Introduction

A reconstruction of the history of progress made in identifying, describing, and treating the condition we call endometriosis is neither simple nor easy because for almost 90 years endometriosis and adenomyosis, with the possible exception of ovarian endometrioma, were considered as one disease called “adenomyoma.” As such, historians must deal first of all with a controversy over who was the first to identify the benign, non-neoplastic presence of ectopic endometrium within the uterine wall or in the peritoneal cavity and structures. In addition, they must be aware that the early history of endometriosis is interwoven with the early history of adenomyosis, since it was not until the mid 1920s that the two conditions were finally separated.

Who identified endometriosis?

The history of medicine is full of controversies over who “discovered” a specific disease. In certain cases this is due to a desire to attribute the discovery to a researcher from a given country; in others, it is due to conflicting evidence, as sometimes disagreement focuses on the criteria utilized to attribute the discovery.

The latter situation is typical of endometriosis, a condition that does not lend itself to a purely clinical diagnosis. This is why, before embarking on a search for who “discovered” (a better word is definitely “identified”) it, it is necessary to fix a set of criteria, first and foremost what constitutes the “essence” of endometriosis. Some favor clinical descriptions, rather than histology or pathogenesis. Knapp, for instance, believed that the first descriptions of endometriosis can be found in Theses and Dissertations published in Belgium and The Netherlands during the second half of the 17th century [1], whereas Batt believes that endometriosis was discovered when the presence of heterotopic endometrial tissue was first described, even though the conditions were all labeled “sarcomas” [2].

We are of the opinion that the identification of the conditions we today distinguish in peritoneal and ovarian endometriosis and in adenomyosis (globally here called END-AD) must be based on the observation of the presence of endometrial glands and stroma outside the uterine cavity and on the specification that this invasion was “benign” in nature. Using these criteria, we will critically examine published information on the history of endometriosis.

The first information that needs to be evaluated is contained in a publication by Vincent Knapp [1]. In it, he explained that the disease we name endometriosis was already identified 300 years ago. His conclusion was based on a series of 11 inaugural dissertations presented at European universities between 1690 and 1795. The Disputatio Inauguralis Medica de Ulceribus Uteri by Daniel Christianus Schröner presented at the University of Jena in 1690 is now sometimes cited as the first description of endometriosis [3]. However, close scrutiny of some of the original manuscripts from this period has shown that the descriptions evidenced signs of inflammation such as pus, uterine wounds or erosions that were linked to manipulation, an abortion or a syphilitic lesion. The symptoms described were those of an infection and included pain, insomnia, fever, vaginal lesions or erosions that were linked to manipulation, an abortion or a syphilitic lesion. The symptoms described were those of an infection and included pain, insomnia, fever, vaginal lesions, dysuria, purulent urine (if the lesion involved the bladder) or purulent stool (if the lesion involved the intestines). There were no descriptions in the Disputatio Inauguralis or in the other later dissertations that could be interpreted as being indicative of endometriosis. Sadly, Vincent Knapp passed away a few months after publication of his manuscript and a letter to the Editor of Fertility and Sterility remained without response [4].

A point that has been overlooked is that, without a microscope, these early authors had no way to even predict the presence of endometrial tissue outside the uterus. Therefore, applying the
above-mentioned criteria, it becomes a physical impossibility for endometriosis to have been described during the 17th and 18th centuries. In addition, in those days abdominal surgery could not be performed and so, either the lesions were superficial and therefore could not be “endometriotic” in nature, or they could have been observed only at macroscopic autopsy examination and there is no trace of this having been the case.

More complex is the situation with regard to Carl Rokitansky, who in 1860 described what Batt called “three phenotypes of endometriosis containing endometrial stroma and glands” [2]. The first consisted of two varieties labeled Sarcoma adenoids uterinum (invading the uterine muscular wall) and Cystosarcoma adenoids uterinum (a cystic variety associated to myometrial hypertrophy). The second, named Cystosarcoma adenoids uterinum polyposum, invaded the endometrial cavity forming a polyp and the third Ovarian-Cystosarcom invaded the ovary [5]. In an early paper on the history of endometriosis [6] we omitted any reference to Rokitansky on the basis of the “malignant nature” of his descriptions. Indeed, Rokitanski specifically mentioned:

… a sarcoma tissue in the form of papillary excrescences grow into the space of the cyst-like degenerated tubules. The slit-like, lacunar clefts scattered within the sarcoma produce on cross-section a granular appearance. The circumscribed nodes, which can be shelled-out, and appear incorporated in the sarcoma mass, doubtless originate from the filling of the great cyst spaces by intruding tumor tissue – a common appearance, which is especially pronounced in cystosarcoma adenoids mammarium.

To us, this is the description of a malignant tissue. Batt, however, insists that, in spite of the nomenclature, Rokitanski was aware of the benign nature of these invasions and that therefore he was the first to identify “the benign invasion of endometrial glands and stroma into the peritoneal cavity and organs” [2].

Setting aside the question of the nature of the lesions observed by Rokitansky, it is their origin that created a fierce controversy, with pathologists of the fame of von Recklinghausen [7] contending that lesions that were then called “adenomyoma” were the result of displacement of Wolffian or mesonephric vestiges.

When we examine the many and detailed descriptions of “mucosal invasions” of the peritoneal cavity and organs published at the end of the 19th and during the early part of the 20th century, we must conclude that the majority of pathologists rejected the hypothesis that the glands they observed were “endometrial.” As late as 1918, Lockyer, in detailing the various theories on the origin of epithelial glands and stroma found in the pelvis outside the uterine cavity, was unable to resolve the question of their origin. He wrote: “Nothing but the topography of the tumor, nothing but laborious research entailing the cutting of serial sections in great numbers, can settle the question as to the starting point of the glandular inclusions for many of the cases of adenomyoma” [8]. Therefore, earlier researchers who described mucosal invasions in the abdominal cavity, but failed to consider these invasions as being made of endometrial cells, cannot be considered as having “discovered” END-AD.

