It's NOT "All in Your Head"

Claire Conway

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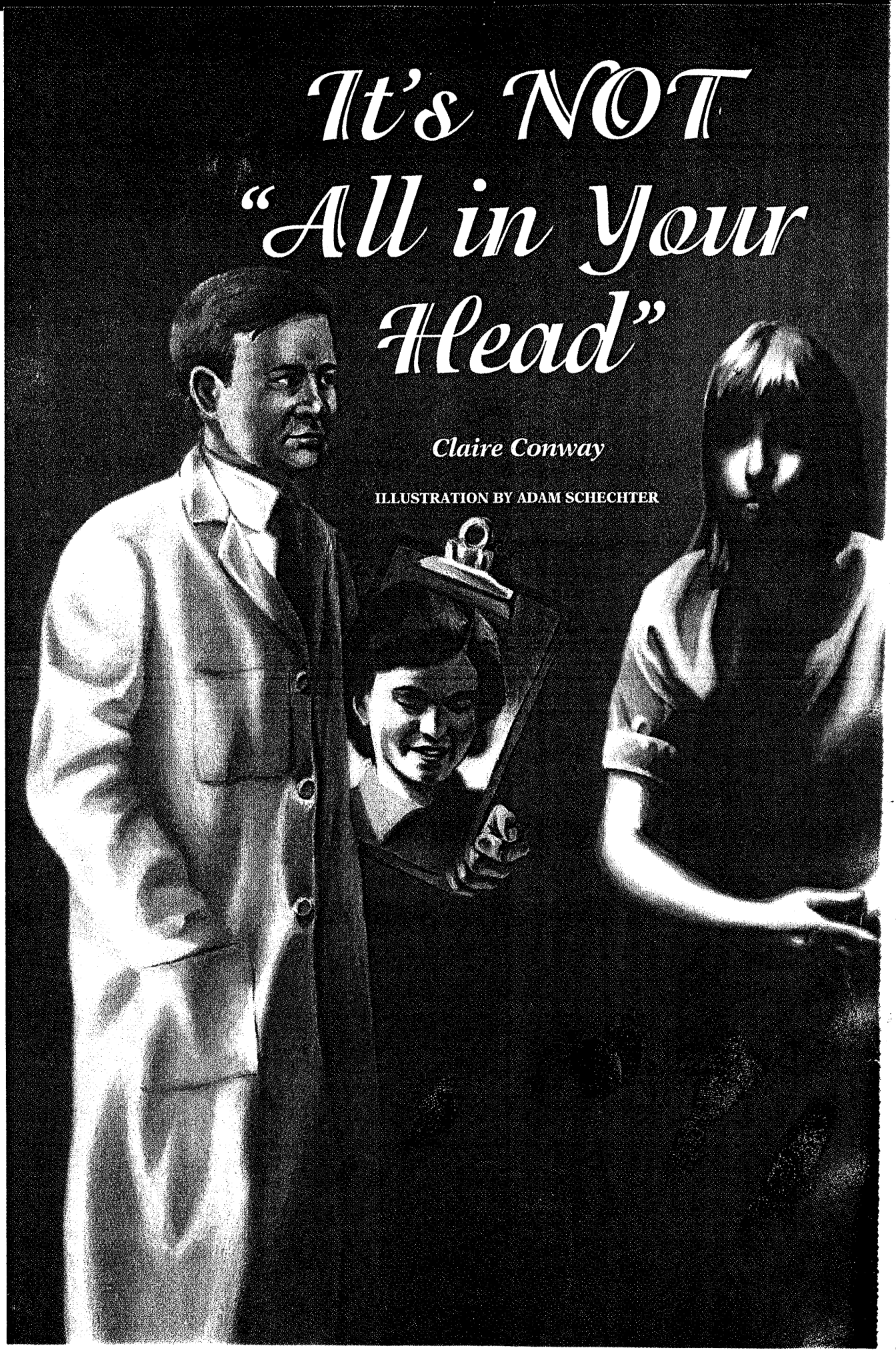


Finding Relief

Even though a cure is still out of reach, many women find relief from the excruciating pain of endometriosis through surgery, hormone treatments, or a combination of the two.

