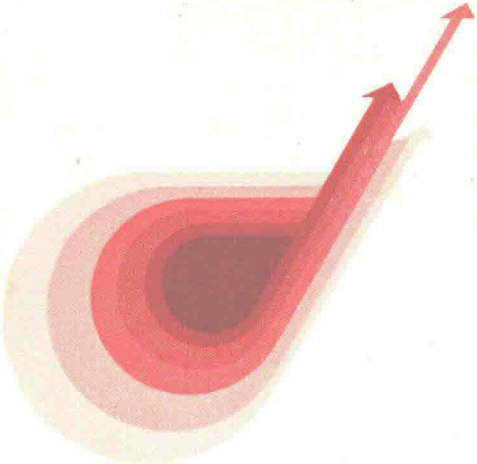

recent advances in endometriosis

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March, 1975

editor: Robert B. Greenblatt, M.D.

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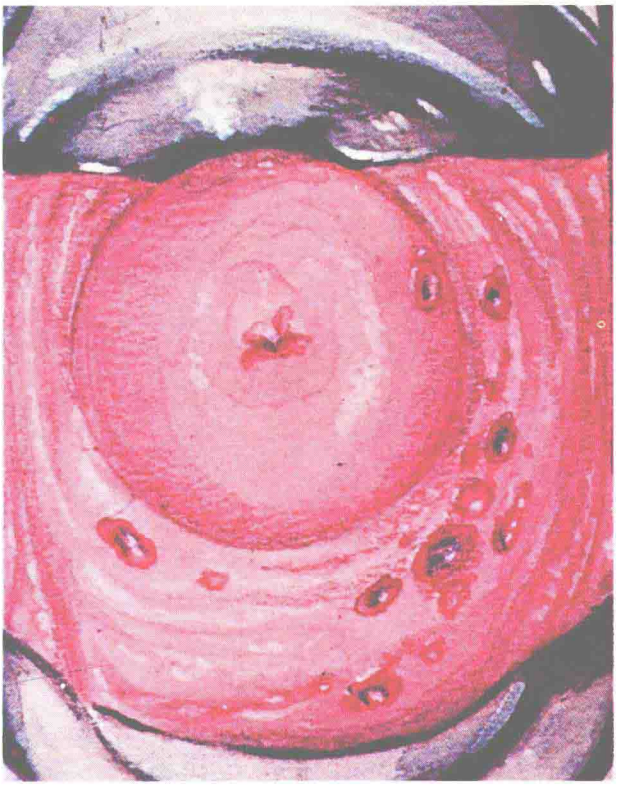
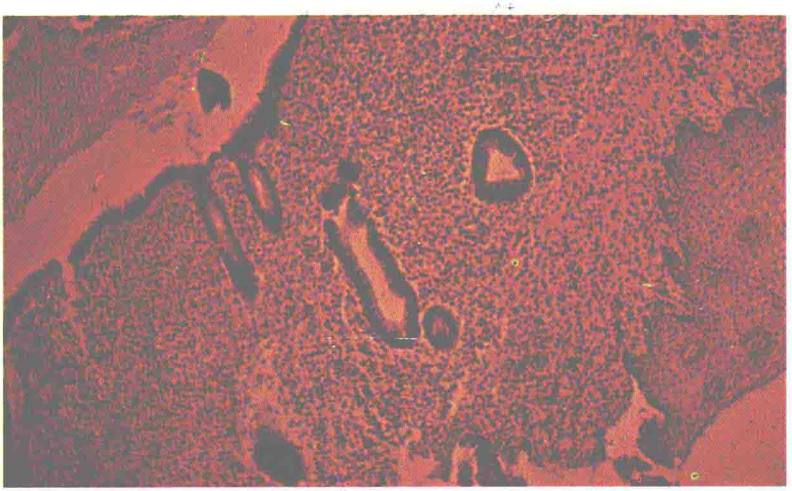


A. Artists drawing of a rare case of endometriosis involving both cervix and vaginal mucosa.



B. Photomicrograph of a histologic section through vaginal lesion illustrating endometrial glands, stroma, and vaginal mucosa.