It was the surgeon Thomas Cullen (Fig. 1.1A) who described for the first time both the morphological and clinical picture of END-AD. In the preface to his book Adenomyoma of the Uterus, Cullen [9] wrote in 1908:

One afternoon in October 1882, while making the routine examination of the material from the operating room I found a uniformly enlarged uterus about four time(s) the natural size. On opening it I found that the increase in size was due to a diffuse thickening of the anterior wall … Examination of the(se) sections showed that the increase in thickness was due to the presence of a diffuse myomatous tumor occupying the inner portion of the uterine wall, and that the uterine mucosa was at many points flowing into the diffuse myomatous tissue.

Over the following years Cullen collected 90 uteri with adenomyomata and described the various presentations of “adenomyomata” in the myometrial wall, uterine horn, subserosa and uterine ligaments and showed in the uterus the continuity between the endometrial glands and the glandular structures...
deep in the myometrium (Fig. 1.2). In addition, he was the first to describe decidualization of the stromal cells during pregnancy, providing the functional proof that the cells were of endometrial origin (Fig. 1.3). He was also the first to describe the symptoms of the uterine adenomyoma, and concluded rather optimistically:

I cannot help feeling that anyone who reads the chapter on symptoms will agree with us that diffuse adenomyoma has a fairly defined clinical history of its own and that in the majority of cases it can be diagnosed with a relative degree of certainty.

In 1920 Thomas Cullen [10] drew a scheme with the classic sites of adenomyotic lesions in the pelvis (Fig. 1.4). Adenomyoma involved ectopic endometrial-like tissue in the myometrial wall, rectovaginal septum, hilus of the ovary, uterine ligaments, rectal
wall, and umbilicus. There is no doubt that Cullen considered uterine adenomyoma, ovarian endometriosis, and deep endometriosis as one disease characterized by the presence of adenomyomatous tissue outside the uterine mucosa.

It is customary to consider John A. Sampson (see Fig. 1.1B) as the discoverer of endometriosis and indeed, his work on peritoneal and ovarian endometrioma provided the first theory on the pathogenesis of the disease. His original observation came when he operated on women at the time of menstruation and found that the peritoneal lesions were bleeding similarly to what happens in eutopic endometrium (Fig. 1.5) [11]. This proved to him that the tissue outside the uterus was of endometrial origin. In 1927 Sampson postulated that the presence of endometrial cells outside the uterus was due to tubal regurgitation and dissemination of menstrual shedding [12].

Clearly, peritoneal endometriosis became the signature of the disease and with the introduction of laparoscopy in the 1960s, a golden tool became available for visual diagnosis and surgical therapy. As a result, endometriosis was divorced from the uterus and research became focused on how fragments of menstrual endometrium implant on peritoneal surfaces and invade the underlying tissues. Since menstrual regurgitation and implantation could not explain a variety of ectopic localizations, other mechanisms were proposed, such as peritoneal metaplasia, transportation through veins or lymphatics, embryonic vestiges, transformation of bone marrow and stem cells.

### Clinical issues

#### Awareness in the clinic

During the mid-20th century, endometriosis became a major clinical issue. In 1932 Hill Jr [13] reported on a series of 1200 patients who, between 1927 and 1931, were operated upon for pelvic pathology. In 135 women (11%), aberrant endometrium was detected at microscopy. Amongst these cases, 20 had adenomyomata of the uterus and 115 peritoneal endometriosis. The majority of the patients were between 20 and 45 years of age, with the youngest being 16 years old and the oldest 61. Thirty percent of the patients were sterile. As menstrual problems were absent in 51%, the aberrant endometrium was assumed to have caused little if any of the menstrual disorders and the symptoms were believed to have been caused principally by the associated pathology. The most important individual symptom was pain and tenderness over the site of the growths during the menstrual period; this, however, was the exception and not the rule. On the other hand, acute complications of endometriosis were also described during this period, such as the spontaneous rupture of an endometrial ovarian cyst [14] and obstructing rectovaginal endometriosis [15].

Pelvic pain related to menstruation was, according to Counseller [16], the principal reason for seeking relief through surgery. There was usually a 10-year history from the onset of disease and the symptoms were progressive. Surgical treatment was either radical or conservative, depending on the extent. In cases of uterine adenomyosis, conservative treatment was performed by complete excision of the lesions from the myometrium plus a presacral neurectomy when the lesion was limited to the uterus. Other heterotopic lesions were treated by complete excision whenever possible or by surgical loop diathermy or partial resection when the lesions were located in the sigmoid or the rectovaginal septum.

In the 1940s endometriosis was described as a not uncommon disease, with various clinical appearances. At times a widespread distribution of lesions within the peritoneal cavity was noted. The majority of the lesions occurred on the peritoneum, cul-de-sac, rectovaginal septum, and ovaries. Less frequent locations included the umbilicus, the round ligaments, rectosigmoid, and laparotomy scars. Larger lesions may consist of a more or less solid tumor, an adenomyoma, or may be in the nature of a hemorrhagic cyst. Surgery was the treatment of choice. In this connection,

![Figure 1.5](image-url) Endometriotic implant on the ovary showing shedding and bleeding of the endometrium-like tissue at the time of menstruation. Reproduced from Sampson [11] with permission from American Medical Association.
Benson and Sneed argued in 1958 that confusion had developed because of the unfortunate and illogical inclusion of uterine adenomyosis with pelvic endometriosis, which, according to them, only occasionally co-exist [17].

In terms of pathogenesis, Javert [18] developed a composite theory of benign metastasis on the basis of his surgical experience with 1371 patients over a period of 17 years. He observed that the spread of benign endometrium is essentially the same as for endometrial carcinoma, with direct extension into lymphatics or blood vessels of the myometrium, or between the muscle bundles, thereby producing adenomyosis uteri, while exfoliation and implantation of endometrial cells at menstruation, during curettage or from a nidus in the tube produced lesions on peritoneal surfaces; finally, lymphatic and venous spread produced lesions in adjacent or distal organs. He explained the increase in the number of cases during the last 4 years of his observation by the tendency towards smaller families, widespread use of contraception, fewer cervical dilations, fewer uterine suspension operations and the use of more intravaginal tampons during menstruation. He believed that pregnancy was the best prophylactic and curative treatment for endometriosis, since it interrupts the cyclical home-o-plasia during which time the endometrium lies dormant. Javert favored hysterectomy and bilateral salpingo-oophorectomy as the procedure of choice in older women.

