Endometriosis and adenomyosis have long been considered as one entity with a common, although unknown, aetiology (Meyer, 1919). After the term endometriosis was coined (Sampson, 1927), it was widely used for the intrauterine and the extrauterine variety of the disease respectively (Coussellor, 1938). However, it was the theory of tubal spread of normal endometrial cells by retrograde menstruation as the cause of pelvic endometriosis (Sampson, 1927) that finally led to consideration of both localizations of ectopic endometrial growth as different entities. If Sampson’s theory were correct, then infiltrative and expansive growth of endometrial glands and stroma with hyperplasia of surrounding muscular tissue into the depth of the myometrium would differ from pelvic endometriosis not only by localization but also by pathogenesis. Consequently, although the frequent association of endometriosis with adenomyosis was recognized (Emge, 1962; Pratt, 1972), it was suggested that the term ‘endometriosis’ should be used exclusively for endometrial growth beyond the confines of the uterus and that the term ‘adenomyosis’ should be used only for intrauterine ectopic endometrial growth (Ridley, 1968).

Recently, it was suggested that there were three types of endometriotic lesions, peritoneal, ovarian and rectovaginal (Nisolle and Donnez, 1997). While peritoneal endometriosis would result from transabdominal shedding and implantation of endometrial cells, ovarian endometriomata would result from metaplasia and rectovaginal endometriosis, with endometrial glands and stroma as well as muscular tissue displaying the composition of adenomyomata, would arise from Müllerian remnants.

It has been suggested the existence of principally two phenotypes of endometriosis, superficial endometriosis including ovarian endometriomata and adenomyosis (Brosens, 2000). While superficial endometriosis would arise from the shedding of superficial endometrium (SE) (and the term endometriosis should be restricted to this variety), adenomyosis would result from basal endometrium (BE) and the subendometrial myometrium (junctional zone myometrium; JZM; archimyometrium) (Werth and Grudsew, 1898; Noe et al., 1999) and would preferentially present at certain locations (Cullen, 1920), particularly the uterine myometrium, the uterine ligaments and the rectovaginal septum. Superficial endometriosis would not develop into deep infiltrative endometriosis, because they both were different entities.

We have recently suggested that endometriosis originates at the uterine level and constitutes primarily a disease of the archimetrax (Leyendecker et al., 1998; Noe et al., 1999) since altered endometrial cells with a higher potential for growth on peritoneal surfaces gain access to the peritoneal cavity, and so adenomyosis merely constitutes a special variant of endometriosis. Meanwhile, we have extended our studies and found further evidence that pelvic endometriosis with all its phenotypes are sequelae of uterine adenomyosis or its early manifestations, and that both endometriosis and adenomyosis constitute a pathogenetic entity (Kunz et al., 2000). Several lines of evidence support this notion.

Firstly, the eutopic endometrium in endometriosis shows alterations similar to those which occur in the endometriotic lesions that are not found in the endometrium of women free of disease. These alterations include signs of increased inflammatory response, such as the increased expression of monocyte-chemotactic protein-1 (MCP-1) (Jolicoeur et al., 1998) and the increased colonization with macrophages (Leiva et al., 1994), signs of increased proliferation (Wingfield et al., 1995) and of increased biochemical activity, e.g. pathological expression of P450 aromatase (Noble et al., 1996; 1997) resulting in increased tissue concentrations of oestradiol (Takahashi et al., 1989).

Secondly, women with endometriosis show a significant increase in uterine peristaltic activity in comparison to women free of disease. At mid-cycle, in women with endometriosis, the peristaltic activity becomes dysperistaltic, resulting in a breakdown of directed sperm transport (Leyendecker et al., 1996). Moreover, in women with endometriosis the intrauterine pressure is increased in comparison with women without the disease (Bulletti et al., 1997; Mäkäräinen, 1988).

