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ENDOMETRIOSIS*

Two Hundred Cases Considered from the Viewpoint of the Practitioner

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ENDOMETRIOSIS is a frequent, not a rare, disease. In a recent test period, controlled to the extent that during it all the clinic's operations were done by one operator, there were among the female patients 78 cases of acute appendicitis and 107 cases of microscopically verified endometriosis.

The natural course of this disease is from various stages of severe pain through dyspareunia and sterility, with all the marital disharmonies attendant on those complications, to pelvic invalidism. Endometriosis, however, is one of the few diseases with proportionately serious results for which there is a specific treatment—castration. Less radical therapy is effective if the diagnosis is made even moderately early.

Unfortunately the diagnosis is oftener missed than made. Of the last 200 patients in this clinic with external endometriosis, — to which this paper is limited, — most of whom had previously been examined by one or more physicians and several of whom had been explored, only 6 entered with a diagnosis of endometriosis. No other disease of comparable frequency and severity has had, in our own experience, so low a diagnostic index. Yet the means of diagnosis are at hand. Endometriosis has a cardinal symptom, a pathognomonic sign and an unmistakable gross appearance. Also, it occurs in a sharply limited group of the population.

The missed diagnosis is not a phenomenon peculiar to New England. Nor is it the fault of the practitioner. Despite the excellent reports on endometriosis, we have found no definite description of what we believe to be its fundamental clinical syndrome. Furthermore, there is a widespread assumption that the condition is the private property of the gynecologist. This is unfortunate because endometriosis, like pregnancy, is encountered by all physicians.

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PATHOLOGY

External endometriosis is a growth of endometrium anywhere except where it belongs, in the lining of the uterine cavity; the word "growth" should be emphasized. Endometriosis closely resembles cancer. The cells are more differentiated, but it has the clinical attributes of cancer — speedy growth, spread, invasion and metastasis. Cytologically it is benign; otherwise it is cancer, but a cancer against which there is a specific treatment.

This growth, being endometrium, menstruates. The usual structural unit is an endometrial-walled cyst that menstruates into its own lumen. When the menstrual fluid meets peritoneum, it causes local chemical peritonitis. The cyst wall itself, growing centrifugally, invades the host. Invasion is opposed by growth of fibrous tissue varying in degree with the host.

When the growth occurs in an ovary there is least fibrous counterattack; the cyst enlarges rapidly and tends to perforate because it presumably becomes distended with each period. Blowout can occur, usually immediately before or early in menstruation, and produces a syndrome varying in intensity from that of mild appendicitis to that of ruptured tubal pregnancy. Seepage, as opposed to blowout, for the most part causes only an unusually painful period. Seeping menstrual fluid plasters the ovary first to the broad ligament and later to any contiguous area, with characteristic dense, cancerlike adhesions. Month after month, swellings, new seepages and new adhesions build up the so-called "chocolate cyst" of the usual illustration. It is unfortunate that so advanced a stage is the trademark of the disease. Earlier lesions are recognizable (Fig. 1).

In addition to the ovary, the pelvic peritoneum, visceral or parietal, is invaded either directly or by the droppings from an ovarian endometrioma. Here the lesion eventually becomes a so-called "blueberry spot" (Figs. 2 and 3).

The blueberry spot ordinarily does not exceed a few millimeters, but the surrounding fibrosis may be 1 or 2 cm. in diameter. The fibrosis spreads both in the host tissue and, through adhesion, to adjacent tissues. Octopuslike tentacles of endometrial tissue invade the fibrosis, and the lesion shows radiating stellate lines of contraction as if pulling neighboring tissues toward itself.

Figure 3, which shows endometriotic adhesions compared with those of chronic pelvic inflammation, demonstrates the difference between the thin, sheetlike, stretching adhesions of old inflammatory disease and the solid, stellate, puckering tentacles of active endometriosis. The adhesion of the inflammation, a protective mechanism whose work is done, yields to environment and weakens and stretches. The new growth invades the environs, clawing them to itself.