The treatment of choice is usually laparoscopic surgery to remove or burn away renegade endometrial tissue, called implants. In 1985, Dr. Camran Nezhat, a clinical professor of gynecology and of surgery at Stanford University, first reported on a variation on laparoscopy called videolaseroscopy, a procedure that incorporates a laser and a tiny video camera into the standard technique. The camera, attached to the scope, projects images on television screens above the operating table. The surgeon either excises or vaporizes the endometrial tissue with the laser, depending upon where the endometriosis is located and on the depth of its penetration.

Videolaseroscopy and other laparoscopic procedures have radically improved quality of life for endometriosis patients. Prior to the new technology, doctors commonly performed open abdominal surgery to remove endometriosis. That meant a hip-to-hip, 4-inch to 6-inch incision; a hospital stay of three to five days; and a recovery period of four to six weeks.

"Videolaseroscopy requires only tiny incisions—one is only half an inch and three others are a quarter of an inch," Nezhat says. "And, the best part: The patient either stays one day in the hospital or goes home that same day."

Nezhat is quick to point out that horror stories of unnecessary abdominal surgery and hysterectomies, which could have been circumvented by less invasive laparoscopic surgery, plague the field. Even laparoscopic surgery, if it's done recklessly, can cause scarring and painful adhesions.

"The endometriosis patient really needs to find experts," he says. "Not all gynecologists and infertility specialists are familiar with diagnosing endometriosis. And few gynecologists are experienced enough to treat it conservatively and thoroughly."

Nezhat has pioneered a variety of laparoscopic techniques for treating endometriosis that is deeply infiltrating into the bowel, bladder, and other pelvic and abdominal organs. To treat endometriosis involving these and other uncommon sites—such as the diaphragm—Nezhat teams with Stanford surgeons from thoracic, general, and urologic surgery. As a result, patients with complicated and severe cases of endometriosis come to Stanford from throughout the United States and abroad.

The mission of drug therapy—the second treatment option—is to radically reduce estrogen, which is known to thicken the endometrial lining and spur the growth of misplaced implants. As estrogen wanes, the endometrium atrophies. "For some women, going on oral contraceptives [all month long] is helpful in controlling the disease," explains Dr. Linda Giudice, head of reproductive endocrinology and in vitro fertilization at Stanford. Such a course of the birth control pill halts ovulation and inhibits estrogen production, thereby denying endometriosis its lifeblood.

However, danazol, a synthetic male hormone that functions in nearly the same way, is more effective than the pill at controlling the disease. But its side effects of acne, facial hair, and weight gain make it literally an unattractive alternative. Drugs called GnRH agonists, which lower estrogen to menopausal levels, are also very effective in controlling the disease. Yet they can be taken for only six months because they cause bone loss.

A new therapy to enhance and extend medical treatment may be in the offing. Called add-back therapy, the new treatment entails giving patients small doses of estrogen to ameliorate bone loss and hot flashes. Though promising, add-back therapy is still experimental.

And the seeds of endometriosis remain, ready to sprout again once estrogen fully reenters the cycle.

"Medical therapy has not been very successful," warns Giudice. "It may reduce pain and get rid of the bulk of the disease so that you don't have twice as much the next time you look. But it ultimately does not stop the disease's progression."

And because most medical management of the disease throws the body into the equivalent of early, temporary menopause, women battling infertility are understandably not eager to embark on a drug therapy. For these women surgery is the best option, though a controversial one.

Part of the problem is that scientists don't understand how endometriosis and infertility are related. Though researchers know that 30 to 40 percent of infertile women have endometriosis, they don't know whether one condition causes the other; the two may simply coexist.