In 1955, Henriksen [19] presented a review of 1000 cases of proven endometriosis. The disease was diagnosed on an awareness of the possibility of its existence, a careful history and a thorough retropelvic examination. Although the disease tended to regress following castration, some patients exhibited clinical and histological evidence of continued activity following ovariectomy. Henriksen also noted a frequent involvement of the bowel and concluded that endometriosis is an important possible factor in problems affecting both the small and large bowel. Proper management is based on the surgeon’s appreciation of the natural history of the disease, the evaluation of factors such as age, severity of symptoms, extent of disease, desire for children, and the patient as a whole. He concluded that fortunately, the value of conservatism in the surgical management of the disease was becoming more widely appreciated.

**Introduction of endoscopic techniques**

New pelvic endoscopic techniques were introduced in gynecology in the late 1940s, whereas peritoneoscopy has been utilized in gastroenterology and general surgery since the late 1930s. Initial clinical applications of the new technique were made in the 1940s, soon widened to include differentiating between causes of intra-abdominal bleeding (including bleeding from rupture of a follicular cyst), between appendicitis and salpingitis and in order to decide whether or not gunshot or stab wounds were penetrating into the abdominal cavity.

In 1944 Decker and Cherry [20] proposed culdoscopy as a new procedure for pelvic visualization in gynecology and claimed that the procedure was invaluable in the investigation of pelvic tumors, small ovarian disease, endometriosis, ectopic pregnancy and especially helpful in the detailed study of primary and secondary sterility in women. Starting in 1967, Semm (see Fig. 1.1C) transformed peritoneoscopy into modern laparoscopy by improving the optical system, removing the source of light from the abdominal cavity and creating an automatic control of gas insufflation into the abdomen [21]. Technical improvements in laparoscopy quickly produced new information on endometriosis and expanded gynecological application of endoscopic surgery, to the extent that in the early 1970s leading gynecologists in Europe and the US concluded that laparoscopy was the preferred tool for diagnosis and surgery of endometriosis.

**Attempts to create a classification of endometriosis**

In an editorial published in *Obstetrics and Gynecology* in 1966, Beecham [22] claimed that a tedious effort to detail endometriotic location and lesion “would serve no purpose.” He therefore presented a simple classification scheme of four stages that used physical and operative findings and stated that such a scheme would be appropriate to follow patients being managed by medical or surgical therapies. Others tried staging systems similar to those used for malignancy staging, but these classification methods were unable to correlate staging with clinical outcome. As a result, none of the attempts to classify endometriosis made before 1978 received widespread acceptance.

In a collaborative effort Acosta and co-workers [23] proposed a classification that divided the disease into mild, moderate, and severe based on surgical findings. Using this staging system with retrospective data, a direct relationship was established between initial stage of the disease and pregnancy rates. Disease also was automatically classified as severe in the presence of an endometrioma larger than 2 cm in size. Peritubal and periovarian adhesions separated mild from moderate disease, because ovarian adhesions were recognized as having a damaging effect on fertility. Many physicians objected that this classification system had several disadvantages, because of the arbitrariness of the staging and the inability to distinguish unilateral from bilateral disease. Buttram, then, in 1979 [24], proposed an expanded classification based on the Acosta scheme that allowed for more flexibility and less ambiguity. Despite modifications, none of the classifications received widespread acceptance or use; this prompted the American Fertility Society (AFS) to create a panel to design a classification system for endometriosis; its recommendations were published in 1979 [25].

The AFS classification scheme stratified endometriosis into mild, moderate, severe, and extensive disease and for the first time used a weighted point score that included assessment of the extent of endometriosis (two-dimensional) and presence of adhesions in the peritoneum, ovaries, and tubes. It also allowed for assessment of unilateral versus bilateral disease. The size of endometriomas was weighted differently, as was the presence of filmy versus dense adhesions. An anatomical drawing was included to aid in surgical finding documentation and a cumulative score was attained. From the outset, critics began to point out the shortcomings of the new classification: the point scores were recognized as
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arbitrarily assigned and it was anticipated that changes in the assignment would be based on clinical studies and disease progression or response to treatment. The evaluation of pregnancy success suggested that the AFS classification revealed significant differences only if categories were combined (mild plus moderate versus severe plus excessive). Pregnancy success was also significantly reduced if an ovarian endometrioma was greater than 3 cm or had ruptured [26]. While the features of infertility were emphasized, they were not necessarily related to pelvic pain.

In 1985, in response to all the problems identified, a revised scheme of the AFS classification was presented (the so-called rAFS) [27]. As the new system still had flaws similar to its predecessor, the AFS stated that the system would be subject to revision as clinical data became available. In 1996, Vercellini et al [28] concluded that the endometriosis stage was not consistently related to pain symptoms, while in 1997, Guzick et al [29] stated that the use of an arbitrary weighted system for assigning scores to individual categories of disease, or for computing a total score, has limited the overall effectiveness of the classification system to predict pregnancy. Limitations of the rAFS classification include arbitrariness of the scoring system, limited reproducibility, failure to consider the morphological type of the lesion and a limited value of the system to aid in the evaluation and management in the setting of pelvic pain. These and other critical opinions led in 1997 to the publication of a Revised American Society for Reproductive Medicine classification of endometriosis: 1996 [30].