Courtesy of Robert B. Greenblatt, M.D.

Contents

FOREWORD

A monograph dealing with the subject of endometriosis is long overdue. Save for uterine fibromyomata, the commonest gynecologic disorder in our population is endometriosis. It is indeed a disease of reproductive life and for many years was believed to affect women mainly between the ages of 30 and 40 years. With the popularization of culdoscopy, and now of laparoscopy, early diagnosis is possible and it now appears that endometriosis presents quite frequently in teenagers. Every young woman with dysmenorrhea should be suspect; the leading cause of infertility in women in their twenties is endometriosis.

Endometriosis has earned the sobriquet of "benign cancer," because ectopic endometrial tissue is destructive by local extension; is invasive through lymphatic spread; and reaches distant organs, such as the lung, through the blood stream. To be sure, it is rarely a fatal disease but rather the great gynecologic crippler. A greater awareness of the incidence of this disease and its protean manifestations is imperative for early diagnosis, so that treatment may be undertaken before the damage is too great.

Various therapeutic regimens are extant that have proved helpful in lessening pelvic pain and discomfort and in overcoming infertility — basically, these consist of conservative surgery and/or hormonal therapy. Estrogens and/or progestogens, and androgens have been employed with a modicum of success, in perhaps as many as 40-50% of the victims of this disorder.

A new weapon has now been added to our armamentarium against endometriosis — an antigonadotropic agent, danazol. This steroidal agent is mildly androgenic and mildly anabolic, and is a distant cousin to ethisterone, the first oral progestogen. Danazol offers another but significant new approach in the management of a difficult-to-manage disease.

This book represents the contributions of several outstanding scholars interested in the field of endometriosis who met for a symposium in Augusta, Georgia, in March 1975, under the aegis of Excerpta Medica and the Medical College of Georgia. I wish to express my gratitude to each of the contributors and to Dr. George Farrar, Director of Medical Affairs of Excerpta Medica for his cooperation.

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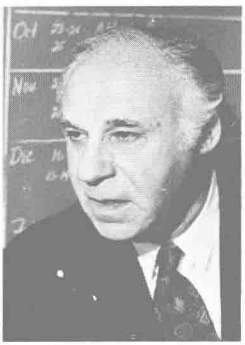

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Endometriosis: The Nature of the Problem and Approaches, Old and New, to Solving It

What is Endometriosis?

In simple terms, it is the growth of ectopic endometrium. This endometrial tissue, as a rule, undergoes cyclic changes and is therefore hormone-dependent. It is no longer considered an exotic disease but one that occurs with greater frequency than any other gynecologic disorder, with the exception of uterine fibromyomata. Endometriosis is thought to be on the increase and continues to be a most enigmatic disease, affecting women during their reproductive years. Although Sampson's contribution of 1921 first elicited the attention of gynecologists the world over, it should be recalled that in 1920 Cullen published an important dissertation on "The Distribution of Adenomyomas Containing Uterine Mucosa," at which time he presented case histories of so-called "external adenomyomas" [i.e. endometriosis] in 10 or 11 different sites.

How Common is this Disorder?

In 1941, Meigs found gross evidence of endometriosis in 36% of 400 consecutive private female patients at laparotomy with pathologic confirmation in 28%. Holmes, in 1942, reported eighty proven cases of "external" endometriosis among 307 gynecologic laparotomies, an incidence of 26%. He stated at that time that it was a disease of middle menstrual life, occurring most frequently between 30 and 45 years of age. Meigs, 20 years after his original report, claimed that first signs and symptoms of the disease did not appear until 13 to 19 years after the onset of menarche, suggesting a long latent period for its development.

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The concept, so long current, that endometriosis seldom occurs before 30, and rarely before 25, is no longer substantive nor tenable. With a greater awareness of this condition, and with increasing use of culdoscopy and endoscopy, the diagnosis of this disease is being confirmed much earlier in a larger number of cases, of necessity revising our previous ideas about the age-incidence of endometriosis. We must now consider this disorder as one that may occur anytime from a few years after the menarche until the onset of the menopause.