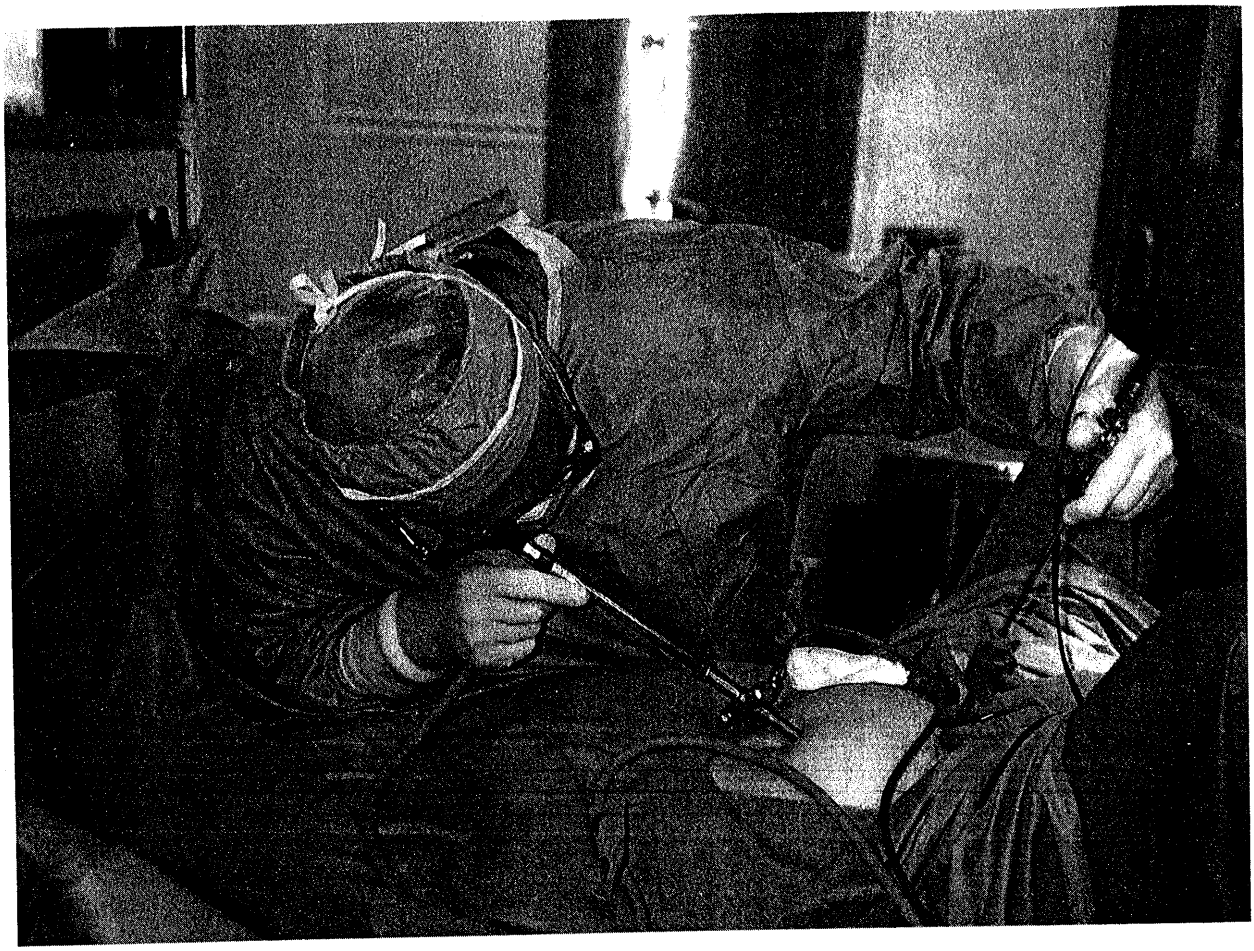
But scientists suspect that fertility may be inhibited by endometriosis in two ways.

"One is by causing scar tissue around the fallopian tubes and ovaries, preventing the sperm and egg from meeting," explains Nezhat. And scarring in the posterior cul de sac—the area behind the uterus that is thought to be where the tube actually picks up the egg—may also create a literal wall between egg and sperm.

The second scenario is a little more complicated. Some scientists believe that extensive endometriosis creates an environment inhospitable to conception. "The body's immune system is actively trying to suppress this disease by fighting it off with antibodies that might actually cause harm to the egg and sperm," says Dr. David Adamson, a clinical professor of gynecology and obstetrics.