Blueberry spots tend to occur in groups, to coalesce and, with their fibrosis, to build up the cancerlike nodules that are the pathognomonic sign of endometriosis. Such conglomerate tumors cause extensive distortion or, in the sigmoid, stricture.

The densely adherent tumors and the intestinal involvement of late endometriosis may cause unusual difficulty for the surgeon and consequent danger for the patient. Despite the fact that all endometriosis, with the possible exception of that in more advanced sigmoidal strictures,[1] regresses after removal of the ovaries, merely reaching the ovaries to remove them may be dangerously difficult. It is fair to say that endometriosis is a disease that progresses at variable rates but in the direction of death until arrested by the menopause.

We have begun to recognize what we believe to be earlier forms of endometriosis than any of those described above. There are also less frequent forms, such as endosalpingiosis[2] and the debatable lesions described by Goodall,[3] all of which are beyond the scope of this paper.

Endometriosis may appear in the appendix, appendix stumps, laparotomy scars, the cervix, the bladder mucosa, the vaginal wall, along the ureter, hernial sacs, the groin, the vulva, the umbilicus, the small intestine, the abdominal and mediastinal lymph nodes and probably the lung, biceps muscle and forearm.

Internal endometriosis (adenomyosis, adenomyoma) is probably a different disease.

Diagnosis

Endometriosis tends to occur in childless women, in whom pelvic symptoms are likely to be ascribed to neurosis. The variety of places in which lesions occur and the triple action of the disease (as neoplasm, chemical irritant and presumptive hormone manufacturer) make almost any symptom possible. Also, endometriosis often accompanies other symptom-producing pelvic diseases, especially fibroids. A basic syndrome, however, can probably be identified in spite of all the adventitious symptoms. The picture has three parts: a cardinal symptom, a pathognomonic sign and a specialized susceptibility.

Cardinal Symptom

In our experience increasing dysmenorrhea is almost always present, provided the disease causes any symptoms. One hesitates to call the pain dysmenorrhea, which suggests cramps. This pain may be a cramp but it may also be an ache in the left lower quadrant, an acute stab near the appendix, a soreness in the rectum or a discomfort in the back. It may be sharply localized, or it may radiate to the sacrum or thigh. The nature and location of the pain are not important. What is significant is its relation to menstruation. This relation may vary: usually, the pain and the period are synchronous, but occasionally the pain precedes or follows the period; in 1 patient the pain accompanied ovulation rather than flow.

Of course, many lesions cause dysmenorrhea. The criterion of endometriotic pain is *increase*. Increasing dysmenorrhea is not the same as acquired dysmenorrhea. The pain of endometriosis may be acquired — that is, it may start after previously painless periods. Or it may be an increase of existing pain. In either event the increase continues and cumulates. Eventually pains meet across the month, and there is no longer intermenstrual remission but only menstrual exacerbation. Contrariwise, the pain of old pelvic inflammation may decrease at menstruation, possibly from hyperemia.

The severity of the pain is no index of the extent of the lesion. One of the puzzles of the disease is the patient with severe pain but slight lesion, or vice versa. By and large, the pain is more consistent with peritoneal lesions than with those limited to the ovaries. The likeliest to escape diagnosis is the endometrioma that slowly builds up within an ovary, without seepage and without peritoneal implant, and bursts without warning. One should be wary of appendicitis that occurs on the day preceding menstruation.

What proportion of patients who have increasing dysmenorrhea do not have endometriosis? Unfortunately the clinic lacks a symptom index, so that the answer cannot be given in numbers. Our impression is that the fraction is small.

