapeutics, achieving some success in treating mild to moderate disease (167, 168).

However, in these pre-video days, the awkward manner in which laparoscopy was performed—bending over and squinting with one eye closed into the scope's tiny aperture—limited its operative utility to only the simplest procedures. Even then, only the era's few virtuosos—Bruhat, Cohen, Frangenheim, Gomel, Manhes, Palmer, Semm, and Steptoe—could perform laparoscopy in its cumbersome pre-modern form. For the vast majority of surgeons, pre-video operative laparoscopy was infeasible and ineffective. For the vast majority of women with endometriosis; even those with mild cases but especially those with severe, multiorgan disease, it was almost as though nothing had changed: the inescapable reality was that multiple laparotomies and hysterectomies remained the only viable surgical choices until the introduction of videolaparoscopic surgery in the late 1970s.

Treatment Options: 1900s–1970s

As mentioned, the period between 1900 and 1970 was characterized by unprecedented advances in medicine. It was a time when bacteria took a backseat to penicillin, and when the average life span in the developed world nearly doubled. Yet when it came to the treatment of endometriosis, only five effective therapeutic options were offered in this same 80-year time frame:

1. Subtotal and/or total hysterectomy, with bilateral salpingo-oophorectomy
2. Hysterectomy with conservation of ovaries
3. Conservative approaches, such as excisional techniques
4. Treatment with radium
5. Hormone treatments

Within these categories, many nuances continued to be debated. For example, there continued to be deliberations about whether to preserve the ovaries. Meanwhile, although Cullen used radium on the rectum for any pathology that was left after surgery, radiation therapy was thankfully abandoned by about the early 1950s. Discussions also continued about whether vaginal or abdominal hysterectomies were best. By the mid-20th century, abdominal hysterectomies had clearly prevailed in Germany, Britain, and the United States, but the vaginal route continued to be favored in France.

By the 1950s, some women were already undergoing multiple laparotomies for endometriosis. In the early half of the 20th century, patients undergoing abdominal surgeries could expect to receive enemas of turpentine, boiled brains for lunch, alcohol and strychnine for any postoperative cardiac events, arsenic for anemia, and mortality rates of between 5% and 10% (100, 169) (Fig. 61). By the mid-1950s, after the introduction of improved anesthetics, blood transfusions, and intravenous therapies, mortality had dropped to about 25 in 1,000 (169).

Video-Assisted Laparoscopic Surgery "V.A.L.S."

In the late 1970s, Camran Nezhat introduced video-assisted laparoscopy. Prior to this, even mild cases of endometriosis were being treated by laparotomy. By 1984–1986, Nezhat reported successful treatment of extensive endometriosis, which proved that it was possible to treat even the most extensive endometriosis by laparoscopy (170, 171) (Figs. 62 and 63). Within a few years, at the 44th annual meeting of the American Fertility Society in October of 1988, the first successful laparoscopic treatment of endometriosis of the bowel was reported by Nezhat (172). Another milestone was achieved when Nezhat became the first to report on laparoscopic radical hysterectomy, with paraaortic and pelvic node dissection (186, 187). The first laparoscopic hysterectomy reported by Reich in 1989 was another highlight of the late 1980s (202). In subsequent years the Nezhats reported on the successful laparoscopic treatment of the most complicated benign and malignant pathologies, including endometriosis of the bladder, ureter, diaphragm, liver, and lung. Important new advances in minimally

invasive treatment options for endometriomas were also introduced by the Nezhats (173–182).