Finally, in endovaginal sonography (EVS) and magnetic resonance imaging (MRI), women with endometriosis exhibit a significant expansion of the archimyometrium (‘halo’ in EVS or ‘junctional zone’ in MRI respectively) over controls, which is similar or identical to the images obtained in adenomyosis (Leyendecker et al., 1998; Kunz et al., 2000). The depth of the archimal invasion was correlated with the age of the patients. Histologically, this expansion involves all components of the archimetrax as the glandular and stromal endometrium as well as the subendometrial myometrium (M.Herbertz, M.Noë, G.Kunz, G.Mall and G.Leyendecker, unpublished data).

With respect to both, uterine hyper- and dysperistalsis as well as archimetal expansion in women with endometriosis there was no correlation between the extent of these alterations and the grade of the disease (Leyendecker et al., 1996; Kunz et al., 2000). Thus, there was no indication that in minimal and mild endometriosis (superficial endometriosis) the archimetrax would be restricted to this variety), adenomyosis would result from basal endometrium (BE/JZM; Brosens, 2000) was not involved in the disease process. In contrast, the data indicate that there are uterine dysfunctions and adenomyotic changes of the archimetrax or its early manifestations in all phenotypes of endometriosis, e.g. superficial or infiltrative endometriosis.

If our theory is correct that adenomyosis and its early manifestations constitute the primary lesion with pelvic endometriosis being merely a sequel, then the aetiology of endometriosis is primarily the aetiology of adenomyosis.

As the prevalence of adenomyosis is very high (Bird et al., 1972) its cause or causes are most probably not spectacular but rather related to the normal process of reproduction.
Trauma such as induced by pregnancy and delivery followed by endometrial proliferation into muscular dehiscencies has been long discussed (Emge, 1962; Ferencyz, 1998) and gained recent support by circumstantial evidence derived from the finding of adenomyosis following endometrial ablation (McLucas, 1994; Yuen, 1995; McCausland and McCausland, 1996). Adenomyosis has been characterized as the disease of the parous pre- and peri-menopausal woman (Parazzini et al., 1996) with the highest incidence during the fourth and fifth decade of life (Bird et al., 1972). Our own data have shown that adenomyosis is also present in young infertile women with endometriosis (Kunz et al., 2000) and in particular in those with severe dysmenorrhoea (G.Leyendecker, unpublished).

We have recently suggested that it is the specific morphological structure of the archimetz and its specific function of directed sperm transport that predisposes to chronic microtraumatization and chronic inflammatory and proliferatory response at the fundo-cornual raphe of the archimyometrium in the midline of the anterior and posterior wall of the uterus that results from the fusion of the two paramesonephric ducts (Werth and Grusdew, 1898; Leyendecker et al., 1998; Noe et al., 1999). There, the circular fibres of the stratum subvasculare form, in fundal direction, a decreasing angle as they separate into those of the cornua and the tubes (Figure 1). With respect to directed sperm transport, the unpaired uterus is still functioning as a paired organ (Kunz et al., 1998a) which, in view of its continuous action must lead, in time, to muscular distensions at the fundo–cornual raphe. Within 1 min following application of technitium-labelled macroospheres of sperm size at the cervical os, ~30% of the radioactivity reaches the tubes, thus demonstrating the enormous power of the uterine peristaltic pump (Figure 5 in Kunz et al., 1996).

Sonographically, discontinuations of the ‘halo’ of the archimyometrium that represent endometrial infiltrations usually first appear in the midline of the uterine corpus (G.Leyendecker, unpublished data) (Figure 2) as does focal thickening of the ‘junctional zone’ in MRI (Figure 15 in Reinhold et al., 1998).