The history of increasing dysmenorrhea probably bears some relation to the pessimism of many authors about diagnosis. Although appraised as the chief and characteristic symptom of the disease as early as 1929 by King and Fiddes,[4] its significance has remained relatively unrecognized: in two hundred articles reviewed, increasing dysmenorrhea was emphasized in twelve, mentioned passingly as one of the possible symptoms in seventeen and omitted altogether in the remainder. Before we appreciated this symptom only 20 per cent of our cases were diagnosed before operation; at present

FIGURE 1. *Photograph of Ovary (x 1).*

An early chocolate cyst, 4 mm. in diameter, illustrates the importance of **visual** *exploration of the pelvis. Cysts less than 1 mm. in diameter can be identified — if one looks instead of feels.*

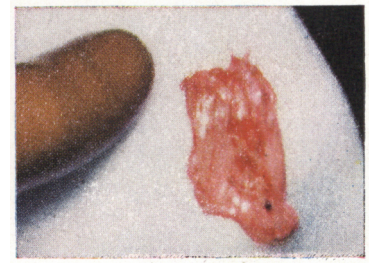

FIGURE 2. *Photograph of Piece of Excised Pelvic Peritoneum (x ¾).*

This shows, below, a small "blueberry spot" and, above, "red roughening."

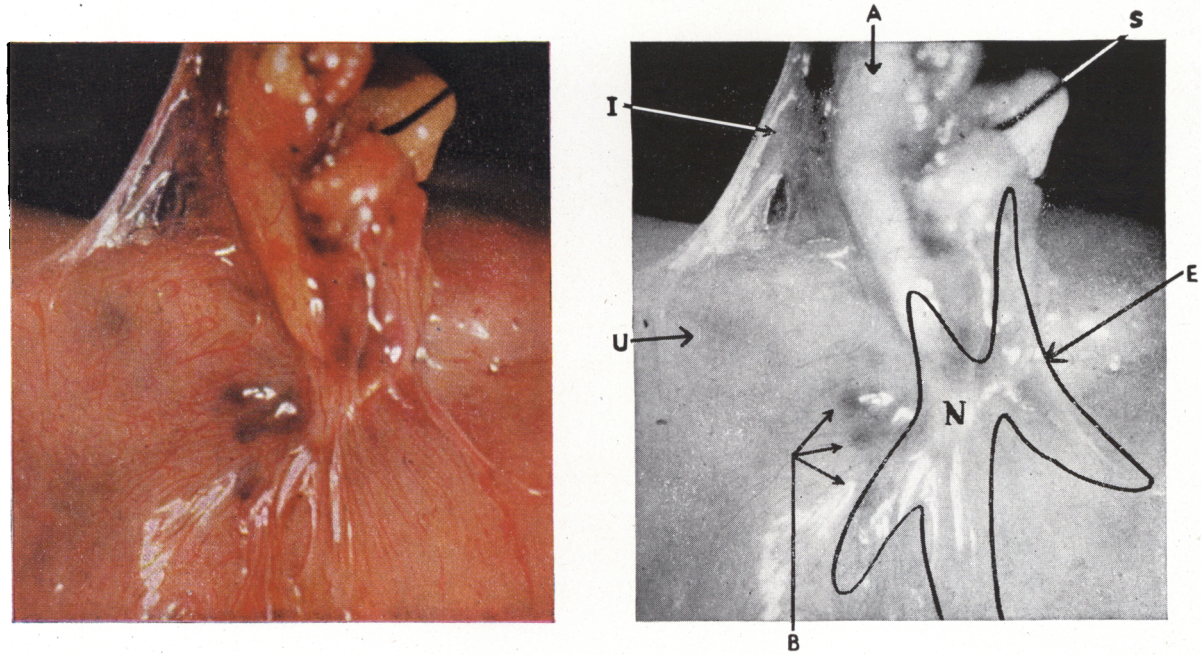

FIGURE 3. *Photograph of Both Inflammatory and Endometriotic Adhesions between an Appendix Epiploicum and the Uterus (x 2).*

U *is the uterus,* A *an appendix epiploicum, and* S *a retracting suture. This illustrates certain differences in appearance and in nature between endometriosis and chronic pelvic inflammation. The inflammatory lesion* (I) *is thin, sheet-like, stretching. The adhesion of endometriosis* (E) *is strong, solid, contracting; note the typical stellate lines of puckering. "Blueberry spots" appear at* B, *and the endometriotic nodule at* N.

