

## DEBATE

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### The endometriosis syndromes: a clinical classification in the presence of aetiological confusion and therapeutic anarchy

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**Clinical confusion and inappropriate management continues to surround endometriosis. It is poorly recognized that the disorder can exist in two different morphological forms that have different symptoms, signs and prognosis. Earlier classification systems have been useful for research but are of limited value in aiding day-to-day management. In the clinic, two discrete phenotypes can be defined by the presence or absence of palpable nodules in the deep pelvis. Patients with such nodules with or without associated ovarian endometrioma usually have severe symptoms with significant risks of bowel and urinary tract involvement. The predominant histological feature of these lesions is extensive fibromuscular hyperplasia (adenomyoma). These patients will often need extensive surgical intervention. Patients without such palpable lesions usually have the classic superficial subperitoneal lesions with endometrial-like glands and stroma on histological examination. This group often has less severe symptoms and has little risk of developing serious associated problems. These lesions may be helped by medications and/or simple ablative surgery. It is suggested that these collections of symptoms and signs or syndromes be named after the pioneers who first described the lesions. Cullen's syndrome can be used to describe those patients with severe symptoms of endometriosis associated with palpable pelvic nodules. Sampson's syndrome can describe those with similar symptoms associated with a structurally normal pelvis.**

*Key words:* adenomyoma/classification/Cullen/endometriosis/Sampson

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#### Background

Endometriosis is as enigmatic today as it ever has been. Its fundamental cause continues to elude us and its protean manifestations continue to surprise us. The disorder we call endometriosis can be a condition that presents as an incidental finding in asymptomatic women or as a disorder of such severity that the sufferer's quality of life is destroyed. Diagnosis of the extent and location may be simple and self-evident or complex in the extreme. Treatments may be cheap or extraordinarily expensive. Mild analgesic agents and/or simple hormone therapy may be appropriate in many cases, whereas for others nothing less than major extirpative surgery will suffice. Therapeutic operations may take a few minutes or many hours. In this confused situation, the wrong therapeutic option is often chosen.

Much recent research work has concentrated on the earliest stages of the genesis of endometriosis and much of the most informed opinion about this disease has concentrated on the investigation of superficial lesions. 'Red' and 'black' implants scattered over the peritoneum represent the iconic image of endometriosis to most gynaecologists. Everyone concerned with the management of endometriosis recognizes this type of presentation. A hard, nodular lesion invading the deep pelvic structures is another clearly documented but clinically less well

recognized manifestation of endometriosis. Classification confusion, with both phenotypes being collected under one all-inclusive name, can lead to misunderstanding when trying to compare results and outcomes. Without careful definition of the type of disease, almost any therapeutic option can be chosen and justified, and so in effect therapeutic anarchy exists. In these increasingly closely managed times in health care, this confusion may also lead managers and health care funding agencies to question why some surgeons are able to 'adequately' treat endometriosis with drugs or simple operations, while others insist on extensive and radical surgery for apparently the same condition registered in the same diagnostic category. From a clinical, if not also an aetiological point of view, 'endometriosis' seems to be two different types of disease processes collected together under a single generic name. This paper seeks to present evidence to suggest the reality of this 'two forms of endometriosis' concept, and the possibility of developing a simple clinically useful method of differentiating them.

#### Clinical confusion

The American College of Obstetrics and Gynaecology (2000) has recently recommended that it is efficacious to give empirical treatment with GnRH agonists to patients with

chronic pelvic pain consistent with endometriosis without preliminary laparoscopic diagnosis. This recommendation is based on the results of a randomized controlled trial (Ling, 1999) that demonstrated a significant improvement in pain in those treated with GnRH agonist compared to placebo. An expert consensus group subsequently endorsed these conclusions (Gambone *et al.*, 2002). It should be noted that almost 20% of the group thought to have endometriosis had no

evidence of the disease at subsequent laparoscopy. The key message from this group of papers is that accurate diagnosis of endometriosis is not necessary before commencing treatment. They also suggested that pragmatic treatment of patients without definite diagnosis is preferable to exposing large numbers of patients to the risks and potential complications of diagnostic laparoscopy.