When Does Endometriosis First Manifest Itself?

An appreciation of the fact that endometriosis can occur in the teenager demands that we alter our views about the nature of the problem, so that active therapeutic measures may be undertaken when much may still be accomplished. What are the facts about the occurrence of this malady in the very young woman? In 1946, Fallon observed nine patients under the age of 20 in a series of 225 histologically proven cases. Bruser (1955), Depp *et al.* (1956), and others reported on its occurrence in young women. More implicit was the report from the Mayo Clinic of a series of 3,358 cases collected over a period of 30 years; 68 were younger than 25, and 12 were under 20 years of age. Schifrin *et al.* reported 15 cases of endometriosis in patients 20 years of age or younger. An anomaly of the genital tract, enhancing retrograde menstruation, was present in six patients. In 1974, Bullock in the United States and Gautier in France again brought the problem to our attention with reports on endometriosis in the teenager.

Why is it Important to Make the Diagnosis Early in the Course of the Disease?

The sequelae of progressive ectopic endometrial proliferation lead to increasing infirmity (dysmenorrhea, dyspareunia, pelvic discomfort, etc.) but also to infertility. It is therefore obviously desirable, whenever possible, to stem or slow down its progression while reproductive function is still intact, and before endometriosis can destroy the ovaries, or extensive disease makes panhysterectomy obligatory.

Woman's new role in society, it has been conjectured, has had some effect on the increasing incidence of endometriosis: greater sexual freedom, promiscuity, late marriage, delayed pregnancy, or a modern way of life. At any rate, the sobriquet "disease of civilization" has been applied.

How Does Endometriosis Develop?

We are aware that accidental transplantation of viable endometrium following hysterotomy accounts for endometriosis of the rectus muscle or in an abdominal scar

(Figure 1). But, is sloughed endometrium viable? Sampson, in 1921, suggested that fragments of endometrium are regurgitated during menstruation through the oviducts, subsequently inplanting on the ovaries and other pelvic structures. This concept of retrograde regurgitation has recently been confirmed on laparoscopic

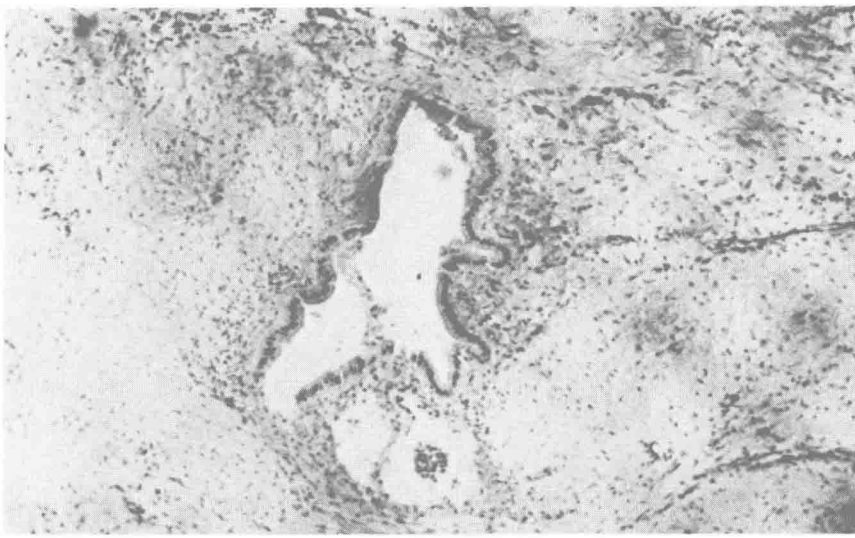

Figure 1 Endometriosis of abdominal wall (Reproduced from Greenblatt, R. B., and Suran, R. R.: Surg. Clin. North America, *April 1949, W. B. Saunders Co.)*

examination performed during menstruation. The well-designed experiments of Scott, and Te Linde and Wharton proved that endometriosis could occur in monkeys by inverting the uterus to divert the menstrual flow into the peritoneal cavity. However, six or more menstrual cycles were necessary to produce artificial endometriosis, and Ridley demonstrated that desquamated endometrium was capable of inducing endometriosis when injected subcutaneously into humans (Figure 2).