According to recent data (Prefontaine et al., 1996; Noble et al., 1996; Kitawaki et al., 1997), the P450 aromatase is not expressed in normal endometrium. However, our own data indicate that, in normal endometrium and the underlying myometrium, a transient expression of this enzyme occurs in the very early proliferative phase of the menstrual cycle (J.Becker, M.Noé, G.Kunz, G.Leyendecker, C.Noé, unpublished data). In adenomyotic tissue, in the eutopic endometrium of women with endometriosis as well as in endometriotic tissue such as the stroma of an ovarian endometrioma high expression of P450 aromatase could be demonstrated (Yamamoto et al., 1993; Noble et al., 1996, 1997; Kitawaki et al., 1997). The expression of P450 aromatase in adenomyotic/ endometriotic tissue may, therefore, be viewed as pathological in that it appears to be continuously expressed in comparison to normal endometrium. It is, however unclear, whether the expression of P450 aromatase is resulting from chronic proliferative processes at the level of the basal endometrium or whether the chronic expression of this enzyme constitutes one of the initial events. In any event, the chronic expression of P450 aromatase results in chronically increased tissue concentrations of oestrogen with various feed-forward effects as delineated recently (Leyendecker et al., 1998). Hyper- and dysperistalsis (Leyendecker et al., 1996) as well as increased intrauterine pressure (Mäkäräinen, 1988; Bulletti et al., 1997) may result from locally-increased oestrogen concentrations (Kunz et al., 1998b) as well as from archimetrial hyperproliferation that may both in turn increase chronic trauma.

Cells with an increased but varying potential of proliferation (Gaetje et al., 1995; Wingfield et al., 1995; Starzinski-Powitz et al., 1998) gain access to the peritoneal cavity where they implant and develop into endometriosis. In addition to the invasive potential of the cells, local factors may determine whether or not infiltrative endometriosis ensues (Koninckx et al., 1998). Infiltrative growth is usually restricted to the urinary bladder, the rectum, the sacrouterine ligaments and the recto-vaginal septum.

The seeding of altered cells by adenomyosis may change during the course of the disease. Profuse seeding in the beginning may decrease with adenomyotic nodule growth into the depth of the myometrium, leaving the superficial

Figure 1. Modified original drawing from Werth and Grusdew (1898) showing the architecture of the subendometrial myometrium (archimyometrium) in a human fetus uterus. The specific orientation of the circular fibres of the archimyometrium results from the fusion of the two paramesonephric ducts forming a fundo–cornual raphe (Noe et al., 1999) in the midline (dashed rectangle). The peristaltic pump of the uterus, which is continuously active during the menstrual cycle, is driven by co-ordinated contractions of these muscular fibres. Directed sperm transport into the dominant tube is made possible by differential activation of these fibres. By the time muscular distensions at the fundo–cornual raphe result in the formation of gaps and the endometrial stroma loses, at the endometrial–myometrial interface, its functional counterpart that results in endometrial proliferation into these gaps. This figure is reproduced from Arch. Gynäkol., Untersuchungen über die Entwicklung und Morphologie der menschlichen Uterusmuskulatur. Werth and Grusdew, 55, 325–409, Figure 6, 1898. © Springer-Verlag.
explain the extreme variability or pleiomorphism of the clinical
appearance of endometriosis. The latter may be completely
asymptomatic and may be found at a prevalence of up to 30%
during laparoscopic sterilization in women with their last
pregnancy 10 or more years ago (Moen, 1991). Archimetrial
invasion into the depth of the myometrium may explain
persisting subfertility and dysmenorrhoea in women with
minimal-to-mild endometriosis following eradication of the
endometriotic lesions (Hull et al., 1986; Adamson and Pasta,
1994; Leyendecker et al., 1996; Wood, 1998). Little invasion
into the myometrium may explain the absence of discomfort
dysmenorrhoea in some patients that present with diffuse
peritoneal endometriosis including ovarian endometriomata
(G.Leyendecker, unpublished). Infiltrative endometriosis such
as recto–vaginal endometriosis might persist in the presence
of ceased seeding from the uterine adenomyotic nodule,
while the superficial endometriotic lesions might have healed
resulting in the impression of recto–adenomyotic nodules
as a singular entity. Finally, adenomyosis might penetrate
the uterine serosa with ensuing massive peritoneal endometriosis
(Jones and Jones, 1981).