This conclusion appears to conflict with the well-recognized problems associated with our collective inability to make an early accurate diagnosis of endometriosis. The observed mean delay between onset of symptoms and diagnosis of endometriosis is 12 years in the USA and 8 years in the UK (Hadfield *et al.*, 1996). More recently, further studies from Norway (Husby *et al.*, 2003) and Brazil (Arruda *et al.*, 2003) confirm these findings and indicate delays in diagnosis of 6.7 and 7.0 years. In contrast to the Ling (1999) study, these reports suggest that a more rapid and accurate diagnosis of endometriosis may be helpful to patients.

The evidence as to whether to treat or not treat in the absence of a firm diagnosis remains confused. The dilemma is whether to withhold early diagnostic laparoscopy with the risks of delaying accurate diagnosis when this may be disadvantageous and of giving inappropriate medications to patients without an indication or to sanction the widespread use of early laparoscopy that is not without risks and significant cost implications. Together these apparently conflicting studies surely indicate the need to ensure that patients are correctly assigned to the appropriate level of investigation, but how can this be achieved?

#### ‘Two types of endometriosis’

The majority of patients with endometriosis have only minor degrees of the disease associated with mild or moderately severe symptomatology. The absolute prevalence is unknown and is dependent on the clinical source of the patients. The presence of superficial endometriosis in asymptomatic infertile

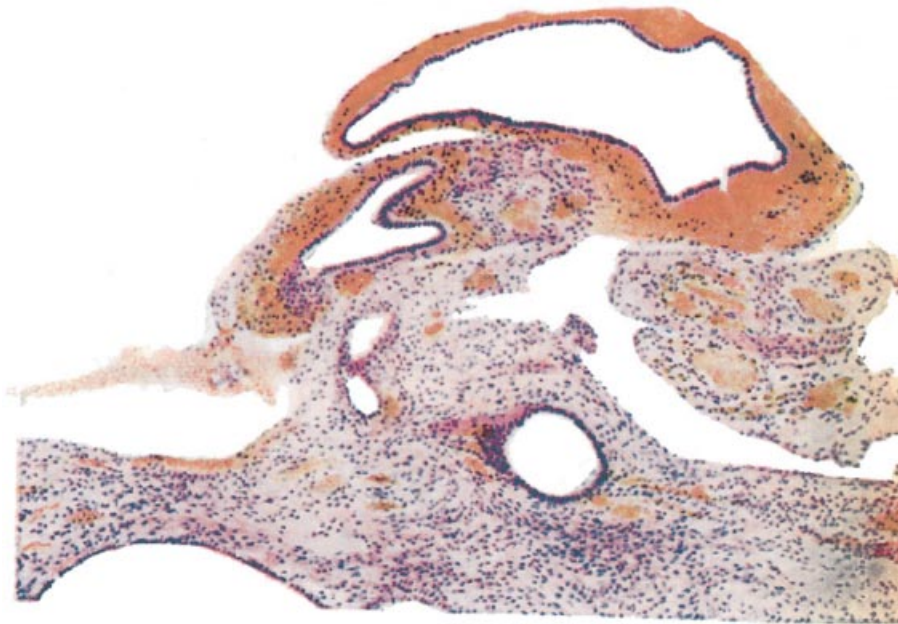


John Albertson Sampson

Figure 1. John A. Sampson.



Figure 2. Sampson's illustration of a superficial implant (imp) on the surface of an ovary.