The introduction of video-assisted endoscopy by Nezhat, together with his foresight to treat even the most advanced pathologies endoscopically, revolutionized modern-day surgery and transformed minimally invasive surgery into a truly viable discipline that will eventually replace almost all forms of open surgery. The increasing application of advanced operative laparoscopy is a direct consequence of the surgical ingenuity of the early pioneers (172, 183–185). Multiple studies have established that laparoscopy results in lower morbidity, better visualization of areas difficult to access thus allowing for more precise dissection, decreased blood loss, decreased postoperative pain, and faster recovery (173). Over time, the extent of laparoscopic dissection expanded. After the outcomes of video-assisted endoscopy consistently proved superior to open surgery, it was clear that even the most extensive pathology could be managed endoscopically. Therefore, since the 1980s, our facility has been performing and advocating for a minimally invasive approach for almost all surgical procedures (188, 189). As we have reported over the years, essentially the only limiting factors of video-assisted endoscopy are the skill and experience of the surgeon and the availability of proper instrumentation (171, 176). Initially, our declaration that almost all laparotomies can be avoided was not popularly received. It was not until 2004 that the *New England Journal of Medicine* recommended and encouraged the same advanced methods and techniques for the same exact procedures that we were the first to introduce nearly two decades earlier. Ironically, too, these same procedures now recommended over open methods are the same ones that were being called “barbaric” just a few years ago (172, 190).

In a strange way, it may be endometriosis that we have to partially credit for shaping the course of surgery away from large incisions and toward video-assisted laparoscopy. After all, if bowel resections and debulking of extensive and infiltrative pelvic endometriosis, some of surgery’s most difficult procedures, could be accomplished laparoscopically, this meant that practically any other procedure also could be performed by this technique, providing the same significant benefits to patients.

Endometriosis has influenced surgical history in other surprising, even counterintuitive ways. For example, even though women had been undergoing abdominal surgeries at least since McDowell’s debut surgery of 1809 (191, 192), it is curious to note that the multitude of morphologies that endometriosis can take was not fully recognized until late in the 20th century. For example, even though Cullen, Sampson, and others had reported on extragenital endometriosis in the early 1920s (126, 193), many years went by before researchers realized it could also infiltrate arteries, blood vessels, bone, brain, and the diaphragm. The anguish of preteen and teenage girls with endometriosis also was nearly completely overlooked for most of the 20th century because it had been assumed that this age group was only rarely if ever afflicted. As modern research now demonstrates, the disease has been found in patients as young as 8 years to as old as 91 years, as was first reported by Babes in 1882 (100, 107, 194, 195).

As for its prevalence in teenagers, a recent study by Opoku-Anane and Laufer found that as many as 98% of teenagers who report chronic pelvic pain that is unresponsive to conventional therapy have endometriosis.

Because of lingering beliefs associating pelvic pain with promiscuity, women continued to be blamed for their illnesses. Women from U.S. minority communities have been especially susceptible to being misdiagnosed with diseases that imply sexual transgression. Don Chatman was the first to scientifically debunk these views in 1976 with his seminal article “Endometriosis in the Black Woman,” in which he reported that as many as 21% of African American women with pathology-confirmed endometriosis had been mistakenly diagnosed with pelvic inflammatory disease (PID) (196). Yet nearly 20 years later, dismal statistics were still being reported: one study from 1993 found that “as many as 40 percent of African American women [were] misdiagnosed as having a sexually transmitted PID when in fact they [suffered] from endometriosis” (197). The study did not provide the corresponding rates of misdiagnoses that occurred in other groups, which makes it difficult to make comparisons between different populations, but it is clear that en masse misdiagnoses of women with endometriosis have been the norm.

However, of all the misconceptions about endometriosis, it is arguably the centuries-old notion linking pelvic pain to mental illness that seems to have been most responsible for causing diagnostic delays and chronic indifference to women’s complaints of pain. Indeed, for most of the 20th century, women experiencing pain without any perceptible organic cause were often assumed to be hysterical or mentally unstable. With such mass misdiagnoses pervading the landscape of women’s medicine, until recently many patients with endometriosis were just as likely to be sent to a psychiatrist as a gynecologist when their inexplicable, multiorgan symptoms were mistaken for psychosomatic disorders instead (198). In short, despite its presumably ancient presence among us, endometriosis continued to evade the clinical gaze, eluding all attempts to understand its enigmatic essence, even after the large incisions of laparotomies should have helped surgeons detect its presence.