70 per cent are so diagnosed, and the missed 30 per cent consists principally of patients with painless ovarian endometriomas or with early endometriosis discovered at operation for other disease or of patients who, for one reason or another, were admitted directly to the hospital without passing through the clinic. There are lessons in this last group: they were admitted by a member of the house staff; the interview with a member of the clinic was — in war days — brief; and the endometriosis was recognized for the first time at operation.

A change in the time or amount of menstrual flow is also a symptom of endometriosis. Often — and from our experience, we believe, erroneously — it is called the chief symptom. In this series it was present in a third and absent in two thirds of the cases. It is therefore of no diagnostic value. The symptom may help, however, by bringing to the physician patients who recognize irregularity as pathologic but who accept periodic pain as woman's normal lot. In every case of menorrhagia, therefore, inquiry should be made regarding dysmenorrhea.

Jarring of the pelvis, from walking on a hard sidewalk, riding on a rough road, coitus, defecation or even sitting down suddenly, may increase the pain of endometriosis. The absence of this symptom means nothing. Its presence, which connotes some serious pelvic peritoneal irritation, always suggests but is not diagnostic of endometriosis. Like menorrhagia, however, this variation may cause women who accept so-called "normal dysmenorrhea" in silence to consult a physician.

Pathognomonic Sign

Pain on movement of the cervix at vaginal examination has the same pathologic significance as the pain on jarring referred to above — that is, it signifies a serious variety of peritoneal irritation; it is also frequently present but is not pathognomonic. The pathognomonic sign is the hard, fixed, invading nodule of endometriosis. The characteristic feel of this structure is a matter of tactile memory and not to be learned from print, although if one's tactile imagination is active, Figure 3 will suggest how it ought to feel. It is nearest like the feel of cancer metastases, and to the extent that it cannot always be differentiated from these it is not pathognomonic; usually, however, it can be differentiated, and then it is definitive. Certain stratagems are useful in the search for the nodules. Rectal palpation is often more rewarding than vaginal, and combined, simultaneous rectal and vaginal examination is more satisfactory than either alone. The posterior-vault peritoneum and the uterosacral ligaments, on whose anterior reaches many of the nodules occur, can be tensed for better palpation by pushing the cervix forward by the finger or pulling it downward by a tenaculum. Examination midway between periods, followed by re-examination at the beginning of the next period, may show the nodule to be tenderer on the second occasion.

Unfortunately, nodules large enough to be palpable often indicate advanced disease, and nodules may be present but out of reach. Actually, pelvic examination substantially contributed to diagnosis in a little less than half of our cases in which the diagnosis was made. Despite a pelvis normal to palpation, therefore, the diagnosis should be made from the history alone.

Specialized Susceptibility

The occurrence of endometriosis is largely limited to one group of people. The diagnosis should not be rejected because a patient is outside this group, but the possibility should be considered in every patient within it. This group consists of women who are not having children — the sexually dormant, whether married or single.

It is often said that endometriosis causes sterility. It is true that women with advanced endometriosis are and those with early endometriosis may be sterile. Yet at least 26 cases of coexistent pregnancy and endometriosis have been collected,[5] and this series adds a probable 10: in 2 cases old endometriosis was shown at operation soon after miscarriage, 1 patient had a ruptured tubal pregnancy and old endometriosis and 7 patients had become pregnant since the estimated onset of the disease. Parenthetically, in these 7 the pregnancies seemed temporarily to have arrested the endometriosis.

