CHAPTER 7

Regeneration

(UTERUS)

As Dr. Linda Griffith fingered the lump of flesh beneath her left bra strap, her heart sank. It felt hard and firm, like a piece of cartilage. Could it be a cyst?

It was January 2010, and the forty-nine-year-old bioengineer was sitting among a sea of suits at a biotech conference in Singapore. Realizing she was feeling up her own boobs in a room full of well-dressed men, she slipped off to the bathroom to do a more thorough check. *Not good*, she thought as she eyeballed her chest in the mirror. Within a week she had flown back to the states, gotten a mammogram, ultrasound, and biopsy, and been diagnosed with triple-negative breast cancer—known as the worst kind. That meant her tumor was unresponsive to hormone therapy and other forms of targeted treatment.

Griffith braced herself. It would be a grueling year, one marked by constant fatigue, gastrointestinal side effects, and long nights spent in the hospital hooked up to an IV. But in a strange way, it would also be a wonderful year. As soon as she told her dean, he granted her another sabbatical year. Friends and family stopped by to offer cards, home-cooked food, and condolences. As her cropped blond hair fell

out and the ruddy color faded from her cheeks, they reassured her she still looked great. Her husband, who was also her collaborator and co-director of her bioengineering lab at the Massachusetts Institute of Technology, provided a steadfast source of support.

Compared to Griffith's previous experience with reproductive disease, it was like night and day. Since puberty she had suffered silently from a common, painful condition called endometriosis. In it, cells similar to the lining of the uterus escape into the pelvis and take root, where they respond to the body's hormones, growing thicker before shedding and attempting to bleed. Breast cancer, on the other hand, was something that everyone recognized and empathized with. Compared to endometriosis, she likes to say, it was a walk in the park. "Not like a super beautiful day . . . like a stormy-day walk in the park," she adds. "But it was like, people understood."

The contrast wasn't only in how people treated her. It was in how doctors treated the two diseases. With breast cancer, doctors immediately biopsied her tumor, analyzed it, and categorized it so they could guide her into the right treatment. Tests checked for the presence of simple biomarkers—receptors for estrogen, progesterone, the protein HER2—that gave clues about how the tumor would progress and what treatment it would respond to. With endometriosis, there were no known biomarkers. There was no good classification system. And there were no treatment options other than surgery or hormone suppression, both of which had serious drawbacks. "There's no metrics," says Griffith.

Griffith was sick of hearing doctors describe endometriosis in terms of myth rather than science. She knew her disease could be explained in terms of data and biology. It just required viewing the uterus for what it was: not some mythical center of womanhood but an organ like any other, deeply connected to everything around it, trading in immune cells, stem cells, and vital fluids. In other words, it was part of a complex biological system. And as a bioengineer, that's how Griffith was trained to think: in terms of living systems made up of interlocking networks.

Endometriosis, like breast cancer, was not one disease but many, a

hydra of many heads. To get a handle on it, you needed to look at entire networks of immune cells and how intervening in one pathway might affect all the others. She began talking to her husband, Dr. Doug Lauffenburger, who had been studying breast cancer for over a decade, about how to take a similar approach to classifying endometriosis patients.

Over the next year, Griffith held lab meetings from her hospital bed in between chemotherapy sessions, directing her lab to look for networks of molecular markers in endo patients. "We transformed our lab meetings, literally," says Dr. Nicole Doyle, a postdoctoral fellow in Griffith's lab at the time. "We just showed up for her chemo treatments and would sit there with her. That diagnosis had to adapt to her life, not the other way around."

Griffith's team started by analyzing peritoneal fluid, the fluid found inside the abdominal cavity where endometriosis lesions usually appear. They identified networks of inflammatory markers and used them to group together patients who tended to have more pain and worse fertility problems. In 2014, they published the first study to propose a way to categorize endo patients into subtypes—the first step in building a similar classification system that already existed for breast cancer. "That was really us together, because it was Doug's vision of systems biology but filtered through my practical connection to the clinic," Griffith says.

Throughout chemo, Griffith never seemed to waver in her positivity. When she shaved off her hair, she threw a lab party. Lauffenburger took it harder. For him, watching his wife suffer from this new foe, after battling the old one for so long, was torture. When it came to cancer, "I viewed it as a terrible thing," he says.

Griffith saw it differently. She took a curse and turned it into a gift. "It was a terrible thing, but a good thing, scientifically," she says.