When surgeons converted to video-assisted laparoscopy, they gained a completely new understanding of the anatomy. For the first time, too, surgeons were able to consistently visualize atypical lesions that before might have easily been mistaken for normal tissue but under magnification could clearly be seen as pathological formations. Such stunning visualization had never been obtained while performing diagnostic laparoscopies by the old method of peering into an eyepiece, or even from the vantage point of the supposedly superior view afforded by large laparotomy incisions (199) (Fig. 64 and Fig. 65). Using the new technique allowed for visualization of lesions as small as 400 μm for red and 150 μm for clear lesions (129).

With an improved ability to visualize pathologies that had gone undetected for centuries, video-assisted endoscopy contributed to an era of greater understanding about the true nature of endometriosis, anatomy, and other disorders, finally uncovering what patients had been

FIGURE 61

Operating room from about the mid-20th century. (Reproduced courtesy of the U.S. National Library of Medicine and the World Health Organization, Call No. PPO44534, WHO, box 1.)

Nezhat. Endometriosis in history. Fertil Steril 2012.

suffering from all along (129, 200). By the late 1980s, newly converted video laparoscopists began to report similar clinical findings, overturning nearly a century of statistics that had misrepresented the true prevalence and severity rates of endometriosis (129, 201). As one report from 2011 concluded, many now believe that with “the enhanced magnification available with modern-day laparoscopy, virtually all endometriosis can be identified.”

FIGURE 62

Camran Nezhat, circa 1980, performing videolaparoscopy with one of the early video camera prototypes.

Nezhat. Endometriosis in history. Fertil Steril 2012.

Surgical Progress: 1980s–1990s

After the excellent results of video-assisted laparoscopy became apparent, more moments of envelope-pushing were made by such pioneers as Abrao, Adamyan, Adamson, Brosens, Canis, D'Hooghe, Donnez, Dubuisson, Falcone, Fazleabas, Fusi, Griffith, Hunt, Koninckx, Koh, Lee, Luciano, Mage, Malinak, Martin, Matzoni, Mencaglia, Miller, Minnelli, Nisolle, Olive, Perry, Possover, Pouly, Redwine, Reich Ussia, Vercillini, Vilos, Wattiez, and Zupi, to name but a few, all of whom had achieved crucial milestones and made substantial refinements in surgical techniques and technologies (183, 185).

FIGURE 63

Image from 1977 showing how laparoscopy used to be performed, bending over and squinting with one eye closed to peer through the small aperture. (Reproduced with permission of the Royal Society. *Proceedings B*, 1977;195[1119].)

Nezhat. Endometriosis in history. Fertil Steril 2012.

FIGURE 64

Evolution of Videolaparoscopy

Circa late 1970s



Circa early 1980s



Today



The evolution of videolaparoscopy cameras and incisions. (Images of cameras and videolaparoscopy scars courtesy of Dr. Camran Nezhat. Image of laparotomy scar reproduced with permission of Dreamstime.com and photographer Rasumrok1, image no. 15610695.)

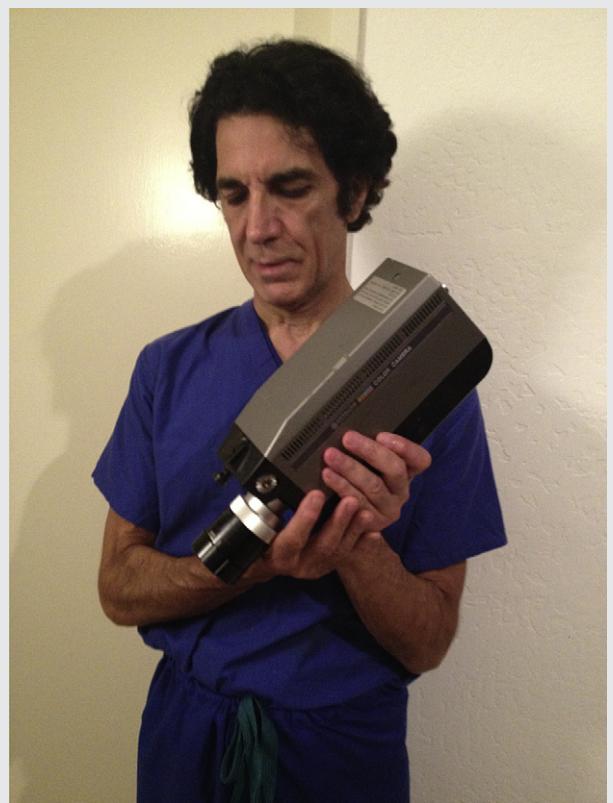
Nezhat. Endometriosis in history. *Fertil Steril* 2012.