Diversity of lesions

Peritoneal endometriosis

In the 1980s it became evident that peritoneal endometriosis has multiple appearances including microscopic foci, early-active (red, glandular or vesicular), advanced (black, puckered), and healed (white, fibrotic) forms. These lesions may represent replacement of mesothelium by an endometrial epithelium or endometrial polyp formation [31,32]. However, the anatomical distribution of ectopic endometrium, as assessed by laparoscopy in a series of 182 consecutive patients, supported Sampson’s hypothesis of retrograde menstruation as the primary model of development of endometriosis [33]. Laparoscopic observations [34] suggested that early lesions appear and disappear “like mushrooms on the peritoneal surface.” The importance of even very small lesions became evident when, in a prospective study of artificial insemination in women with minimal endometriosis, Jansen [35] found reduced fecundability. Awareness of the existence of subtle endometriosis produced an increase in the diagnosis of endometriosis, although clinical significance of early lesions remained controversial [36–38]. From all published evidence, Evers [39] concluded that peritoneal endometriosis appears to be a dynamic disease, especially in the early phase, with subtle, atypical lesions emerging and vanishing again. The dynamic phase of the disease may involve a varying interval of each patient’s life (e.g. a period of amenorrhea or pregnancy). Laparoscopy at the end of medical suppression of the activity of the implants may lead to the erroneous conclusion that treatment has been effective. The final answer to the question of whether endometriosis is a progressive disease will have to come from long-term prospective investigations studying spontaneous evolution of peritoneal lesions without therapeutic interference.

Vercellini et al [28] analyzed the prevalence and severity of dysmenorrhea, intermenstrual pain and deep dyspareunia in relation to morphological features of peritoneal endometriosis. A statistically significant association was observed only with deep dyspareunia. Fresh, papular, atypical lesions might cause functional pain, whereas “old,” black nodules immersed in infiltrating scars might provoke mainly organic pain. Belasch et al [40] found a high prevalence of superficial endometriosis in biopsies from the uterosacral ligaments in both patients with chronic pelvic pain and asymptomatic (fertile and infertile) women.

Rectovaginal endometriosis

As in the case of infertility, investigators found poor correlation between lesion characteristics or stage of disease and pelvic pain. Cornillie et al [41] noted a strong correlation between pelvic pain and the depth of invasion, with severe pelvic pain in the presence of implants more than 10 mm deep. Lesions more than 5 mm deep were also found to be histologically more active than superficial lesions. Koninckx et al [42] found no correlation between types of endometriotic lesions, total surface area of endometriosis-invaded areas, and amount of pain.

Three subgroups of deep endometriosis were suggested by Koninckx and Martin [43]: type I is conically shaped and seems to be formed by infiltration; type II is deeply located, covered by adhesions and probably formed by retraction; type III is a spherical nodule located in the rectovaginal septum and causes the most severe and largest lesion. They considered type III as a form of adenomyosis.

In the late 1990s, rectal endoscopic ultrasonography was proposed to diagnose the presence of deep bowel infiltration and select patients for surgery [44,45].

In recognition of some of the shortcomings of the rAFS classification in the evaluation of pelvic pain, the American Society for Reproductive Medicine (formerly the AFS) formed a subcommittee which developed a form for the preoperative assessment of pain quality and location on examination and their correlation with operative findings, including adhesion type, description of peritoneal lesion type by morphological appearance and the mean diameter and depth of invasion [46].

Ovarian endometrioma

Ovarian endometriosis can present itself as chocolate cysts of various size, deep non-cystic lesions, surface pits and plaques, and very early lesions. In an detailed study of 29 ovary specimens with chocolate cysts, Hughesdon [47] found that in all except three cases, the ovarian endometrioma was a pseudocyst with an essentially similar structure: the ovary is adherent to the posterior side of the parametrium, the inside is constituted by invaginated ovarian cortex, endometriotic tissue is found at the site of adhesion.
and a thin layer of superficial endometrium-like tissue extends to cover partially or fully the invaginated cortex (Fig. 1.6).

Hughesdon described four further characteristic features of ovarian endometriomas (Fig. 1.7). First, primordial and ripening follicles are found in the wall of the cyst. Second, the ovary does not invaginate uniformly, but remains on one side more or less normal. Third, on the extended side the wall is relatively thin and the attenuation of layers on this side is usually too great to reveal the original structure. Fourth, the identity of the cortex on the inner side is frequently obscured by smooth muscle metaplasia.

Hughesdon concluded that ectopic endometrium does not simply erode its way into the ovary: the ovary is actively invaginated, thus providing a pseudouterus. The structure demonstrated that the relation to the surface is primary and not secondary, such as would have been implied by Sampson's [11] original title of “perforating hemorrhagic cysts of the ovary” and by Halban’s lymphatic theory [48]. Hughesdon also discussed the few cases with so-called “deep” ovarian endometriosis and demonstrated on serial sections that although deep, non-cystic lesions are, in a gross sense, in the ovary, the associated layering shows that they have originated at the surface. He concluded that
the findings weigh heavily against the benign lymphatic metastasis theory and favor a surface origin by implantation or metaplasia.

Using an endoscopic technique, Brosens et al [49] investigated a series of endometriotic cysts in situ in young women with infertility and confirmed that the wall of the cyst is cortex. In a few cases ovulation has occurred in the cyst and both cavities were linked. In such cases the endometrial tissue colonized the luteal cyst, showing that, under such circumstances, endometriosis can invade the ovary. They distinguished two types of endometriotic cysts: the red type which is lined by a surface epithelium and a thin layer of highly vascularized stroma without glands covering partially or completely the whitish or slightly pigmented wall, and the black type where the wall is lined by dark, pigmented and fibrotic tissue with scanty vascularization. They also found that at the site of invagination and adhesions, the cortical wall was retracted and the implants were of the mucosa type with glandular structures. They suggested that surgery should be adapted to the type of endometrioma by ablation of the superficial endometriotic lining for the whitish wall and excision of the fibrotic wall for the black wall and the implants at sites of inversion and adherence.