Griffith started her career not in reproductive medicine but in tissue engineering, sculpting organs like liver and bone. She was an architect;

her materials were the building blocks of life. As one of the few women in her field, she made an effort not to draw attention to her gender. "I was working on all the things that guys were working on," she would say. "It didn't ever occur to me to work on a women's thing."

She grew up fearless, a tree-climbing Girl Scout in Valdosta, Georgia. From a young age, her parents instilled in her the idea that there were no limits to what she could achieve. She spent her time running barefoot outdoors, climbing trees, and earning her black belt in karate. When she was sixteen, she replaced the family's car radiator. In her family, "there was nothing we couldn't do, whether you're male, female, whatever," recalled her younger sister, Susan Berthelot. "We had a lot of confidence, and a lot of love, and a lot of freedom. A lot of freedom to take risks."

But when Griffith hit puberty, her body began imposing limitations on that freedom. Her period was a wrenching affair, bringing with it stomach-turning nausea, stabbing pain, and a heavy, unstoppable flow. When she was thirteen, her gynecologist prescribed her birth-control pills, a scandalous proposition—"in the South especially, it was not done," she says. Her mother, at a loss, gave her gin.

Unable to control what was happening inside her body, Griffith focused on what she could control: math, and building things. She went to Georgia Tech on a scholarship to study chemical engineering. But her physical problems only grew worse. She found herself failing tests when she was on her period, and going to the campus infirmary to get shots of Demerol, a powerful opioid. Once, during a chemistry class, the room started to spin. She tried to make it back to her dorm, but somewhere along the dirt path, she fainted. Another student, who she had a crush on, found her and drove her home. Too weak to open the door, she threw up all over his backseat.

By the time she went to UC Berkeley to get her PhD in chemical engineering, she had developed an elaborate period regimen: She wore all-black outfits, inserted three Super Plus tampons at once, and swal-

lowed more than thirty Advil tablets a day. Yet most doctors were less interested in her symptoms and more interested in how she managed to take so many painkillers without getting a stomachache. When she consulted one male doctor, he took a look at her pixie cut and wiry, athletic build and diagnosed her as "rejecting her femininity."

"I felt like I was being gaslighted," she says.

Her real diagnosis came by accident. It was November 1988, and she had recently moved to Cambridge, Massachusetts, to complete a post-doc in a tissue engineering lab at MIT and live with her first husband. After prodding her doctor about her pain for six months, an ultrasound revealed a small cyst on her left ovary. Draining it would be a same-day procedure, in-and-out, her doctor said. But when she woke in the Brigham and Women's Hospital in Boston, it was the next day. She looked down and saw a row of staples along her midriff, holding together a six-inch incision.

While she struggled to gain clarity, her gynecologist came into the room to explain the situation. Her husband was already sitting beside her.

The problem was not Griffith's ovary, her doctor said, but her uterus. She had a chronic disease called endometriosis. It was common, striking as many as 1 in 10 women, trans men, and nonbinary people who menstruate. Because nobody had taken her pain seriously enough to examine her, Griffith's disease was particularly advanced: her ovaries, bladder, and intestines were all fused together with a sticky, speckled tissue that resembled the lining of her uterus. They'd cut out as much as possible, and burned off the rest. There was little else they could do.

Griffith could only hold on to one thought: she had a real disease. "To have someone tell me something's wrong with me, it was a huge relief," she says.

Her doctor laid out two options: She could go on Danazol, a powerful steroid that would stop her body from producing estrogen

and put her into a state of temporary menopause. Or she could get pregnant.

She recalls her then-husband answering for her: "We'll have a baby."

Griffith, though she had always wanted children, opted for the Danazol. Two years later, she left the husband and began her career in tissue engineering, a brand-new field that wielded the power to sculpt new organs from living cells. She developed an artificial liver, figuring out how to create polymer scaffolds in the lab and seed them with living blood vessels. In 1997 she created an iconic creature called the "earmouse" by injecting a human ear-shaped scaffold with cartilage from a cow's knee and growing it on the back of a lab mouse. Her work in the lab of MIT chemical engineer Robert Langer helped jumpstart tissue engineering, which today provides artificial skin and organs to millions of burn and injury victims. "She published, I'd say, some of the seminal papers in this field," says Langer.

Yet she never thought of turning her organ-making skills to the uterus. "Psychologically, it wasn't something I wanted to think about," she says. "I just wanted to pretend like it wasn't happening."

Endometriosis was her burden, work was her escape, and never the twain shall meet.