New technologies developed specifically for video-assisted endoscopy were also finally becoming available, allowing surgeons to branch out even further in the minimally invasive direction. Novel laparoscopic techniques such as single-port laparoscopy, introduced by M. A. Pelosi, were developed, as well as robotic technologies such as Intuitive Surgical's da Vinci robot, developed by a team led by Ajit Shah and Phil Greene of Stanford Research International.

Other Achievements: 1980s–Present

Throughout the 1980s and to the present time, breakthroughs in basic science research have continued (203). Russell and Jansen were the first to report on nonpigmented lesions in 1986, with Koninckx, Martin, and Redwine independently reporting similar findings soon after. Although the CA-125 glycoprotein was initially introduced by Bast in 1983 as a serum marker for epithelial cancer of the ovary, within a few

years Barbieri would publish his landmark 1987 study on its role as a potential biomarker for endometriosis. Koninckx and Martin were also early investigators of CA-125 and reported important new findings. Meanwhile, Redwine and the team of Koninckx and Martin separately reported groundbreaking new research on deep infiltrative endometriosis (DIE). Their reports led to a sea change of new awareness about DIE, which had been particularly poorly understood and commonly overlooked. The 1980s also marked a time when extensive research on the gonadotropin-releasing hormone (GnRH) agonists and prostaglandin inhibitors was underway. By 1997 Hornung et al. (204) achieved progress in understanding how immunologic dysfunction might play a role in the development of endometriosis. Linda Giudice of the University of California at San Francisco has achieved tremendous insights into the genetic and molecular pathways involved in the development of endometriosis.

FIGURE 65

Nezhat holding one of the first video cameras he used when he first introduced videolaparoscopy.

Nezhat. Endometriosis in history. Fertil Steril 2012.

Many organizational innovations also have been made, including the founding of the Endometriosis Association in 1980 by co-founders Mary Lou Ballweg and Carolyn Keith, the Endometriosis.org in 2005 by Lone Hummelshoj, and the Endometriosis Foundation of America in 2009 by co-founders Padma Lakshmi and Dr. Tamer Seckin. Many world congresses on endometriosis are now being held, but the first one was The World Congress on Endometriosis, held in Clermont-Ferrand, France in 1986.

More data on the genetic pathways of endometriosis also have been reported. A study headed by Hugh Taylor of Yale Medical School found a mutation in part of the KRAS gene that is associated with abnormal endometrial cell growth and decreased progesterone receptor levels. Compared with the general population where only 5% are estimated to have this mutation, in their study group of 150 women with endometriosis, 31% were found to carry a variant allele of the gene which altered its binding with let-7 microRNA (205). Another intriguing new report suggests that viable stem cells present in menstrual blood may be triggering the development of endometriosis; if true, this would give new credence to the retrograde menstruation theory of pathogenesis and would also help explain how and why endometriosis can recur despite multiple surgeries. Advances in the under-

standing and treatment of endometriosis-associated ovarian carcinoma have also been highlighted in recent decades (206, 207).

FINAL THOUGHTS

In looking back at how far we have come, it is heartening to see that such extraordinary progress has been made. However, as one practitioner remarked in 2004, we are still in a state of “aetiological confusion and therapeutic anarchy” when it comes to the study and treatment of endometriosis (208, 209). Not surprisingly, many questions remain unanswered, but what we can say with reasonable assurance is that endometriosis appears to be an old disease that has affected women for millennia. Allusions to its insidious presence are documented in ancient medical texts dating back more than 4,000 years. That endometriosis appears to have such an ancient lineage makes it all the more surprising that it is, for the most part, still an enigma. Perhaps most remarkably, some treatments have remained the same for hundreds of years with only minor variations.