**Figure 3.** Sampson's illustration of the histology of a superficial implant.

patients varies between 20 and 50% (American College of Obstetricians and Gynecologists, 2000), and even among women unexposed to sperm, deposits were found in 32% of cases (Matorras *et al.*, 1996). Similar lesions were found in 2–5% of patients having sterilization procedures (Strathy *et al.*, 1982). Multiple superficial deposits scattered widely across the pelvis, broad ligaments, ovaries and abdominal cavity are features of this type of lesion (Sampson, 1927a). The classic illustrations of Sampson (Figure 1) show small blood-filled lesions on the peritoneum, the ovary (Figure 2) and the surface of the bowel. Subsequently laparoscopic studies have revealed several variations in the gross morphology of such peritoneal endometriosis (Jansen and Russel, 1986; Redwine, 1987; Stripling *et al.*, 1988; Martin *et al.*, 1989; Nisolle *et al.*, 1990). The characteristic histology is of deposits of endometrial-like glands and stroma (Figure 3) sometimes with evidence of menstrual shedding (Sampson, 1924a). Even these peritoneal lesions have recently been shown also to contain smooth muscle cells, but in this situation this element is usually not clinically apparent (Anaf *et al.*, 2000). These superficial lesions may be symptomatic and associated with both infertility and pain. Various medical treatments including progestogens (Prentice *et al.*, 2000), Danazol (Selak *et al.*, 2001), oral contraceptives (Moore *et al.*, 2003) and GnRH agonists (Prentice, 2003) have been shown to be effective with none being more efficacious than the others. CO<sub>2</sub> Laser ablation is effective in the relieving pain associated with minimal, mild and moderate endometriosis (Sutton *et al.*, 1994). Laparoscopic surgery (Marcoux *et al.*, 1997) but not medical therapy (Hughes *et al.*, 2000) has also been shown to be of benefit in treating infertility associated with superficial disease. A proportion of superficial lesions is, however, asymptomatic and the clinical importance of this group has been questioned. A study from Norway demonstrated that there appears to be

little risk that asymptomatic minimal endometriotic lesions will become symptomatic (Moen, 2002) and a study from the UK showed that minimal endometriosis was not significantly associated with pelvic pain (Thorton *et al.*, 1997).

The second clinical manifestation of endometriosis is that associated with more severe symptoms and signs. Thomas Cullen (Figure 4) described a condition that he called adenomyoma of the rectovaginal septum (Cullen, 1920). He characterized these lesions as tumours of non-striated muscle with islands of uterine mucosa scattered throughout them, that arise from behind the cervix and that spread laterally to blend with the anterior wall of the rectum and the uterosacral ligaments. He noted that the disease might also invade the broad ligaments, encircle the ureter and break through into the vagina (Figure 5). He commented that 'many will have undoubtedly seen these lesions, but may not have recognized them. They are of unusual importance, and if overlooked will, in time, cause the patient to become a chronic invalid'. He ventured the view that 'In less than 10 years, I feel sure that the surgeon will recognize and operate on these 'adenomyomas of the rectovaginal septum' long before the wall of the rectum or the broad ligament have been involved'. Sadly, 83 years later these views seem rather optimistic, for this type of lesion is frequently missed and/or subjected to multiple ineffective therapies. These adenomyoma require surgical removal that has been shown to be effective in a number of large series (Redwine, 1991; Donnez *et al.*, 1997; Redwine and Wright, 2001; Abbott *et al.*, 2003) and most recently in a placebo-controlled randomized controlled trial (Abbott J, Hawe J, Hunter D, Holmes M, Finn P and Garry R, unpublished data).

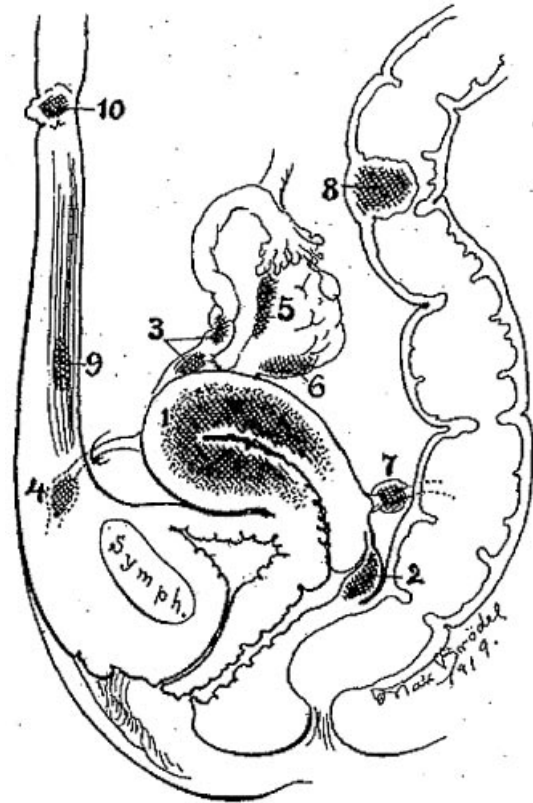
Cullen's term of 'adenomyoma' is purely descriptive and gives no hint as to the possible source or cause of the lesion. These lesions show marked fibrosis in almost every case and associated smooth muscle metaplasia in 88% of cases in