Few physicians dispute the notion that thorough surgical removal of severe endometriosis improves a woman's chance of getting pregnant. By surgically paring back the disease in severe cases, the immune system can temporarily pull back its troops and the surgeon can clear a path to allow sperm to nab an egg. Yet in mild disease some doctors claim that treatment of endometriosis does not improve fertility rates.

Nezhat adamantly disputes the notion. He contends that pregnancy rates do not improve in mild cases because the surgeon is often not skilled or thorough enough in removing the implants. In fact, Nezhat has reported that nearly 65 percent of his patients struggling with infertility—a mix of women with mild or severe disease—were able to conceive after treatment.—*C.C.*



A physician performs a laparoscopy, the standard process for diagnosing endometriosis. By means of a lens on a lighted fiber-optic tube—a laparascope—the doctor can examine the problematic areas in detail.

stay. Some women get lucky, their remission may last years—perhaps until menopause, and then it completely disappears. But endometriosis is chronic. Often it is cleared through treatment, only to slowly build back up again.

New Leads

Frustrated by the short-lived fixes for pain and infertility that current treatments provide, scientists have their eyes wide open for clues to finally conquer this debilitating, chronic disease.

Over the last few years researchers have been pursuing four leads, yet all are still in the early investigational stages. Each theory points a finger in a different direction, from genetics or the environment to immunology or cellular biology.

The first lead, and the most concrete, is an international clinical study to discern whether the disease has a genetic component. Scientists throughout the United States are also intrigued by a potential environmental villain—the industrial pollutant dioxin—as the cause of endometriosis. At Stanford two professors of obstetrics and gynecology are breaking from the pack to investigate the hunch that endometriosis is an allergic reaction to the body's own sex hormones. And another group of Stanford researchers has just made a discovery that challenges long-held

assumptions about what actually initiates menstruation. The finding gives scientists new hope for a better understanding of endometriosis, and perhaps a new angle of attack.

Many researchers believe that our genes are the obvious place to start searching for the cause and the cure.

"If a sister or mother has endometriosis, a woman's chance of having it is probably twice as high," says Adamson.

Is endometriosis carried in the genes? The jury is still out.

However, scientific evidence has not yet proved that estimate. Dr. Stephen Kennedy of Oxford University in England is heading an international study to confirm the genetic link. Stanford researchers are participating by collecting DNA from women whose siblings and mothers have endometriosis. At this point, however, the data are still being compiled, and a definitive answer will be years in the making.

Dioxins, often associated with medical and municipal waste, pesticides, and bleached paper and pulp products, have also been implicated in endometriosis. These industrial pollutants mimic estrogen, often upsetting the human immune system. Dioxins are known to bind to hormone receptors in the human body, thereby blocking our natural hormones from performing their role in sexual development.

Ballweg made the connection between dioxin and endometriosis after she heard about a study of dioxin's effects on infertility. Researchers at the University of Wisconsin, Madison, had systematically exposed monkeys to the pollutant, which lingers in the body for 14 years. When Ballweg tried to find more information on the study, she learned that the research project had concluded, but the monkeys were still being cared for at the university's animal facility.

Through the Endometriosis Association, Ballweg raised funds to examine the monkeys for endometriosis. Sherry Rier, Ph.D., of the University of South Florida College of Medicine took on the project and reported that 79 percent of the animals had developed endometriosis. Rier also found that the more dioxin the monkey had been exposed to, the worse the case of endometriosis.

Monkeys that were able to get pregnant passed the dioxin along to their infants through breast feeding. "The mother monkeys dumped more dioxin per kilogram of weight for their infants than they received themselves," notes Ballweg. "We have to ask, are we setting up our children? Is this genetic or environmental? It might be a real cross between the two."

Epidemiological studies currently under way in Italy, where there was a major dioxin explosion in 1976, may lead to an answer. Dr. Brenda Eskenazi of the University of California, Berkeley, is investigating whether the young women exposed at that time now have endometriosis.