In the 1980s, when Griffith was first diagnosed, medical textbooks had dubbed endometriosis "the career woman's disease." Doctors stereotyped their patients as "underweight, overanxious, intelligent, perfectionist, white, of high social and economic standing, between 30 and 40 years, with regular menstruation and ovulation, who regularly delay childbirth," according to one study that examined these biases. They commonly prescribed marriage and pregnancy as "cure," with the medical reasoning being that, since hormones can trigger the lesions to grow, tamping down the female hormone cycle could relieve women

of the disease. Even though this logic has been roundly refuted, doctors still recommend pregnancy as treatment today.

Given that endometriosis was seen mainly as disease that robbed women of their fertility, pregnancy "was almost viewed as a two-for-one benefit," says Dr. Elizabeth Stewart, who performed Griffith's first surgery. "It's clear there was some sexism in the approach to endometriosis then. I think there's still some now."

Yet the idea that Griffith and other women with endometriosis were somehow to blame for their own suffering goes back further than that. To understand why, we have to return to ancient Greece.

To Greek physicians, the uterus was no ordinary organ but a beast that prowled, hungry for sex and motherhood. "An animal within an animal," wrote the second-century physician Aretaeus of Cappadocia. "In a word, it is altogether erratic." (The penis, too, was referred to as an animal, so this concept wasn't all that uncommon in Greek times.) Compared to man, woman was wetter and spongier of flesh, yet her uterus was light and dry. This meant it was always on the hunt for moisture, a quest that brought it in contact with other internal organs. When it didn't achieve its aims, it grew sullen and melancholy, causing mayhem throughout a woman's body. It squished up against the intestines, lungs, and heart, which could make her faint, spasm, or choke.

This "extremest anguish," Plato wrote, was caused by a woman allowing her womb to remain barren too long after puberty. The uterus, Hippocratic texts declared, was "the origin of all diseases."

The most commonly described condition was *hysterikê pnix*, meaning "suffocation of the womb," when the uterus lurched up and down the body. Widows and young, unmarried women were especially vulnerable to this malady. But when the womb wandered off, it could be tempted back by scent. To attract it upward, a physician waved sweet-smelling substances in front of the lady's nose; to bring it downward, he instead put them near her nether regions. Other treatments were less endearing. One was fumigation, in which hot air was blown

up through a reed into a woman's vagina.* Another was bandaging the abdomen tightly to keep the womb in place. Yet another was bloodletting, achieved by applying leeches to the cervix or labia.

Today, the word "hysterical" is often used a way to write off women as irrational and overemotional. But in ancient Greece, it was a medical diagnosis. The ultimate cure was always the same: the holy trinity of marriage, sex, and pregnancy. Intercourse, it was thought, introduced moisture and stirred up the body's fluids. Babies, meanwhile, were the uterus's raison d'être: they weighted it down and kept it in its proper place. The Greeks described the uterus as an oven in which the seed of the male is cooked to form new life. But an oven must be occupied, or it overheats. Similarly, if a woman stayed barren too long, she would be susceptible to womb movement and its accompanying sickness. A womb, like a woman, must be occupied.

You'd have thought the advent of human dissection would have cleared up the notion that the womb wanders. Not so. In the second century, Galen, while studiously ignoring the clitoris, confirmed that the uterus was not actually a free-roaming organ: it was anchored to the pelvic walls by flexible ligaments, or membranes. Galen concluded that uterine diseases were actually caused by these ligaments swelling with blood, male seed, or unfertilized female seed, which decayed in the womb and produced harmful vapors. Thanks to a woman's wetter nature, she needed to bleed every month to get rid of her body's excess fluid and avoid such a fate.

Those who came after Galen knew about the uterine ligaments, yet many simply incorporated this new anatomy into the old framework. Some said the womb still moved, but was pulled back by extra-stretchy ligaments. Others continued to recommend scent therapy, with the rationale that it could relax or constrict the ligaments. The idea of the wandering womb traveled from West to East, and held sway over medicine for centuries, writes Helen King, a

* Not unlike today's steam douches.

professor of classical studies at the Open University in the UK, in her book chapter "Once Upon a Text: Hysteria from Hippocrates." Even Victorian-era smelling salts borrowed from that same logic, promising to revive a swooning woman by coaxing her uterus back to where it belonged.*

Why did the idea of the wandering womb remain such a resilient concept, even after anatomical progress had proved it wrong? King, who studies attitudes toward menstruation in ancient Greece, has a theory: "It's a very useful way of keeping women in their place," she says. "It keeps women focused on childbearing. It means other options become a threat to their health."