Thomas Stephen Cullen

**Figure 4.** Thomas Cullen.

addition to the classical combination of endometrial glands and stroma (Itoga *et al.*, 2003). These tumours have a substantial mass that can usually be palpated on careful vaginal examination. Such deeply located endometriosis is found only in the cul de sac (55%), the uterosacral ligaments (34%) and the uterovesical fold (11%) (Cornillie *et al.*, 1990). This group found no deep lesions of endometriosis in the ovarian fossa or scattered across the peritoneum. The intensity of the patient's pain is strongly correlated with the depth of the lesion (Cornillie *et al.*, 1990; Koninckx *et al.*, 1991; Chapron *et al.*, 2003a). This type of lesion produces not only intense dysmenorrhoea, but also severe non-menstrual pain, dyspareunia and dyskesia (Redwine, 1991; Garry, 2000). The location of the lesion is correlated with the nature of the symptoms, for example dyspareunia is associated with uterosacral involvement and non-cyclical pelvic pain and dyskesia with bowel involvement (Fauconnier *et al.*, 2002). In addition to various types of pain, patients with deep endometriosis have profound disturbance in quality of life and sexual activity as assessed by a number of validated instruments (Garry *et al.*, 2000; Redwine and Wright, 2001; Abbott *et al.*, 2003). In a series of patients with this type of deeply infiltrating endometriosis 58% of patients had disease principally in the uterosacral ligaments, 18% in the cul de sac, 16% involving the bowel and 8% the bladder (Chapron *et al.*, 2003b). The histology of this type of lesion has been described repeatedly over the years (Cullen, 1920; Sampson, 1921 and 1927b; Reich *et al.*, 1991; Koninckx and Martin, 1992; Donnez *et al.*, 1997; Brosens and Brosens, 2000; Itoga *et al.*, 2003). The nodules have three histological

**Figure 5.** Cullen's diagram illustrating the distribution of adenomyomata.

components characterized by endometrial-like glands and stroma surrounded by much fibrosis and smooth-muscle hyperplasia (Anaf *et al.*, 2000). This type of histological lesion can be best described as an adenomyoma.

It is well recognized that endometriosis is associated with infertility. Reduced chances of conception appear to be associated with both superficial and deep phenotypes of endometriosis. Despite the clinical importance of this symptom its presence or absence does not seem to help in the clinical classification of endometriosis and so more detailed review of this major area has not been performed in this study.

Although deep cul de sac endometriosis or adenomyoma can cause severe pain and distress such lesions alone seldom threaten survival. However, some aggressive forms of adenomyoma may be potentially life threatening. This occurs when it involves the bowel, ureter and bladder or when the lesions undergo malignant transformation (Garry, 2001).

The intestines are involved in between 5–15% of patients with symptomatic endometriosis (Jubanyik and Comite, 1997). Usually only the serosal surface of the bowel is involved for example in only 5.4% of 3037 cases of endometriosis requiring laparotomy in one series (Weed *et al.*, 1987). Such lesions produce anatomical distortion and associated bowel dysfunction that may be improved by correction of the anatomy without the need for excisional bowel surgery (Reich, 1991; Donnez *et al.*, 1997). Deeper colo-rectal endometriosis may, however, produce an obstructive syndrome and/or cyclical rectal bleeding. Formal bowel resection is then required (Weed