Nonetheless, Sampson's theory fails to explain certain observations. We have noted that the serosa of the appendix removed during pregnancy may show a decidual-like change and that similar changes have been observed on the surface of the ovary following exogenous gonadotropins (Figure 3). The mesothelium, it appears, may be hormonally stimulated, but why did six or more months elapse before endometriosis developed in the monkey during the aforementioned experiments of Te Linde *et al.*? Could it be that the mesothelium undergoes metaplasia to functioning endometrium following repeated insults (blood detritus, inflammation, congestion)? And finally, how does one explain endometriosis of the umbilicus? Could residual remnants of embryonic mesothelium eventuate into endometrium? The coelomic mesothelium indeed has pluripotential properties. Furthermore, simple

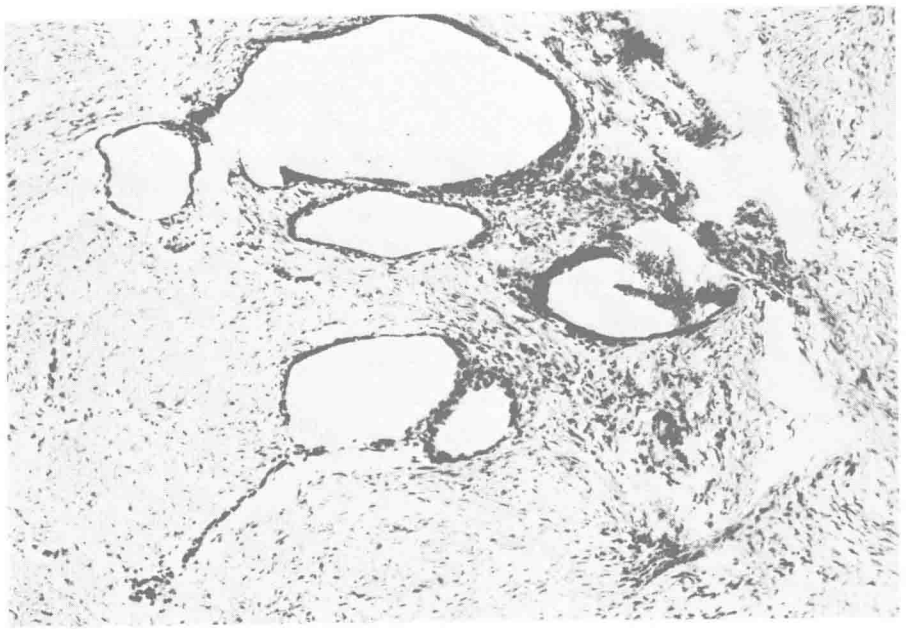

Figure 2 Endometriosis at site of implantation of shed endometrial fragments in human. (Ridley, O. H. and Edwards, I. K.: Am. J. Obst. Gynec., 76:*783, 1958)*