In the 1980s imaging techniques such as magnetic resonance imaging [50–52] and transvaginal ultrasonography [53–55] were used to differentiate ovarian endometriomas from other non-endometriotic masses. While ovarian endometriomas are easily detected at laparoscopy and ultrasonography, small ovarian endometriomas may go unnoticed unless they are detected by puncture [56]. Nezhat et al [57] have proposed to distinguish between three types of ovarian endometriomas according to size, cyst contents, ease of capsule removal, adhesion of the cyst to other structures, and location of the superficial endometrial implants relative to the cyst wall. Nisolle et al [58] suggested that peritoneal, ovarian, and rectovaginal endometriosis are three different entities with a different structure and pathogenesis, respectively implantation, metaplasia, and mesodermal müllerian differentiation.

Stage V endometriosis
Canis et al [59] proposed to add a most severe stage of endometriosis to include patients with extensive disease, especially with bilateral dense adhesions; the addition of this stage is justified in their view by the fact that poor results in terms of restoring fertility are consistently obtained with conservative therapy alone. Using their revised classification scheme, a plan to proceed quickly toward in vitro fertilization (IVF) would be uniformly recommended for all stage V patients. It must be stressed that in patients with severe endometriosis, Pal et al [60] found with IVF a reduced fertilization potential of preovulatory oocytes.

Malignancy
In 1990, Heaps et al [61] reviewed a series of 205 cases reported in the English literature of malignant neoplasms arising from endometriotic foci. The ovary was the primary site (79%), whereas extragonadal sites represented 21%. Endometroid carcinomas accounted for 69% of the lesions and the remaining cases included clear cell carcinomas, sarcomas, and rare cell types. Heaps suggested that the actual frequency of malignancy arising in endometriosis may be higher than reported.

### Modern therapeutic approaches

#### Hormonal therapy
The hormonal management of the symptoms associated with endometriosis was made possible almost 70 years ago, by the availability of the first synthetic steroid hormones and, interesting enough, androgens preceded estrogens as therapeutic agents.

#### Androgen therapy
The first suggestion to utilize the newly identified steroid hormones as therapeutic agents came from Geist and Salmon [62] who, in 1941 in an article in JAMA, advocated the use of androgens in gynecological disorders. Following this lead, in 1943 Hirst [63] reported the results obtained with the use of testosterone propionate in two cases of women with severe endometriosis: treatment resulted in a reduction in swelling and relief of pain and he recommended the use of this form of treatment when radical surgical excision was contraindicated or refused by the patient.

The following year, Miller [64] published a case of endometriosis of the rectal wall and ovaries, treated preoperatively with testosterone propionate. He stated: “Testosterone propionate can be used in diminishing the activity and decreasing the size of the lesions in endometriosis so that radical surgery can be performed with less danger.”

In spite of the positive results obtained, the undesirable side-effects of hirsutism, acne, and deepening of the voice occurred sufficiently often to cause the clinician and patient considerable concern. For this reason, androgen therapy never really took off and other avenues began to be explored. In 1958, commenting on the use of androgens, Kistner [65] noted that “androgenic substances, while adequately documented as having produced desirable results in endometriosis, probably exert their effect through inhibition of gonadotrophic substances although direct effect of the substance upon the endometriotic area has been suggested.” This awareness prompted endocrinologists and gynecologists to test other gonadotropin-inhibiting substances.

#### Estrogens
In the late 1940s, the availability of a non-steroidal, synthetic estrogen, diethylstilbestrol (DES), prompted another line of experimental treatment for severe endometriosis.

We know today that estrogens are intimately involved with the growth of ectopic endometrial foci and therefore, with today’s wisdom, estrogens would be, if anything, contraindicated. Indeed, although in all likelihood not an endocrine disease, endometriosis
does not manifest itself in the absence of estrogens. Indeed, even when the disease manifests itself in postmenopausal patients, usually it appears in women treated with estrogens [66,67] and, in the rare occurrence in non-treated postmenopausal patients [67], it is believed that symptoms are the consequence of the progression of the estrogen-independent fibrosis, not of the growth of new foci [68]. At the same time, there is evidence that estrogens are not necessary for the endometrium to implant itself ectopically and indeed, grafting studies in nude mice and rabbits have shown that estrogens are required for the success of the implantation process [69,70]. Also, the recently reported presence of endometriotic foci in human fetuses [71] may be evidence of an estrogen-independent process.

In contradistinction to this, proliferation and growth of ectopic implants need the presence of estrogen. For instance, in castrated monkeys, hyperplastic-decidualized endometrial tissue transplanted into the peritoneum retains viability for more than 4 weeks, even without exogenous hormonal support, but the administration of supplemental estrogen and/or progesterone is required to sustain these endometrial plaques for periods of up to 16 weeks [69]. In addition, in a rat animal model experimentally implanted with human endometrial cells, following ovariectomy there is a complete regression of the implants, to the point that, 2 months later, no viable endometrial cells can be detected, even histologically. However, administration of estradiol cypionate to these animals leads to the recurrence of implants [72].

Finally, although endometriosis has been observed in the urinary bladder of men with prostatic carcinoma [73,74], in the case of pure gonadal dysgenesis [75] and Turner syndrome [76,77], streak gonads [78] and in a woman with a Rokitansky-Kuster-Hauser syndrome [79], all these patients had endogenous or exogenous estrogens, alone or in combination with a progestin. Therefore, the concept that estrogens are necessary in order to have active ectopic endometrial foci so far goes unchallenged.

This large body of knowledge did not exist and could not even be guessed when the first attempts were made to treat women with severe endometriosis with estrogens. The first to do so was Karnaky [80] who, in 1948, reported apparently good results with increasing daily doses of up to 100 mg/day of DES to obtain amenorrhea. In his report he reached an intriguing conclusion: “Endometriosis is not stimulated to grow by large continuous doses of stilbestrol, but small doses of stilbestrol may stimulate it.” In his series, five patients became pregnant after stilbestrol was discontinued. With today’s knowledge, the offspring of those pregnancies should have been followed very closely, although second-generation clear cell vaginal cancer has been usually attributed to use of DES in pregnancy, not before it [81].