and Ray, 1987; Possover *et al.*, 2000; Kavallaris, 2003). This is required in about 1.2% and 16% of those with adenomyoma (Donnez *et al.*, 2001; Redwine and Wright, 2001; Chapron *et al.*, 2003b). It was noted in Donnez's series that no case of bowel involvement was found without associated adenomyoma. The histology of this type of lesion had been clearly described previously (Cullen, 1920; Sampson, 1921). 'Cullen described a case who had a recto-vaginal growth of typical adenomyatous tissue and a separate tumour that projected into the sigmoid consisted of normal rectal mucosa but with greatly thickened muscular tissue. Scattered throughout the muscular tissue were uterine glands surrounded by the characteristic stroma.' The rectovaginal lesion and the lesion within the bowel had identical histological features predominated by muscular hyperplasia that both authorities termed adenomyoma. It is clear that bowel endometriosis is usually multifocal and effective therapy will need to remove all deposits (Chapron *et al.*, 2003b; Kavallaris *et al.*, 2003). Malignant change in colonic endometriosis has been documented. The rate of progression is unknown but is uncommon. In a recent series, 17 cases were reviewed of whom nine developed in patients taking unopposed oestrogens (Jones *et al.*, 2002). A similar lesion has been described after using long-term tamoxifen therapy (Bese *et al.*, 2003) and a clear cell carcinoma of the rectum has also been described in a 40 year woman with severe endometriosis treated on a long-term basis with medroxyprogesterone acetate (Pokieser *et al.*, 2002).

The urinary tract is involved in 1–4% of women with endometriosis of which around 90% involve the bladder (Jubanyik and Comite, 1997). Full thickness bladder lesions are less common and were found in only 17 of 9200 (0.2%) women with symptomatic endometriosis (Donnez *et al.*, 2000). The histological features are consistent and are similar to uterine adenomyosis with foci of endometrial-like glands surrounded by thin rims of endometrial-type stroma surrounded by muscular tissue (Fedele *et al.*, 1992; Donnez *et al.*, 2000). Both these groups suggested that these lesions should be considered as bladder adenomyosis. This condition was not, however, associated with uterine adenomyosis (Donnez *et al.*, 2000; Vercellini *et al.*, 2002). Malignant transformation of bladder endometriosis although rare has been described repeatedly (Al-Izzi *et al.*, 1989; Vara *et al.*, 1990; Balat *et al.*, 1996; Nezhat *et al.*, 2002) and must represent a risk if bladder lesions remain untreated.

Ureteral endometriosis is even less common, with an incidence of <0.1% of all cases of endometriosis (Donnez and Brosens, 1997). However, this group, in a later prospective study confined to cases of rectovaginal endometriosis reported that 4.4% of all cases (18 of 405) had associated ureteral endometriosis (Donnez *et al.*, 2002). Each case of ureteral endometriosis was associated with extensive rectovaginal disease and all but one arose from large nodules of >3 cm in diameter. The histology of these lesions is again mainly composed of hyperplasia of smooth muscle with some glands and scanty stroma (Ferenczy, 1998; Donnez *et al.*, 2002). Obstructive uropathy that may lead to renal cortical atrophy and severe loss of renal function can occur with this type of lesion. The author has observed two young women with totally

non-functioning kidneys that developed as a consequence of prolonged undiagnosed endometriosis. Ureteral endometriosis therefore appears to be due to direct lateral extension of rectovaginal nodules and like the 'parent' lesion the predominant feature is myohyperplasia (Donnez *et al.*, 2002).

### Classification

Thus we appear to have one phenotype of endometriosis that is superficial in location, is associated with relatively minor symptoms and is amenable to simple treatments and a second phenotype associated with deep lesions, more severe symptoms and potentially serious complications that may require extensive surgery to relieve. How did we come to use the single term 'endometriosis' to cover this apparently disparate group of conditions? It would appear that John Sampson laid the seeds that others then developed. In his early writings Sampson used the term adenomyoma to describe deep lesions. In one of his earliest works he observes that 'if (adenomas) are invasive they may cause adenomyoma of the uterus by invasion of the uterine wall from without or adenomyoma of the uterosacral ligament, round ligament, rectovaginal septum, rectum, sigmoid etc' (Sampson, 1921). Thereafter he used the term less and less frequently preferring the term endometriosis. He felt that this was a better term for displaced endometrial tissue. His view was that the term endometriosis was the most appropriate to describe the presumed source of the ectopic endometrium (Sampson 1925). Thus Sampson's term was chosen because it indicated what Sampson believed, but what is still not yet proven, to be the origin of the condition.