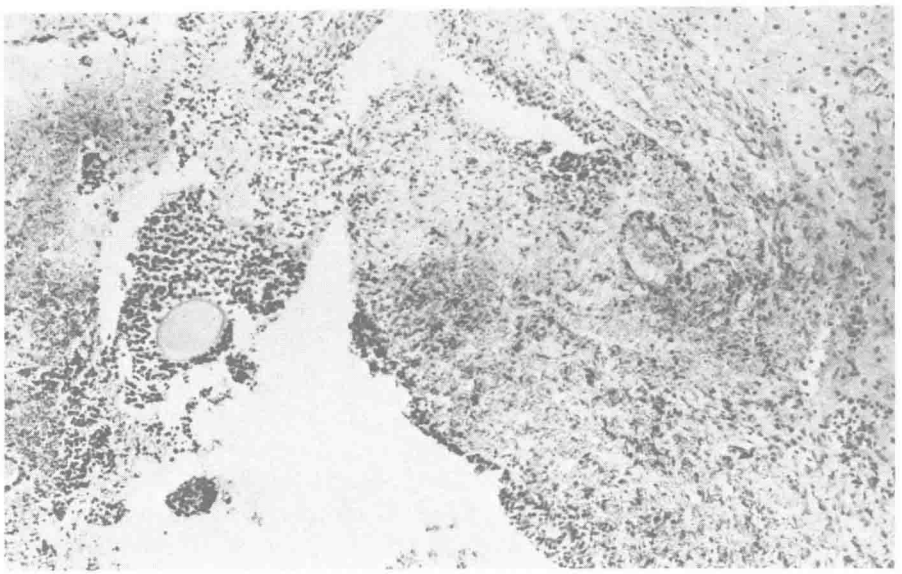

Figure 3 Arrow points to decidual reaction on surface of human ovary following a course of gonadotropins. (Reproduced from original paper) Greenblatt, R.B.: Office of Endocrinology, Medical College of Georgia, Augusta, Georgia

transplantation of viable endometrium, implantation or regurgitated menstrual blood, coelomic metaplasia due to hormonal stimulation or irritants, etc., do not explain all cases of ectopic endometriosis. How does one account for the presence of endometrial tissue in the lungs, pleura, pericardium, arms, thighs, vulva and pelvic lymph nodes, or of the cervix (Figure 4)?

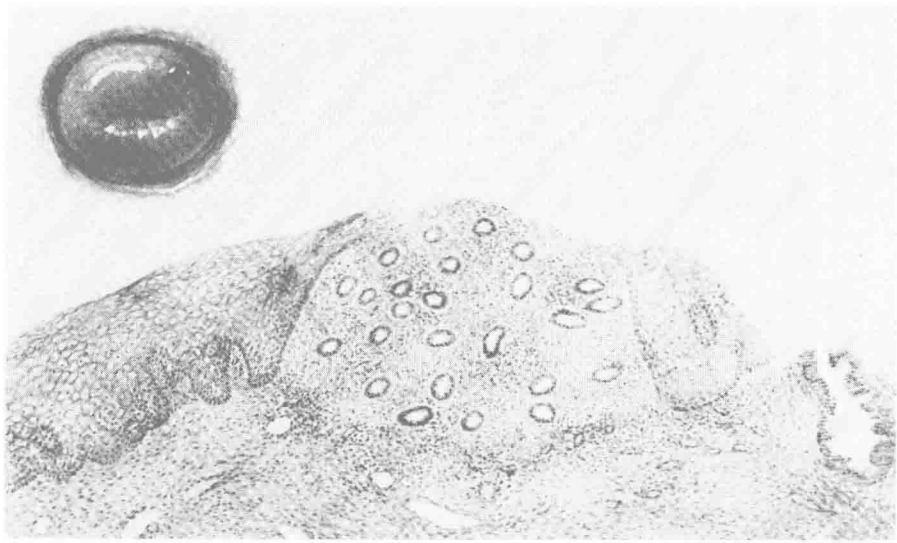

Figure 4 Endometrial implant on portio of cervix. (Camera lucida drawing by Jack Wilson. Reproduced from Greenblatt, R. B. and Suran, R. R., Surg. Clin. North America, *April 1949, W. B. Saunders Co.)*

Halban suggested that all heterotopic areas of endometriosis, wherever found, were metastatic growths originating in the endometrium and reaching their destination via the lymphatics. It should be recalled that Sampson, too, demonstrated endometrial tissue in lymph nodes and blood channels and suggested that dissemination of benign endometrial tissue may occur through the lymphatics or blood stream (Table 1).