While the explanations for hysteria shifted, one thing remained constant: It was a biological disease, with biological causes. Although it tied a woman to her reproductive biology, it at least gave her a solid diagnosis, a name for her pain. By the twentieth century, that would start to change. Soon, medicine began thinking of hysterical women not as patients afflicted with a bodily illness but as neurotic women whose problems were all in their heads. By 1900, the word "hysteria" had lost virtually any connection to the uterus.

What accounts for this dramatic shift? For that we can, once again, thank Freud.

A Frenchwoman leans backward in a swoon. Her eyes are closed, her corseted breasts thrust forward. A crowd of bearded gentlemen lean forward in their seats. In the center of the scene, depicted in the 1887 painting *Une leçon clinique à la Salpêtrière* (A clinical lesson at the Salpêtrière), a gray-haired man in a black suit gestures toward her. He

* The sixteenth-century physician William Harvey, though he made great strides in understanding how blood circulated in the body, also wrote that hysteria was brought on by "unhealthy menstrual discharge" related to "being too long unwedded."

is illustrating her stance: passive and objectified, draped over the arm of an assistant, in the *arc en circle*, the classical posture of the hysteric. This, for decades to come, would be the iconic image of hysteria.

The gray-haired man in the painting is Jean-Martin Charcot, a neurologist and director of the Salpêtrière, a mental asylum and teaching hospital outside Paris. Charcot would gain renown for identifying diseases like multiple sclerosis, aphasia, Tourette's syndrome, and ALS, which in France is still sometimes known as Charcot's disease. But his pet interest was always hysteria. In the 17th century, hysteria had nearly died an undignified death, becoming wrapped up not in science but in witchcraft, demons, and sorcery. Charcot rescued it from the ashes. While others ridiculed it as an affliction of witches and malingerers, he argued that hysteria was in fact an organic disease—just one that lived in the brain, not in the reproductive organs.

By Charcot's time, psychiatric hospitals like the Salpêtrière had spread across Europe, many of them filled with so-called hysterics. The standard nineteenth-century treatments were every bit as brutal as those of ancient Greece: leeches, pills, arsenic, opiates, induced vomiting. Charcot had his own methods. Every Tuesday, within a five-hundred-seat amphitheater he had created for this purpose, he would demonstrate a hysterical attack by hypnotizing a patient using the sound of a gong or tuning forks. He had come to think of these attacks as a finely choreographed dance, taking fifteen to twenty minutes, in which the victim went through the same steps: a rigid posture, standing straight up; grand, circuslike gestures of the limbs (Charcot was a great fan of the circus); and finally, fainting backward in a dramatic arch. He illustrated these steps with colored chalk on the blackboard.

Charcot's demonstrations were dramatic and vaguely erotic, filled with writhing and moaning. He claimed to be able to stop an attack by using experimental methods like hypnotism, "animal magnetism," and electricity. (He also believed hysterical episodes could be triggered or stopped by pressing on the ovaries, and invented a brutal-looking device called an "ovary compressor" to do just that.) Ultimately, his

performances would be revealed as fraudulent, and hysteria would disappear as a diagnosis in Paris. But that didn't stop one young neurologist from taking up its mantle.

In 1885, one of Charcot's audience members was a medical student named Sigmund Freud. Freud, who had been working in the neurology lab of Ernst Brücke comparing the brains of frogs, crayfish, and lampreys, had come to Paris for six months to study under Charcot. Like others in the audience, he was stunned by what he saw. He was especially intrigued by Charcot's work on male hysterics, and his attempts to show that the disease stemmed not from the uterus but from some invisible injury to the nervous system. He would take these observations one step further: in his opinion, the heart of this disease was not a physical injury but a "psychological scar produced through trauma or repression" that manifested in physical symptoms.

Freud returned to Vienna eager to convince his colleagues of the merits of hypnosis in treating hysteria. Yet when he began lecturing on male hysteria, he was met with ridicule. "But, my dear sir, how can you talk such nonsense?" he was told by one incredulous older surgeon. "Hysteron (sic) means the uterus. So how can a man be hysterical?" Freud disagreed. It was a mistake, he wrote, to link hysteria to the womb. The word itself was a "precipitate of the prejudice, overcome only in our own days, which links neuroses with diseases of the female sexual apparatus."

Hysterical symptoms like nervous coughs, painful breathing, migraines, anxiety, and muteness could affect men or women, he argued. "Hysteria behaves as though anatomy did not exist or as though it had no knowledge of it," he wrote in 1893. Freud had reversed the symptoms: rather than menstrual problems causing anxiety and neuroses, now it was neuroses and anxiety manifesting as biological symptoms. The wandering uterus was no longer literal, but metaphorical.