Our research also revealed that the theories used to conceptualize women’s illnesses throughout the ages were highly susceptible to the influences of culturally determined notions of illness. This was a timely reminder that medical beliefs are never just the products of objective science but are equally likely to be reflections of the shifting whims of social norms. We also can see that, on some level, pelvic pain has been believed for centuries to be the deserved consequence of presumed depravity on the woman’s part—their imagined madness, weakness, or promiscuity manifesting as otherwise inexplicable cases of chronic pelvic pain.

As for the centuries-long, unsolved mystery of hysteria, we believe that enough credible evidence exists to substantiate our hypothesis that hysteria was most likely endometriosis in the majority of cases. Even though hysteria was largely discredited in modern times, nevertheless it continued to exert tremendous influence on attitudes about women and illness for most of the 20th century.

Sadly, this painful legacy of diagnostic disarray continues. Even today, many women with endometriosis report that they are told “it’s all in their heads,” a throwback to the hysterical concept. And, with reports from as recently as 1995 finding that, on average, over 50% of women with chronic pelvic pain were found to have no “organic” basis—this meant that essentially half of all women who sought medical care for pelvic pain remained medical castaways, with some still considered hysterical or mentally unstable (198). Such diagnostic oversights have been most likely contributing to the rarely discussed phenomenon of unnecessary, “nontherapeutic” appendectomies: according to some studies, as many as 52% of all emergency appendectomies performed in women turn out to be unwarranted (210–216). As a consequence of these centuries-old misconceptions, women today still face considerable challenges in securing a diagnosis: on average, 6 to 7 years pass before a woman is correctly identified as having endometriosis (155). And, perhaps most surprisingly, we continue to recommend pregnancy as a form of treatment, the same prescription offered over 4,000 years ago.

In terms of technologic challenges, there have been many breakthroughs, but we are still years away from introducing an accurate, noninvasive diagnostic test. Meanwhile, the majority of hysterectomies for endometriosis are still being performed abdominally instead of with minimally invasive methods. Despite nationwide training efforts, only a small fraction of surgeons can perform some of the more advanced laparoscopic techniques, leaving the choice of laparotomy as the default response.

Lessons learned. As for the lessons learned from this retrospective review spanning over 4,000 years, the repeated observations made in Greco-Roman medical traditions especially have provided us with a greater appreciation of the potentially significant affects endometriosis can have on teenagers. Perhaps we should be refocusing our efforts on earlier clinical screenings and intervention for this population. Intervening at this early age could potentially reduce damage to organs and possibly even induce a remission.

We also discerned patterns of social practices that potentially offer insight into both historical and modern epidemiologic trends. For example, the fact that the Hippocratics were advising that changes in marriage practices be made partially in response to an endometriosis-like illness would seem to indicate that the disorder was believed to be fairly widespread. Since their inferences about prevalence rates were drawn from a comparatively small population pool, this in turn would suggest that the Hippocratics may have had rates that were somewhat higher than the 5%- 15% range commonly cited today. Other epidemiological inferences can also be made based on these historical findings. For example, if the Hippocratics were indeed encountering endometriosis enough to view it as a fairly common disorder, we might need to rethink contemporary theories which implicate dioxins, PCBs, and other modern chemicals as causative agents.

Still, despite the lingering challenges and ambiguities, it is clear that we have achieved appreciable progress. Instead of enduring excruciating pain or multiple laparotomies, women now have promising medical treatments as well as minimally invasive surgical options that can treat the disorder while preserving fertility. And, finally, patients at least now have a chance to be properly diagnosed, freeing them from thousands of years of misdiagnoses, when their menstrual pain was presumed to be an inescapable, biological destiny.