TABLE 1
Histogenesis of Endometriosis

1) Accidental transplantation following hysterotomy
2) Regurgitation theory of Sampson
3) Mesothelial metaplasia of Meyer
4) Lymphogenous spread (Halban)
5) Hematogenous spread

The nature of the problem, therefore, reduces itself to early recognition of an ever-increasing disorder, and the means that may be taken to minimize the damage to the victim's emotional stability, physical well-being and reproductive capacity.

Histopathology

It is well that a word be said about the typical histopathologic findings necessary to confirm the clinical and gross diagnosis of endometriosis. The presence of endometrial glands with its accompanying stroma is the *sine qua non* for histologic diagnosis. However, many a chocolate cyst of the ovary may have lost its lining by lysis, destruction or pressure, and confirmatory histologic diagnosis may not be possible. Admittedly, not all chocolate cysts are endometrial in origin, since an old hemorrhagic follicular cyst or a hemorrhagic corpus luteum may contain chocolate colored material. Chocolate cysts, in the presence of typical symptomatology, however, probably should be regarded as endometriotic in origin.

Many times, hemosiderin-discolored foci are found in cul-de-sac, or are present on the serosa of the bladder, uterus, and bowel, which on biopsy merely reveal pigment-laden macrophages and fibrous connective tissue. Such findings, in the presence of severe dysmenorrhea, should be regarded tentatively as evidence of endometriosis.

It is believed that endometriosis may not be readily apparent in all cases despite typical symptomatology. In the florid cases, endometriosis may be quite destructive, involving one or more pelvic structures, *e.g.*, the ovaries (Figure 5), the fallopian tubes (Figure 6), or bladder, large bowel and uterosacrals (Figure 7). At times, extensive endometriosis is found in the absence of pelvic pain, dyspareunia or dysmenorrhea.

Signs and Symptoms

Signs and symptoms vary considerably from patient to patient; commonly encountered are one or more of the following:

1) Dysmenorrhea that has increased from a few hours on the first day to pain lasting several days.
2) Progressive acquired pelvic pain associated with, or occurring just prior to, or after, menstruation.
3) Nodular mass in the cul-de-sac or induration of the uterosacral ligaments —tender to palpation.
4) Fixed retroversion of the uterus.
5) Unequally enlarged palpably painful ovaries.
6) Dyspareunia.
7) Painful defecation, and/or rectal or low bowel bleeding coincident with menses.
8) Suprapubic pain, especially associated with dysuria and hematuria at the time of menses.

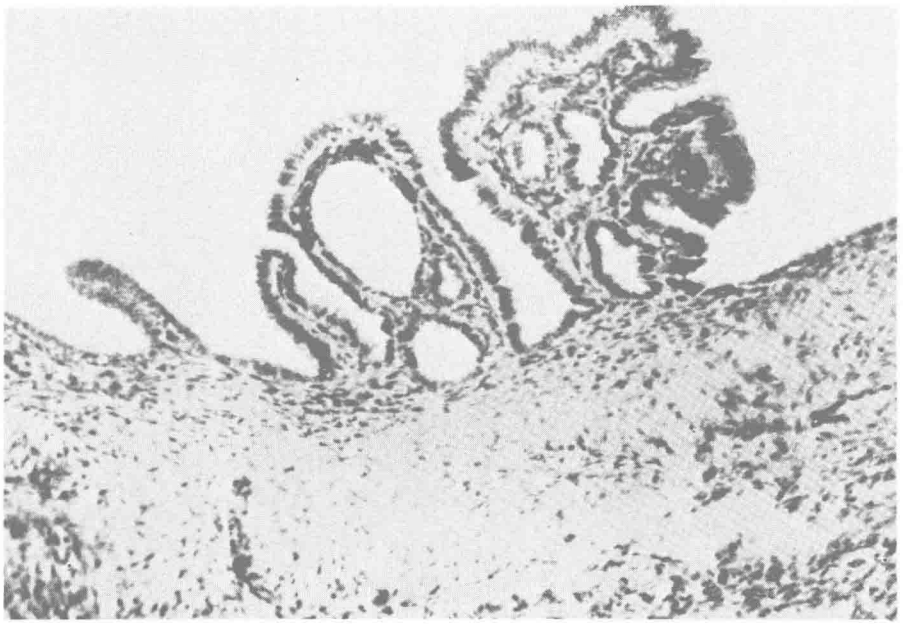

Figure 5 Endometrial cyst of ovary. (Reproduced from Greenblatt, R. B. and Suran, R. R., Surg. Clin. North America, *April 1949, W. B. Saunders Co.)*