In spite of the enthusiasm of its proponents, estrogen treatment of endometriosis did not last, and for reasons only partially related to modern knowledge. In 1958 Kistner [65] wrote: “the unpredictability of permanent relief in endometriosis following the use of estrogenic substances alone” and the fact that “estrogen therapy also has the disadvantage of occasionally resulting in rather profuse break-through bleeding, endometrial hyperplasia and hypermenorrhea at the time of withdrawal of the hormone” make this treatment unwise.

Under the circumstances, a rational approach to the hormonal treatment of endometriosis must involve the use of steroid hormones with the ability of either modulating or antagonizing that of endogenous estrogens.

“Pseudo-pregnancy”
There is indeed a solid rationale for the use of estrogen-progestin combinations for the treatment of symptoms associated with endometriosis and the obvious difficulty in understanding how the administration of an estrogen, especially at high doses, could be beneficial, in particular to patients with advanced endometriosis, the situation is different when we consider the association of an estrogen and a progestin. In this respect, it is well established that the contemporary administration of an estrogen and a progestin results in a partially inactive endometrium.

Although we have ample evidence that ectopic endometrium does not behave in the same way as eutopic endometrium [82] and that, in the same patient, the two can be out of phase with each other at any given time during the menstrual cycle [83], the basic principle of controlled growth under the combined effect of the estrogen-progestin combination remains true.

Historically, knowledge gained during the 1940s and early 1950s allowed the creation of a new concept that went under the name of “pseudo-pregnancy,” the artificial creation of a hormonal situation mimicking that occurring naturally during pregnancy. Meigs [84] was the first to come up with this new idea. He wrote: “It is the author’s belief that avoidance of endometriosis through early marriage and frequent childbearing is the most important method of prophylaxis.” The concept bears striking similarity to the approach taken by Gregory Pincus in creating hormonal contraception [85].

Two researchers share the credit for the advent of “pseudo-pregnancy” as a treatment for endometriosis: Kistner [65] and Andrews [86]. Since “in many patients with this disease, conception is not always possible, either because of unknown factors producing infertility or because marriage is not contemplated,” an artificial situation mimicking pregnancy was able to resolve the impasse [65]. The first experiments by Kistner involved 12 patients to whom large doses of a number of estrogenic compounds (diethylstilbestrol, Estinyl, estradiol valerate) and two progestins (17α-hydroxyprogesterone caproate and norethynodrel) were administered in a “graduate scale” for periods of up to 7 months to produce amenorrhea, as well as a decidual reaction in the endometrium. The pseudo-pregnancy regimen resulted in an improvement of the condition, both subjectively and objectively, except for occasional side-effects like uterine cramps or hypermenorrhea.

Andrews and his group [86] went a step further and, starting from the same observation of beneficial effects of pregnancy on endometriosis, they administered Enovid (norethynodrel plus mestranol) to 23 women with endometriosis. Decidual transformation was consistently demonstrated in the endometrial cavity and was present in the ectopic endometrium in all of the five instances.
in which it was obtained for study. Clinical improvement during therapy was observed in 14 of 17 patients treated because of pain.

To improve the effectiveness of the pseudo-pregnancy regimen, in 1960 Thomas [87] introduced long-acting steroid hormones. He treated 28 women with established endometriosis with an injectable preparation (Delalutin), containing 250 mg of 17α-hydroxyprogesterone caproate and 5 mg of estradiol valerate (administered twice weekly). He recommended that treatment be continued for a minimum of 4–6 months. All patients developed amenorrhea, which persisted throughout the period of hormone administration, and most of the women experienced considerable to complete relief of their symptoms.

The “pseudo-pregnancy” regimen has been used extensively since then for the treatment of endometriosis, although the last paper on the subject was published in 1975. Symptomatic relief of the disease was reported in a majority of cases; pregnancy rates in women who complained of infertility in addition to endometriosis ranged from 10% to 53% [88].

Recently, studies have begun to appear on the use of estrogen-progestin (EP) combinations in the treatment of endometriosis [89,90] and it has been shown that increasing the abnormally low apoptotic activity of the endometrium of patients with endometriosis, while at the same time achieving anovulation, decidualization, amenorrhea and the establishment of a steady EP milieu, contribute to disease quiescence [90].

Other hormonal regimens

During the second part of the 20th century, a number of additional hormonal regimens have been proposed, the first being an antigonadotropic steroid, danazol. Its introduction in 1971 by Greenblatt [91] turned back the clock, since this compound has definite androgenic properties and may produce symptoms not very different from those reported in the 1940s. In 1990, Barbieri published an informative review of the use of danazol [92].

Interesting results have been obtained with the introduction of gestrinone, a steroid with androgenic, antiprogestic and antiestrogenic activities [93]. Fedele and co-workers [94] were the first to compare the clinical effects of gestrinone and danazol, observing a significant decrease of pain-related symptoms (dysmenorrhea, pelvic pain, deep dyspareunia) in both groups, without any significant differences between the two components. The same year, Venturini and co-workers [95] showed that gestrinone significantly reduces serum concentrations of total testosterone and sex-steroid hormone binding globulin (SHBG), whereas free testosterone is slightly but significantly increased. Finally, estradiol is not significantly lowered in comparison with pretreatment follicular phase values.

Given results obtained with a mild antiprogestin like gestrinone, it was logical to expect even better results with the first “real antiprogestin,” mifepristone [96], widely known as the “abortion pill.” Unfortunately, its use in medical abortion has created a situation where, after very promising early clinical studies, for over 20 years no large-scale experimentation has been published. The early studies, conducted by Yen and his group [97,98], demonstrated a significant improvement not only in pelvic pain and dysmenorrhea but also in the rAFS score and therefore, a great potential for the cure of symptoms associated with endometriosis. Today, however, a second antiprogestin, ulipristal, has been marketed (as an emergency contraceptive) and work has resumed on possible applications of antiprogestins in the treatment of a number of proliferative disorders of the female reproductive tract.

Conservative surgery

During the second half of the 20th century, conservative surgery gained momentum and popularity [19] for the treatment of endometriosis as management became based on the surgeon’s appreciation of the natural history of the disease and the evaluation of factors such as age, severity of symptoms, extent of disease, desire for children, and the patient as a whole. For instance, as already mentioned, it was noted that endometriosis tends to regress following surgical castration or spontaneous menopause, although in some patients it continues to exhibit clinical and histological evidence of activity.