The correct classification of ovarian endometriotic cysts greatly preoccupied Sampson. The histology of the lesions has been clarified with most believing they are usually superficial lesions of endometrial glands and stroma on the surface of an invaginated cortex (Sampson, 1921; Hughesdon, 1957; Brosens *et al.*, 1994). About 16% of patients with endometriosis have an associated endometrioma (Donnez, 2001). Malignant change in ovarian endometriosis has long been recognized (Sampson, 1924b, 1925). Sampson ventured the opinion that 'I do not believe that all carcinomas of the ovary are of endometrial origin. Some are however, and possibly the percentage is large'. The prevalence of ovarian cancers associated with endometriosis was between 7.7 and 24% in three large individual unit series of ovarian cancers although it should be noted that these studies might reflect particularly high-risk areas (Fukunagama *et al.*, 1997; Jimbo *et al.*, 1997; Garry, 2001; Oral *et al.*, 2003). In the USA the most common histological types of endometriosis-associated cancers were clear cell 23% and endometrioid carcinoma 23% (Modesitt *et al.*, 2002). In a Japanese study where the incidence of clear cell carcinoma of the ovary is substantially higher in general than in the west, the prevalence of clear cell ovarian cancer was 54% of the total and 42% of the remainder were endometrioid in type (Fukunaga *et al.*, 1997). The standardized risk of developing ovarian cancer in patients with long-standing ovarian endometriosis in Sweden is >400% higher than the normal population (standardized incidence ratio 4.2, 95% confidence interval 2.0–7.7) (Brinton *et al.*, 1997).

GnRH agonists reduce the size of endometrial ovarian cysts but there is no evidence to confirm the efficacy of medical treatment in the reduction of pain associated with such lesions (American College of Obstetricians and Gynecologists, 2000). There is a consensus that ovarian endometriosis requires surgical treatment that may be either excision or ablation of the cyst capsule (Canis *et al.*, 1992; Donnez *et al.*, 1994). Because of this and the facts the ovarian cysts are usually associated with endometriosis in other sites with a high incidence of associated intestinal involvement (Redwine, 1999) and a substantial risk of malignant change it is suggested that ovarian endometriomata are classified along with the deeply invasive lesions despite much work linking their formation with superficial peritoneal endometriosis.

How then can we correctly but conveniently define these two clinically different groups? All readers of this paper will be familiar with the rAFS classification system. Devised as a guide for the management of patients with infertility associated with endometriosis it remains the most widely used system. In 1991 a comprehensive review of this and 12 other classification systems for endometriosis was produced (Groff, 1991).

Since this time a number of alternative systems have been suggested. Martin *et al.*, (1989) and later Cornillie *et al.* (1990) suggested that endometriosis should be classified according to the depth of invasion into superficial (<1 mm), intermediate (2–4 mm), deep (>5 mm) and very deep (>10 mm). This classification showed correlations between the depth of invasion and severity of pain. Although this system has been helpful in aiding understanding of the disease process, it is based on histological measurements and is therefore not relevant to the clinic situation. David Redwine introduced the term Mülleriosis because he believed the term endometriosis is too limiting and that the retrograde menstruation theory is unproven (Redwine, 1987). His theory is an expansion of the theory of Russell who suggested that endometriotic lesions arise from embryonic rests of the Müllerian system (Redwine, 1998). This terminology, like endometriosis before it, is based on a presumed, but still controversial theory of the aetiology of the condition. Nisolle *et al.* (1997) suggested that rectovaginal, ovarian and peritoneal endometriosis should be considered three different diseases with three discrete aetiologies. This group suggest that peritoneal lesions are derived from implantation of shed endometrium, ovarian lesions result from a combination of invagination and metaplastic changes on the ovarian cortex and rectovaginal lesions represent retro-peritoneal adenomyomas derived from metaplasia of Müllerian remnants. This is another classification system based on presumed, but as yet, unproven aetiological mechanisms (Donnez *et al.*, 2001). Brosens and Brosens (2000) suggest that the classification of endometriosis should not be based on depth but on the expression of a specific endometrial activity: either sex steroid hormone dependant bleeding or smooth muscle metaplasia. This theory can be extended to suggest that there are two types of 'endometriosis' one of which behaves like superficial endometrium and the other that resembles basal endometrium in phenotype and function. This latter type is in fact phenotypically identical with adenomyosis. Most recently a classification system for deep endometriosis based on the

anatomical location of the lesion with a recommended preferred surgical treatment for each location has been developed (Chapron *et al.*, 2003b).