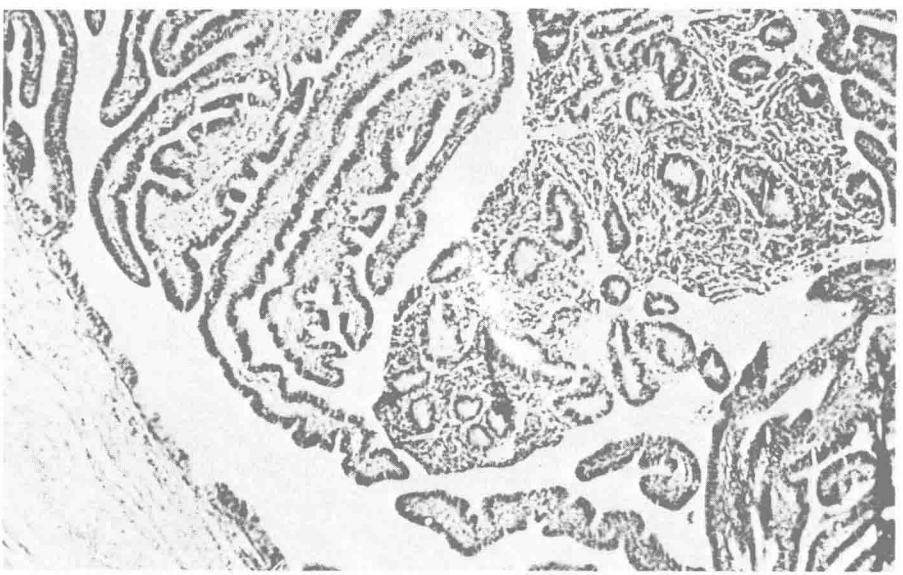

Figure 6 Cross-sections of the left and right fallopian tubes, resected at time of menstruation for sterilization, showing incidental finding of free endometrial fragments apparently viable, within the lumina. (Ridley, J. H., and Edwards, I. K.: Am. J. Obst. Gynec., *76:783, 1958)*

9) Premenstrual staining, hypermenorrhea when not associated with cervical polyp, or intramural or submucus fibromyomata of the uterus.
10) Infertility.