Conservative surgery had the obvious advantage of theoretically preserving fertility and, in 1975 Kistner [99] noted that approximately 40–50% of patients who are desirous of child bearing and who had had conservative surgical treatment would become pregnant. Such pregnancy usually occurs within the first 24 months, although in a few patients, the delay may last 3 or 4 years. Kistner observed that pregnancy rates were influenced by five factors: the extent of disease; the age; having had previous surgery for endometriosis; the duration of infertility before surgery; and the length of postsurgical follow-up. To improve results, he advocated short postoperative periods of pseudo-pregnancy induced by hormonal treatment (see above), if all areas of endometriosis could not be excised. A few years later, Buttram [100] reported pregnancy rates of 73%, 56%, and 40% respectively for patients with mild, moderate, and severe endometriosis. As surgery was most beneficial in the early postoperative period, he recommended that if medical suppressive therapy is to be used in conjunction with conservative surgery to enhance fertility, it should be used preoperatively rather than postoperatively.

Laparoscopy

A major departure from classic gynecological surgery occurred in the early 1970s when Kurt Semm [101] introduced endoscopic methods for hemostasis during surgical pelviscopy, including endocoagulation, Roeder loop ligation, endoligation and endosuture with intra- and extracorporeal knotting. Then, in 1983, he performed the first endoscopic appendectomy. Further advances occurred when Nezhat et al [102] introduced carbon dioxide laser for the removal of endometriotic implants, excision of endometrioma capsules, and lysis of adnexal adhesions. In a series of 102 patients, they reported a pregnancy rate of 60% within 24 months after laser surgery without additional hormonal therapy. Laparoscopic vaporization with carbon dioxide laser became a popular treatment modality for endometriosis-associated infertility, yet few data existed regarding the effectiveness of such an approach.
In the 1980s, laparoscopic surgery became the preferred approach for the treatment of ovarian endometrioma [103] and infiltrating cul-de-sac endometriosis [104]. Laparoscopic techniques were further promoted for the treatment of endometriosis by several pioneers and in 1994 Adamson and Pasta [105], combining their data with the results reported by Hughes et al [106], carried out a meta-analysis and concluded that either no treatment or surgery is superior to medical treatment for minimal and mild endometriosis associated with infertility; in addition, in moderate and severe disease, surgery seems to yield comparable results with both operative laparoscopy or laparotomy. They recommended that prospective randomized trials be performed to confirm these findings but unfortunately, in surgery prospective, double-blind randomized studies are extremely difficult to perform, although Sutton et al were able to conduct such a study and published it in 1994 [107]. They concluded that laser laparoscopy was a safe, simple, and effective treatment in alleviating pain in women with stage I, II, and III endometriosis. A second randomized, controlled trial was published in 1997 by Marcoux et al [108], reaching the conclusion that laparoscopic surgery enhanced fecundity in infertile women with minimal and mild endometriosis.

Ovarian endometrioma

Ovarian endometriomas have represented a major challenge for reconstructive surgery, carrying the risk of inadequate as well as excessive surgery. Nezhat et al [109] noted that in small endometriomas, the cyst wall is superficial and very difficult to remove, while a large endometrioma may develop as a result of secondary involvement of functional ovarian cysts by endometriotic tissues. Donnez et al [110] proposed a combined therapy using a gonadotropin-releasing hormone agonist and carbon dioxide laser laparoscopy. The hormone treatment and drainage after 12 weeks provoked a reduction of the endometrioma size up to 50% of the initial size before surgery was performed. In a large series, they reported, after the combined treatment, a cumulative pregnancy rate of 51% and a recurrence rate of 8% during a follow-up period of 2–11 years.

Bowel endometriosis

Surgical treatment of bowel endometriosis has been controversial, because this localization tends to be limited to the serosa and the muscular coats without penetrating the mucosa, and causes obstruction by fibrosis and kinking of the bowel [111]. Weed and Ray [112] reported on 163 cases of bowel endometriosis, noting that colon and rectal surgeons perform resections of the colon and the ileum and/or cecum, while gynecological surgeons prefer resection of bowel implants, even when they are multiple. In their experience, the bowel mucosa was opened in 15% of implant resection and resection of intestinal implants appeared to be a safe procedure.

Adhesions

The first reports on the use of intraperitoneal adjuncts to reduce postoperative adhesion formation appeared in the literature during the 1980s and gave varying results [113,114]. Reviewing available evidence, DiZerega [115] concluded that although barriers were shown to be safe and effective in human trials, their use did not eliminate adhesions on all patients. At second-look laparoscopy, Canis et al [116] found absence of deep ovarian endometriosis in 92%, but de novo adhesion formation existed in 21% of the treated adnexae and 17% of the contralateral adnexae; they concluded that laparoscopic cystectomy is effective in treating large endometriomas, but that operative difficulties may be encountered explaining the persistence of some endometriomas and postoperative adhesions.

Assisted reproductive technologies

In a prospective study of artificial insemination by a donor program, Jansen [35] reported reduced fecundability in the presence of minimal endometriosis. This observation was confirmed by Simon et al [117] in a retrospective analysis: in comparison with patients with tubal infertility, women with endometriosis have a poor IVF outcome in terms of reduced pregnancy rate per cycle, reduced pregnancy rate per transfer, and reduced implantation rate. Results from oocyte donations showed that patients who received embryos derived from endometriotic ovaries showed a significantly reduced implantation rate as compared to the remaining groups. All these observations suggest that infertility in endometriosis patients may be related to alterations within the oocyte, which in turn result in embryos with decreased ability to implant. From the results of a case–control study from the Yale University IVF-ET program, Arici et al [118] concluded that, in patients with endometriosis, implantation rate is low. Abnormal implantation, which may be secondary to endometrial dysfunction or embryotoxic environment, is a factor in endometriosis-associated subfertility.