As pelvic endometriosis, with all its phenotypes, primarily
results, in our opinion, from adenomyotic lesions that constitute
a pathological proliferation of all components of the archimetra
this part of the uterus with its endo-, para- and autocrine
regulation as well as with its cell–cell interaction at the
endometrial–archimyometrial interface (Fujii et al., 1989;
Brosens et al., 1998) should become a focus of research. The
unravelling of these mechanisms might contribute to the
understanding, how chronic trauma might induce chronic
proliferative and invasive processes and why, on what level
and to what extent hereditary mechanisms (Kennedy, 1997)
and environmental factors such as endocrine disrupters (Rier
et al., 1993; Bois and Eskenazi, 1994; Koninckx et al., 1994;
Eskenazi and Kimmel, 1995; Mayani et al., 1997; Tsai et al.,
1997; Kuchenhoff et al., 1999)) become operative in this respect
and why, finally, some women develop the disease early in
their lives.

In conclusion, the uterus as a phylogenetically paired organ
has become unpaired in the human, by the fusion of the two
paramesonpehric ducts during early ontogeny. With respect to
rapid and sustained directed sperm transport, however, the
uterus has maintained the function of a paired organ. The
function of directed sperm transport is made possible by the
specific architecture of the archimyometrium that is character-
ized by a fundo-cornual raphe (Werth and Grusdew, 1898;
Noe et al., 1999). Both morphology and function predispose
to chronic microtrauma with muscular distensions and reactive
proliferation and invasion of the endometrium into the myome-
trium with metaplastic changes of the stroma into archimetrical
myometrium resulting in adenomyosis. The adenomyotic foci
may seed altered cells with an increased but variable potential
of implantation and infiltrative growth into the peritoneal
cavity with the tubes being the usual but not the exclusive
route. The natural history of adenomyosis as the underlying
disease, the quality of the spread cells as the seed as well as
the topography and the response of the peritoneal cavity with
its serosa and its organs as the bed determine the pleiomorphism
of endometriosis.

endometrium intact. This may be the reason why there was
less expression of P450 aromatase (Noble et al., 1996) and
no deficiency in 17βHSD type 2 (Zeitoun et al., 1998) in the
eutopic endometrium of women with endometriosis obtained
by curettage in comparison to endometriotic lesions. Seeding
might even come to a halt when the adenomyotic nodule might
have ‘burnt out’. This might be the basis for the finding of
only endometriotic scars during laparotomy and of the notion
that every woman has endometriosis once in her life (Evers,
1994).

The natural history of adenomyosis as delineated above may
explain the extreme variability or pleiomorphism of the clinical

Figure 2. Endovaginal sonography of the antefected uterus of a 33
year old woman without dysmenorrhoea and without endometriosis.
In the sagittal image of the whole uterus the archimyometrium
(‘halo’) encircling the endocervix and the endometrium is
completely intact (above). Endovaginal sonography of the
antefected uterus of a 33 year old woman with dysmenorrhoea and
endometriosis. Endometriotic scars and adhesions were present on
the peritoneum of the urinary bladder, the left ovarian fossa and the
left sacro–uterine ligament. There were no ovarian endometriomata
and both tubes were patent. In the sagittal image the
archimyometrium is intact in the cervical region and the anterior
wall of the uterine corpus. In the posterior wall the normal ‘halo’ is
destroyed (calipers) by pathological archimetrial infiltration into the
depth of the myometrium. Together with the thickening of the
posterior uterine wall this is indicative of diffuse adenomyosis and
explains both, dysmenorrhoea and infertility that had been
considered as idiopathic (below).
References


Cullen, T.S. (1920) The distribution of adenomyoma containing uterine three different entities.