An integrated theory of pathogenesis: multiple perspectives. As for the “etiological chaos” that persists, drawing from over 30 years of endometriosis research and surgical experience, which includes by now approximately 14,000 surgeries, several important insights come to mind. The first is that we believe it is time to radically reevaluate the conceptualization of the four main theories of pathogenesis. In our view, all four theories are partially correct. We arrived at this hybrid theory after observing what we suspect to have been all four pathogeneses at play: [1] retrograde menstrual endometrium implanting on peritoneal surfaces and transforming into pathology; [2] a pattern of coelomic metaplastic differentiation of mesothelial cells into endometrium-like tissue; [3] lymphatic and venous spread transporting and depositing endometriosis into areas that cannot be explained by the other

theories; and [4] iatrogenic or direct transplantation, which would explain the presence of endometriosis in surgical scars. Rather than viewing these theories from a zero-sum standpoint, we believe that conceptualizing endometriosis through the framework of an integrated model could potentially lead to significant improvements in preventive and treatment strategies, as well as potentially lead us closer to a cure.

Another important insight that we have gained concerns prevalence rates. Over the years, our views on this subject have changed dramatically after repeatedly noting that a strong relationship between endometriosis and leiomyomas seems to exist. Fibroids arise from a single precursor via monoclonal proliferation. A similar mechanism should be considered and investigated for endometriosis. In fact, if we consider endometriosis and leiomyomas to be of the same spectrum of disease, the missing link is adenomyosis. After all, adenomyosis is essentially endometriosis of the uterine muscle, and an adenomyoma is essentially a tumor of endometriosis of the uterine muscle.

In one of our recent studies, we looked at 131 women undergoing surgical intervention for symptomatic leiomyomas and found that 113 had pathology-confirmed endometriosis, representing an 86% correlation between the two entities (217). Extrapolating from these findings, we then considered the prevalence rates of fibroids. It has been well established that fibroids have a prevalence of 30% to 50% (218). With a world population of approximately 3.5 billion women, that means an estimated 1.05 to 1.75 billion women either have had, will have, or currently do have fibroids. Given our hypothesis that at least an 86% coexistence of endometriosis and fibroids exists, that would suggest that there are 900 million to 1.5 billion women who also either have had, will have, or currently do have endometriosis. This is a far higher estimate than the 5% to 15% prevalence generally cited for endometriosis (219). Physicians have long known that endometriosis is underdiagnosed, but our hypothesis suggests that the incidence in which endometriosis is overlooked is substantially higher than previously thought.

If we begin to solve the enigma of endometriosis and fibroids, we may also be able to open the door to understanding, curing, and preventing reproductive cancers. Every female is born with the potential for both fibroids and endometriosis. A trigger or stimulus which has yet to be fully identified then leads to either the development of fibroids and endometriosis or their suppression by hitherto unidentified protective mechanisms. That trigger may even be found in utero. A 2012 study analyzed 52 female fetuses at autopsy and found endometriosis in four of the fetuses studied (219). To date, however, no studies have looked at the prevalence of adenomyosis, adenomyoma, and leiomyomas in fetuses.

Endometriosis: one name, many diseases. Considering the extraordinary range of morphologies and endlessly disparate reactions endometriosis expresses in response to both surgical and medical interventions, perhaps we are asking the wrong questions. Just as we define cancers today in the plural, we may soon come to recognize endometriosis in the same way: a disorder with multiple phenotypes that share similar molecular mechanisms and reside on the same spectrum, but which

manifest differently in each individual as a result of unique environmental, genetic, or epigenetic triggers: endometriosis, adenomyosis, adenomyomas, leiomyomas . . . with the potential to progress to endometrioid adenocarcinoma. Although the true workings of these biologic mechanisms currently remain under lock and key, what we do know for certain is that more research is needed to uncover the origin of endometriosis. Again, we believe the answer will be closely linked to the origin of fibroids. Another possible research direction that has yet to be explored relates to the fact that the spleen appears to contain a protective environment that prohibits the growth of endometriosis. Discovering what those precise protective mechanisms are could also help lead us to a cure.

All our observations highlight the fact that we need to continually drive forward our efforts to provide better training opportunities for physicians so that endometriosis can be properly diagnosed and treated. This is the only way that we can unravel the enigma of endometriosis and end its devastating reign over so many lives. The clock is definitely ticking as we know that millions of women still live lives awash in anguish, just as they did thousands of years ago, and just as they will centuries from now unless we can steer ourselves faster toward the long elusive cure. Four thousand years is long enough; the time has come to end the empire of endometriosis.

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