We therefore have multiple classification systems based on several different criteria. Some are based on anatomical location, some on functional behavior and some to reflect presumed aetiology. There is, as yet, no agreement about the aetiological antecedents of endometriosis and therefore there can, at this time, be no universally acceptable classification system based on aetiology. Until a definitive aetiological classification can be agreed I suggest that the most useful subdivision will be made on the basis of clinical findings. This could be on the basis of symptoms, signs or a combination of both.

### Classification based on symptom analysis

The relevance of symptom analysis in predicting the severity of endometriosis is confusing. Dysmenorrhoea, pelvic pain, dyspareunia and dyskesia are non-specific symptoms and may be found in patients without endometriosis (Ling *et al.*, 1999), and in association with both mild (Sutton *et al.*, 1994; Ling *et al.*, 1999) and severe endometriosis (Abbott *et al.*, 2003). Moreover endometriosis may be asymptomatic (Moen *et al.*, 2002) or mild and not associated with pain (Fedele *et al.*, 1992; Thorton *et al.*, 1997). Severe dysmenorrhoea, however, does appear to predict the presence of endometriosis with a positive predictive value (PPV) of 63% and 95% (negative predictive value) NPV (Foreman *et al.*, 1993; Naish *et al.*, 1993). Some authors believe the severity of the painful dysmenorrhoea also correlates with the severity of the AFS score (Muzii *et al.*, 1997; Eskenazi *et al.*, 2001) while others have found no such correlation (Grupo Italiano, 2001; Abbott, 2003). Vaginal endometriosis is significantly associated with deep dyspareunia (Vercellini *et al.*, 1996). and the presence of rectal or vaginal lesions are significantly related to the severity of dysmenorrhoea (Chapron *et al.*, 2003a). The type of pelvic pain is related to the anatomical location (Fauconnier *et al.*, 2002). This group has demonstrated that the frequency of dyspareunia increases with the presence of uterosacral invasion, painful defaecation with bowel and vaginal lesions and severe dysmenorrhoea with increased obliteration of the pouch of Douglas. In summary, the severity and nature of the symptoms of endometriosis are associated with the location and depth of the lesions but probably not with the rAFS score.

### Classification based on analysis of findings

The value of pelvic examination as a screening test in asymptomatic pelvic disease has been questioned (Dragisic *et al.*, 2003). Analysis of the findings on vaginal examination in symptomatic patients with presumed endometriosis however suggests that palpable induration or nodules in the posterior vaginal fornix and/or along the uterosacral ligaments appears to be pathognomonic signs of deep endometriosis (Matorras *et al.*, 1996). These lesions are tender and pressure reproduces symptoms. The PPV of such tenderness predicting endometriosis is between 76 and 79% and this rises to 83% with a

specificity of 92% if focal tenderness is located only in the uterosacral ligaments and cul de sac (Ripps and Martin, 1992; Koninckx *et al.*, 1996; Eskenazi, 2001). The accuracy of these findings is further increased if the examination is performed during menstruation (Koninckx *et al.*, 1996). Deep invasive endometriosis is frequently associated with ovarian endometriosis (Redwine, 1999). The co-existence of these two conditions further improves the reliability of the clinical diagnosis. It is possible that it is not the size of ovarian endometriomata but the associated lesions that cause pelvic pain (Porpora *et al.*, 1999).

In summary, the presence or absence of palpable nodular or infiltrative lesions is related to the location and depth of the lesions and reflects the severity of the pain and the risks of severe complications.