In search of the pathogenesis

Initial theories

After the publication of his famous 1927 paper [12], Sampson continued the search for morphological clues to prove his thesis. In 1928 he reported on endometriosis in and about the tubal stumps in women who had undergone salpingectomy or tubal sterilization. He found bits of tubal and uterine mucosa that may have been transplanted by the surgeon both in the immediate field and also in remote areas and reasoned that if such transplanted endometrial or tubal epithelia could grow, they should also grow if transplanted during other types of operations and even in circumstances other than surgical interventions [119]. When transplanted tissue becomes differentiated into a structure resembling endometrium, Sampson defined it as “endometriosis” [120]. His view was supported by several publications on postoperative or scar endometriosis following cesarean section, episiotomy and laparotomy for uterine surgery [121,122].

Not everyone agreed with Sampson and in 1932, Novak (see Fig. 1.1D) developed a different theory: he postulated that the occurrence of differentiation anomalies in the epithelium of
various segments of the genital canal indicated the tendency towards variability of these genital epithelia under certain conditions [123]. He argued that this tendency reflected their common origin from the same mother tissue, the coelomic epithelium. In his view, it seemed unnecessary to invoke the doctrine of “transplantation” to explain endometriosis, since types of differentiation transitions may be seen in ovarian endometriosis, including a tubal epithelium with or without stroma, a uterine epithelium with or without glands and with or without stroma, an endometrium with or without physiological reactivity, with or without hemorrhage. Novak believed that his theory would support the germinal epithelium origin of serous cystadenomas and explain how tubal pregnancies could develop.

Besides the above-mentioned two theories, during the following decades several additional hypotheses were presented to explain the pathogenesis of endometriosis, though no single theory could explain all presentations.

Peritoneal environment
While early studies concentrated on the histogenesis of endometriotic lesions, during the 1980s interest shifted to changes in the peritoneal, ovarian, and uterine microenvironments observed in the presence of endometriosis.

Halme et al [124] demonstrated that retrograde menstruation through the fallopian tubes into the peritoneal cavity is a very common physiological event in menstruating women with patent tubes and concluded that specific factors must be implicated for successful transplantation and the establishment of endometriosis. They noted the increased activation of peritoneal macrophages in infertile women with mild endometriosis [125].

In 1980, Dmowski and collaborators [126] were the first to point to modifications of the immune system in the pathogenesis of endometriosis. This team demonstrated that rhesus monkeys with spontaneous endometriosis have an altered cellular immune response to autologous antigens, suggesting that endometrial cells translocated from their normal location may implant only in women with specific alteration in cell-mediated immunity. The following year, Haney et al [127] demonstrated that endometriosis is accompanied by a chronic intraperitoneal inflammatory process evidenced by an increased number of peritoneal macrophages in infertile women with endometriosis, when compared to normal women or to women with other causes of infertility. Since the peritoneal fluid is in contact with both peritoneal endometriotic implants and the tubal microenvironment in which fertilization occurs, subtle alterations of this fluid and/or its cellular constituents might adversely influence reproduction independently of anatomical compromise of the ovaries or oviducts.

Today, a number of modifications in the peritoneal environment of women with endometriosis have been identified: Oosterlynck et al [128] found that natural killer (NK) activity and cytotoxicity against autologous endometrial cells were both decreased in women with endometriosis and such decrease correlated well with the severity of the disease. Rana et al [129] demonstrated an increased synthesis of cytokines by peritoneal macrophages in women with endometriosis and Oosterlynck et al [130] found that the peritoneal fluid of women with endometriosis contains more angiogenic factors than peritoneal fluid from unaffected women. Shifrin et al [131] and McLaren et al [132] found that peritoneal fluid concentrations of vascular endothelial growth factor (VEGF) were significantly higher in women with moderate-to-severe endometriosis than in women with minimal-to-mild endometriosis or no disease.

In a review of the peritoneal environment in endometriosis, Oral et al [133] concluded that the etiology is likely to be multifactorial, and that the most widely accepted explanation for peritoneal endometriosis is a composite theory of retrograde menstruation with implantation of endometrial fragments in the presence of peritoneal factors able to stimulate cell growth.

Endometrial dysfunctions
In the late 1990s several reports were published suggesting that endometriosis is associated with endometrial dysfunction. Patients with severe endometriosis were found to have defects in endometrial receptivity, including aberrant integrin expression, suggesting decreased cycle fecundity [134]. In 1996, Noble et al [135] demonstrated that both eutopic endometrial tissues and endometriotic implants from patients with endometriosis are biochemically different from normal endometrial tissues of disease-free women. They speculated that the presence of aromatase expression in eutopic endometrial tissues from patients with endometriosis might be related to the capability of implantation of these tissues on peritoneal surfaces. On the other hand, Shifrin et al [131] have shown that VEGF may be important in the active angiogenesis of human endometrium (both physiological and pathological), as it is an estrogen-responsive angiogenic factor that varies throughout the menstrual cycle and is elevated in women with endometriosis. Donnez et al [136] found that VEGF content was higher in the eutopic glandular epithelium of women with endometriosis during the late secretory phase, possibly suggesting a more likely tendency to implant. On the other hand, similarities in VEGF content were observed in the glandular epithelium of the eutopic endometrium of women with endometriosis and red lesions, suggesting that endometriosis probably arises from the peritoneal seeding of viable endometrial cells during retrograde menstruation and that red lesions can be considered as the first stage of implantation. Finally, Leyendecker et al [137] consider hyperperistalsis and dysperistalsis to be responsible for both reduced fertility and the development of endometriosis.

Conclusion
There seem to be three general concepts that evolved during late 20th-century research in endometriosis. First, the evidence of a local peritoneal inflammatory process, supported by the
findings of elevated cytokine and growth factor concentrations in the peritoneal fluid of affected patients. Second, a role for angiogenic factors in the establishment of heterotopic implants. Third, evidence for biochemical differences of eutopic and ectopic endometrium in endometriosis patients; this may contribute to both the pathogenesis and sequelae of this important disorder [138].

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