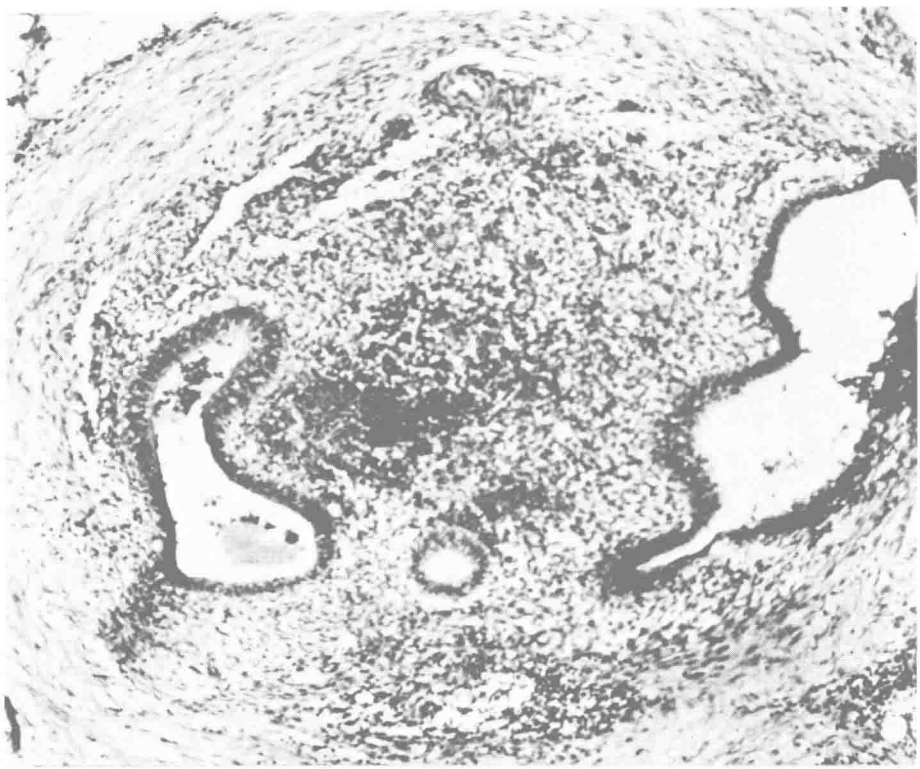

Figure 7 Endometriosis of utero-sacral ligaments.

A definite correlation exists between infertility and endometriosis. Behrman and Kistner demonstrated that if studies of an individual patient showed that ovulation occurred regularly, the oviducts were patent, the endometrium normal, and the postcoital test adequate, the presence of endometriosis was the causative factor of tubo-ovarian adhesions in 24% of 143 women in whom culdoscopy was performed because of infertility. Garcia found endometriosis in one-third of infertility laparotomies (Table 2).

Old and New Approaches to Solving the Problem of Endometriosis

Primary dysmenorrhea occurs only with ovulatory periods; neither dysmenorrhea nor endometriosis are encountered, with rare exceptions, in nonovulatory females. Experience has shown that pregnancy and prolonged suppression of ovulation result

TABLE 2
Endometriosis — Major Complaints

1) Dysmenorrhea
2) Pelvic discomfort prior to and/or after menses
3) Dyspareunia
4) Infertility
5) Hematuria and/or rectal bleeding

in subjective and objective improvement. Every women with dysmenorrhea is a potential candidate for the development of endometriosis, and therefore should be regarded as a suspect and managed accordingly. Grant, with some justification, posed the question "should dysmenorrhea be considered as the cause or the effect of endometriosis in young women?" Bullock and his colleagues performed laparoscopy in 18 young girls with dysmenorrhea and found evidence of endometriosis in nine. Gautier holds the view that functional spasmodic dysmenorrhea is a factor in the causation of endometriosis. It therefore behooves us to employ whatever measures are available that might minimize or eliminate dysmenorrhea.

Aside from surgical procedures, hormonal therapy has been employed with varying degrees of success in the management of this disorder. Testosterone was one of the first hormonal agents to be employed. Prolonged usage or large doses, however, may be accompanied by unacceptable side effects such as acne, hirsutism or voice changes. Large doses of estrogens to suppress ovulation have had their advocates. Kistner introduced the use of classical oral contraceptives (estrogen and progestogen) by inducing pseudopregnancy for periods of up to nine months. Progestogens alone, given orally, and injectable progestational agents such as depo-medroxyprogesterone acetate, have been used to induce prolonged periods of amenorrhea.

A new antigonadotropic agent, danazol, has been undergoing clinical trials for approximately six years and has proved most promising. This agent has antiendometrial properties, and differs from combination oral contraceptives in its pharmacologic and biologic properties. Furthermore, suppression of the hypothalamicopituitary axis is quite temporary, since resumption of ovulatory menses rapidly returns after discontinuation of danazol therapy. Thus, a new dimension in the management of early, as well as advanced, endometriosis is now in the offing to add to our therapeutic armamentarium (Table 3).

Conclusions

Endometriosis is a far more common disease than is generally recognized, and occurs earlier than hitherto acknowledged. In every young woman with dysmenorrhea, the development of endometriosis should be suspected, and the dysmenorrhea should be actively treated to improve menstrual flow or inhibit ovulation. Conservative surgery (D & C, suspension, removal of endometriomata), an-