### Confusion about names

Cullen's original name for deep pelvic disease was adenomyoma of the rectovaginal septum (Cullen, 1920). It is now recognized that endometriosis only rarely involves the true rectovaginal septum (Martin and Batt, 2001; Vercellini *et al.*, 2000) and much more frequently involves the overlying rectovaginal pouch (Martin and Batt, 2001). A variety of other descriptions has been used to describe the anatomical location of these lesions and includes cul-de sac endometriosis (Martin *et al.*, 1989), obliteration of the cul-de-sac (Redwine, 1991) and rectocervical endometriosis (Adamyan *et al.*, 1993; Perry *et al.*, 1995). These three terms were combined to produce an anatomically precise but hardly concise cul-de-sac obliteration secondary to retrocervical deep fibrotic endometriosis (Reich *et al.*, 1991). Other terms that have also been used include pelvic wall-infiltrating endometriosis (Khare *et al.*, 1996), rectovaginal septum adenomyotic nodules (Donnez *et al.*, 1997), retroperitoneal adenomyosis (Donnez, 2001) and rectovaginal endometriosis (Kavallaris *et al.*, 2003). From this review it is not immediately obvious what these lesions should be called or how we should describe their locations.

### The need for syndromes

What then can we conveniently and accurately call these two types of endometriosis? In the absence of an agreed aetiological mechanism or unambiguous symptomatology or even a concise agreed anatomical description, it is perhaps pragmatic at this stage to classify the disease according to the sum of the anatomical location, clinical findings and associated histological appearances. Such a collection of symptoms, signs and findings is a syndrome. Endometriosis appears to be two different syndromes currently collected under the single 'endometriosis' terminology.

The first syndrome may be defined as the combination of symptoms suggestive of endometriosis together with a tender palpable nodular or indurative lesion in the deep pelvis. Such nodules are associated with the histological finding of marked fibromuscular hyperplasia containing islands of endometrium-like glands. This collection of findings is precisely that

described by Cullen in 1920. I would therefore suggest that this collection of signs and symptoms be called Cullen's syndrome. The incidence of this syndrome is not known, but probably represents a fairly small proportion of all cases of endometriosis with estimates of between 1/170 and 1/3800 women (Martin and Batt, 2001). Cullen's syndrome, although relatively infrequent, will include many of those with the more severe symptoms, almost all those at risk of developing malignancy, and all those at risk of lower bowel and urinary tract involvement.

The other syndrome also consists of the symptoms of infertility and/or chronic pelvic pain with dysmenorrhoea, and dyspareunia. This syndrome is, however, associated with the absence of deep pelvic local tenderness, induration or nodule formation. This condition is usually associated with the laparoscopic appearances of multiple classical superficial clear, red, black or white lesions. The histology of such lesions is characteristic by the findings of superficial deposits containing endometrial-like glands and stroma. These lesions have little or no associated myohyperplasia and are those described by Sampson. This syndrome of pelvic pain without focal nodular lesions could therefore be known as Sampson's syndrome. This syndrome is associated with more minor symptoms, less structural change in the pelvis and substantially less risk of major complications.

These suggestions are made in an attempt to familiarize doctors without a special interest in endometriosis with the important realities of differing clinical degrees of endometriosis. Of course from an expert's view this clinical classification is inherently inaccurate and will only produce a fairly crude subdivision. Severe cases may be missed and there will be inaccuracies in assignment and some overlap with both 'syndromes' co-existing. Many cases will have evidence of both superficial and deep disease, and it is quite probable that some lesions will evolve from one syndrome to the other over time. In such circumstances the presence of the clinically most severe group (Cullen's syndrome) would take precedent. This classification makes no attempt to determine the origin of the lesions. They may represent different aspects of a single disease continuum or two (or three) completely different disease processes.

### Conclusions

The proposals are presented as a pragmatic attempt to help the clinicians of all levels of experience in this confused area. The goal is to differentiate 'endometriosis' into clinically important categories to ensure that many patients with mild disease are not over-investigated or over-treated while patients with potentially serious disease are not subject to prolonged delays and the use of multiple ineffective therapies. In general, patients with Sampson's syndrome will be managed with medications and/or with superficial ablation type laparoscopic surgery of the kind provided by many gynaecologists. Patients with Cullen's syndrome on the other hand are unlikely to respond to medical therapy and may require extensive and at times potentially dangerous surgery. For these high-risk patients, delay in accurate diagnosis could be associated with

serious adverse outcomes. These patients should be referred to units with particular expertise in this field as early in the disease process as possible. The universal recognition of the clinical imperatives associated with this syndrome may facilitate the widespread establishment of specialized endometriosis treatment centres.

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