That endometriosis causes sterility is true but is not the point. The significant fact is that endometriosis occurs in women of child-bearing age who are not having children. The phrase "child-bearing age" should be clarified. The youngest patient of whom we have found record was a thirteen-year-old girl in this series. There were also 1 girl of sixteen and 7 of seventeen, eighteen or nineteen years of age.[6] At the other extreme were 3 women of forty-seven to fifty and 1 of fifty-three years of age. All were menstruating, and all, except 2, had been menstruating for at least five years. Shortly after the menopause, endometriosis becomes a relic — 3 patients, ranging in age from fifty-three to sixty-six years, had inactive residua of the disease. To analyze the phrase "are not having children": in this series over two thirds of the 200 women had never had a child. This, of course, is significant. Women with children, however, can have endometriosis, — 59 of the 200 patients did, — as can the mother of a large family — 13 of these mothers had five children or more. The phrase therefore signifies only women who have not had a baby recently — that is, for about five years. In this series there were 14 women who had been pregnant within the five years before discovery of the disease. But 4 of them had artificial endometriosis, caused by operation. In 2 of the 10 patients with spontaneous disease the endometriosis appeared to have started within five years

of delivery. But in each of the other 8 the symptoms of endometriosis, we believed, could be traced back to a fallow period of five years preceding the last pregnancy. In other words, of a total of 190 patients with spontaneous endometriosis — the 10 with artificial disease being subtracted from the total of 200 — the disease seemed to have begun within five years of confinement in only 2 cases.

There is contributory evidence in the thirteen mothers who had five or more children. These women all married young, had their babies early, stopped having babies and, after five years or more, developed endometriosis. Finally, although endometriosis occurs in youth, reports of its appearance before approximately five years of menstrual life are extremely rare.[6]

The most practical item in diagnosis after increasing dysmenorrhea is therefore considered to be a history of about five years of nonpregnancy preceding the disease. And it seems to make no difference whether the nonpregnancy is from inability, indecision or lack of opportunity. Palpable endometriomas confirm the diagnosis but are absent as often as present.

Treatment

Endometriosis is a disease for which a true specific treatment is available. Following ovarian deactivation endometriosis gradually regresses, with insignificant residua. But the price — castration — is high. In the hope of avoiding castration in advanced cases, we have begun to study temporary ovarian deactivation by small doses of radium after confirmation of diagnosis by peritoneoscopic biopsy. Masculinizing, follicular and luteinizing hormones have also been suggested, but the last two are probably as likely to harm as to help.

For such a chemical problem the future may offer a chemical solution that will restrict the surgeon to the taking of biopsies. But today he has a procedure that is reasonably efficient and less costly than castration. This consists in diagnosis while all lesions are young enough to be removed individually without castration and in prophylaxis.

The arbitrary five fallow years discussed above may be new, but there is nothing original about the concept of endometriosis as a disease of the sexually dormant.[7, 8] Meigs[9] calls it a physiologic response to an abnormally uninterrupted menstrual career. If the theory is sound the prophylactic is obvious — more obstetrics would engender less gynecology. Marriage at the age of seventeen and a child every three years would probably abolish endometriosis. It should be remembered that the disease itself, not eugenics, ethics or even common sense, is under consideration. Marriage at twenty and no five years without a baby would perhaps be more sensible.

An excellent opportunity for prophylaxis is offered the practitioner when he refers to the surgeon a woman with appendicitis. Because of the frequency of endometriosis and of other unsuspected pelvic lesions, we believe that it is often fitting for the practitioner to suggest exploration of the pelvis in addition to removal of the appendix. Digital examination can miss an early lesion. But to the eye endometriosis is as unmistakable as chicken pox, so that no pelvis can be said to have been adequately investigated until it has been explored by vision. This necessitates a median incision, which, when routinely used for appendectomy in women, has revealed a surprising amount of endometriosis.