The immune system is under suspicion from another angle, as well. Dr. Wayne Konetzki, a Wisconsin allergist, is convinced that endometriosis is an allergic reaction to one's own sex hormones, either progesterone, estrogen, or luteinizing hormone. He tests his patients for sensitivity to each hormone and, if he detects an allergy, initiates a desensitization program. He exposes the patients to minute doses of the hormone by giving them tablets to dissolve daily under their tongues. By exposing patients to tiny amounts of the offending hormone, Konetzki aids the body in slowly building an immunity to it.

Researchers may not yet know what causes endometriosis, but they do know it's not imaginary.

Though evidence of the treatment's effectiveness is anecdotal to date, Konetzki says his patients' symptoms typically begin to lessen after three menstrual cycles, and pain may disappear entirely after a year. And Konetzki, along with Dr. Arnold Kresch, a clinical associate professor of gynecology at Stanford, is planning to conduct a clinical trial to confirm his findings. Until clinical trials are completed, however, Konetzki's findings remain experimental and some of his peers in the field remain skeptical.

A recent discovery in the lab of Dr. Linda Giudice, head of reproductive endocrinology and in vitro fertilization at Stanford, may shed a little more light on the mechanics of menstruation and, by implication, endometriosis. Experiments by Dr. Juan Irwin, a senior researcher in Giudice's lab, have challenged long-held assumptions about what actually initiates menstrual bleeding.

Since the 1940s scientists have believed that a sustained contraction of blood vessels in the endometrium is responsible for the onset of regular menstrual bleeding. Instead, says Irwin, who published his results in the *Journal of Clinical Investigation,* endometrial cells are responsible for kicking off the events that lead to endometrial shedding and vaginal bleeding.

Here's how it works: Declining progesterone levels signal endometrial cells around the blood vessels that conception has not occurred. In response, endometrial cells called stromal cells release matrix metalloproteinases (MMPs), enzymes that chew up the main components of the blood vessel wall and endometrial tissue, causing the sloughing and bleeding associated with menstruation.

So what does this have to do with endometriosis? If the displaced tissue of endometriosis responds to the same hormonal cues and secretes the same enzymes, it may well explain at least some of the tissue damage caused in the disease.

MMPs have also been under suspicion in a variety of other conditions, including rheumatoid arthritis and tumor invasion. The latter gives Irwin more clues about the protein's possible involvement in endometriosis. He speculates that MMPs might be playing a role, not unlike the one they play in tumor invasion, in the ability of endometrial tissue to anchor itself and start lesions.

Giudice and Irwin recently received a grant from the U.S. Department of Defense to investigate these theories. If they are correct, scientists will be able to refocus their efforts toward a treatment that disarms matrix metalloproteinases or inhibits their creation. Because these enzymes have been implicated in other diseases, such research is already under way.

To date, each of these research leads is merely compelling—none has been confirmed. Even though researchers are years away from a cure, those suffering with endometriosis may find some comfort in the realization that studies are being initiated and dollars spent on a disease they are often told exists "all in the head."

And as women with endometriosis confirm what they've already known—that it's actually all in the ovaries, the fallopian tubes, or the bowels—they are taking steps to alleviate the pain.

And they can stop trying to force that grin. ❑

Most women grin and bear menstruation. At most it's a six-day sentence of discomfort and inconvenience. But for 5 million women in North America those six days a month are not merely an annoyance—they are excruciating. These women have endometriosis, a disorder of the lining of the uterus, or endometrium. In endometriosis some of the uterine lining somehow escapes being shed out of the cervix during menstruation. Instead it scatters about the body, attaching itself to the fallopian tubes, ovaries, bowels, or even to the lungs, causing swelling and scarring in the process. What that translates to in the life of a woman with endometriosis is knees-to-the-chest pain for all or most of her period. For some the pain is akin to—or worse than—labor and delivery. Making it out of bed, much less to work, may be impossible. And estimates associate endometriosis with 30 to 40 percent of women with infertility in the United States, adding emotional insult to personal injury.

To women who harbor the disease, the words *grin and bear it* are fighting words. They've heard them for years from family, friends, and physicians who are ignorant of the painful, mysterious course of the disease. Even doctors who have heard of endometriosis simply may not be educated enough to prescribe the hormone treatments or laparoscopic surgery that can relieve the pain.