In patients with severe dysmenorrhea, even if the symptom is not increasing, exploration is often indicated when lesser treatment fails. If no endometriosis is found, presacral sympathectomy may justify the operation. Endometriosis, which is frequent and painful, causes sterility; it is therefore sound prophylaxis to be radical about deciding to explore in suspicious cases.

Some experienced operators do not bother to excise small lesions; others allow even large lesions to remain but resect three quarters or more of the ovarian tissue in the hope of diminishing ovarian function. To us, both these procedures seem overconservative, for the following reasons: large endometriomas grow from small ones; patients with small lesions may have a great deal of pain, which ceases after removal of the lesions; subtotal oophorectomy, like subtotal thyroidectomy, is a physiologic compromise; and, finally, in several cases, we have observed endometriomas that continued to grow after previous operation or the disease itself had destroyed all but a shell of ovarian tissue.

True conservatism, we believe, consists in spending an hour picking nodules out of a pelvis, even though castration could be done in ten minutes. We have set ourselves the alternative of complete extirpation or castration, and have taken pains and accepted risks to excise the disease whenever excision was possible. One of the 2 deaths in the series occurred from operation for endometriosis, the other from hepatic carcinoma metastatic from the colon in a patient whose incidental endometriosis had not been treated. The few exceptions to the rule were in young girls with extensive lesions in whom the treatment consisted in removal of all the disease that it was mechanically practicable to remove, combined with temporary castration by a small dose of radium. Obviously, the risk of radiating ova that subsequently might become impregnated should be taken only in extreme circumstances.

About half the patients in this series were castrated. To our great disappointment and despite definite improvement in diagnosis and steadily increasing willingness to resect more difficult lesions, the proportion of patients castrated is not significantly lessening. Of the first 100 patients in the series, 52, and of the last 100, 45 were castrated.

All patients in the series are being followed, but end results of treatment for endometriosis should not be quoted before the menopause. Among the castrated patients, recurrence from the use of stilbestrol has been encountered and has so far yielded to withdrawal of the medication. It can be said that radical excision without castration may afford long relief and sometimes results in pregnancy — Payne[10] reported 10 and Haydon[8] 19 patients who became pregnant following operation; Counseller[11] reported ten pregnancies in 7 patients, and 3 of our patients have had one child each.

Recurrence is suspected in 2 of our patients, who are nevertheless being only watched. The 3 patients with recognized recurrences became asymptomatic following irradiation. As Pemberton[12] has pointed out, irradiation is not to be undertaken casually. The dense adhesions of the disease may bind intestine into a dangerously immobile target for the x-rays.

Summary

Endometriosis is a progressive, painful, sterilizing, crippling disease that can be both prevented and cured. Opportunities for prevention and cure are lost because no accurate clinical picture has become generally accepted and because the frequency of the disease is not appreciated.

In the female patients seen in this clinic the incidence of endometriosis was greater than that of acute appendicitis.

Endometriosis is an antivenereal disease — that is, it is associated with sexual unfulfillment. The prophylaxis seems to be early marriage and a child every few years.

Endometriosis is a new growth of menstruating endometrium that, invading and sometimes metastasizing, tends to spread through the pelvis, causing chemical peritonitis, dense adhesions, sterility, destruction of ovaries and stricture of the pelvic intestine. Ovarian hormone is necessary to the progress of the disease. The course, which is reversed by ovarian deactivation, may be arrested by excision of the lesions. To arrest without castration necessitates diagnosis before the lesions have become mechanically unresectable.

Contrary to general opinion, clinical diagnosis is usually possible. It depends on ability to separate from a mass of adventitious pelvic symptoms and signs the following basic syndrome of endometriosis: cumulatively *increasing* pain at the time of the period occurring after about five years of menstruation without pregnancy. Endometriotic nodules are pathognomonic but often not large enough to be felt, in which event the diagnosis should be made on the basis of the history alone.

Because endometriosis can be seen long before it can be felt the practitioner should be as radical about advising surgical exploration as the surgeon is conservative about castration.

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