For now, pain relief is all treatment has to offer, temporarily stemming this chronic condition's tide. Until scientists figure out what causes the senseless sprawl of endometrial tissue to the far reaches of the body, they will not be able to halt it.

Just ask Mary Lou Ballweg, president and founder of the Endometriosis Association, an information clearinghouse and research support group based in Milwaukee. She was first bedridden with the disease for five months in 1979, for six months in 1980, had another spell two years later, and her last in 1990. All told, she had five surgeries—including a hysterectomy—along the way.

"Sometimes the recurrences are due to poor surgical technique," says Ballweg. Unskilled surgeons can damage organs or create adhesions that actually worsen the disease. But many recurrences go unexplained. "We don't understand where [endometriosis] comes from, so how can we understand how it comes back?" she adds.

Two long-standing theories suggest how endometrial tissue meanders throughout the body.

The first and most revered is that of retrograde bleeding. Adherents to this theory believe that the endometrial tissue, instead of flowing out of the uterus through the cervix during menstruation, backs up through the fallopian tubes, into the ovaries, and out into the pelvic cavity, taking up residence wherever it lands. Estrogen spurs the growth of the newly settled tissue; cells break off, are picked up by the lymphatic system, and are ferried about the body. In rare cases the "AWOL" tissue travels beyond the pelvic organs to the lungs, eyes, and brain.

The other theory contends that endometriosis is the result of misplaced

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embryonic cells in the abdominal cavity that start behaving like endometriotic lesions when a girl begins to menstruate.

Endometriosis at Work

Even some doctors think pain is just part of being a woman.

In either case, once they've escaped the uterus, endometriotic implants can take on various forms. They may appear as a smattering of cysts, as bubble-like nodules, or as deep, invasive lesions. Regardless of form, the endometrial implants piously abide by the same menstrual ritual each month. The lesions inflame and bleed according to the menstrual cycle, irritating and killing cells in the tissue they have glommed onto. The irritation launches an immune response.

"Immune cells called phagocytes rush to the tissue to destroy the endometrium," explains Dr. David Adamson, a clinical professor of gynecology and obstetrics at Stanford University.

In severe cases the repetitive injury of endometriosis (or the surgery to treat it) creates raw scar tissue that binds to other tissues or organs in the body to heal itself. Called adhesions, these tangled webs of tissues may fuse ovaries to intestines or the bowels to the abdominal wall.

The renegade tissue can also cause organ damage. "Endometriosis covering the bowel can cause bowel obstruction, or endometriosis of the ureter can block the urine traveling from the kidney to the bladder, causing a silent death of the kidney," says Dr. Camran Nezhat, a clinical professor of gynecology and of surgery at Stanford. Though these cases are rare, one of Nezhat's patients, a 28-year-old, lost her kidney that way. She had approached her doctor about pain in her side and was ignored.

Nezhat, who is director of the Stanford Endoscopy Center for Training and Technology, has pioneered a minimally invasive surgical procedure for removing a segment of ureter damaged by endometriosis and reconnecting the cut ends (see box "Finding Relief"). If this patient's endometriosis had been diagnosed earlier, Nezhat's procedure might have been able to save her kidney. But her physician missed the diagnosis by dismissing the pain.

"Disabling pain during or before menstruation is not normal," insists Adamson. "But there are still a lot of people in our society who think it is just part of being a woman." His advice: If you have a doctor like that, find another.

Diagnosis and Treatment

An informed physician knows the telltale signs of endometriosis: severe pain with periods, chronic pelvic pain, or pain during and after sex. Other women have painful bowel movements around the time of their period. And some experience heavy and frequent periods.

If the patient seems to fit the bill, the diagnostic process should begin with laparoscopy. The surgical procedure, usually done under general anesthesia, is performed with a lighted fiber-optic tube—the laparoscope—that enables a surgeon to probe problematic areas for traces of endometriosis.

If endometriosis is confirmed, the patient has basically three treatment options: surgery, medication, or a combination of the two (see box). Though surgical and medical treatment can relieve women of the infertility and pain associated with endometriosis, it is usually just a temporary