Hysteria, for Freud, was a stepping-stone. Once he had wrested the disease away from medical doctors, he was able to get on with his true project: showing that all neuroses had their basis in the mind, and specifically, in traumatic sexual memories or sexual conflict. Hyste-

ria served as a proof-of-concept for his argument that, by making his patients confront traumatic memories, he could rid them of troublesome physical symptoms. In 1895, he and a colleague, Viennese physician Dr. Josef Breuer, published *Studies on Hysteria*, where he first laid out his sexual thesis. "Hysterics," they concluded, "suffer mainly from reminiscences." In other words, it was all in their heads.

It is perhaps no surprise that the turn away from biological causes and toward blaming women for their illnesses coincided with the rise of first-wave feminism in Europe and the fight for suffrage. As women became more visibly engaged in the outside world, leaving the traditional sphere of the home, doctors began fretting that this unnatural assertiveness was leading to their ill health. Higher education and careers, they feared, might siphon blood from their uteruses to their brains. But their pronouncements soon had an air of blame to them. "Cures" like hysterectomy, ovariotomy, and pregnancy now began to sound more like punishment.*

Instead of blaming women's uteruses, Freud cut to the chase and blamed women.

Freud was never particularly interested in the uterus itself, except as the tabula rasa on which he could build his psychic empire. Besides a few

* Some did recognize that these so-called solutions weren't cutting it. One was Lydia E. Pinkham, a housewife-turned-entrepreneur from Lynn, Massachusetts, who saw that male doctors failed to understand—or lacked empathy for—the needs of their women patients. "What does a man know about the thousand and one aches and pains peculiar to a woman?" she wrote in her widely distributed pamphlet, "Treatise on the Diseases of Women," first published in 1901. In frank, easily understood language, it laid out reproductive anatomy and the biology of ovulation, fertilization, and pregnancy, woman to woman. Unfortunately, the main point was to sell Lydia Pinkham's Vegetable Compound, a proprietary mix of concentrated herbs and roots that claimed to ease the pains of menstruation, menopause, and innumerable other uterine ailments. It was later revealed that the tonic's main ingredient was alcohol.

instances of men wishing to give birth, and one woman who experienced a "hysterical pregnancy" in which she gave birth to nothing, the uterus scarcely shows up in his texts. Yet while gynecological anatomy hardly influenced his theories, his theories would deeply shape gynecological medicine.

Like Charcot, Freud considered the disease as an equal-opportunity neurosis, one that afflicted men as frequently as women. He even once referred to working through his own "little hysteria." Yet the vast majority of his hysteria patients—and almost all of the ones who formed his case studies—were women. (Men with identical symptoms generally got a diagnosis like neurasthenia or shell shock, today known as PTSD.) Women, Freud believed, were by nature more prone to nervous disorders, because of the sexual conflict they faced along their tortuous path to womanhood. And it was women who would bear the brunt of hysteria's legacy.

In 1980, hysteria was finally deleted from the Diagnostic and Statistical Manual of Mental Disorders. Yet it lived on in a group of diagnoses known as the "psychosomatic" disorders. "Hysteria dressed up in modern garb," as journalist Maya Dusenbery called them in her 2017 book *Doing Harm,* these diagnoses were all considered "female" ailments: they were diagnosed ten times more often in women as in men. In reality, Dusenbery argues, women suffer disproportionately from little-known conditions like chronic fatigue syndrome, possibly due in part to differences in their immune systems or other biological differences. Yet when doctors can't promptly explain their symptoms, they get lumped by default into one of these psychological categories.

Meanwhile, diseases that really do stem from the uterus—like endometriosis—still get dismissed as Freudian problems of the psyche.* When Abby Norman first went to her doctors with symptoms of endo-

* Some scholars argue that hysteria, far from being a made-up disease, has always actually been endometriosis in disguise. "If so, then this would constitute one of the most colossal mass misdiagnoses in human history, one that over the centuries has subjected women to murder, madhouses, and lives of unremitting physical, social, and psychological pain," write the Nezhat brothers, three endometriosis surgeons

metriosis as a college student, they dismissed her theories. "You were probably molested as a child and this is just your body's way of trying to handle it," one told her. "This is all in your head," said another. Once she was finally diagnosed in her twenties, doctors assumed that her priority was having children.

"The things that actually did concern me—the pain, the nausea, the complete loss of everything that I loved and that made me happy (food, dance, sex)—didn't seem to carry the kind of weight that concerns about my fertility did," she wrote in her 2018 memoir, *Ask Me About My Uterus*. "How, I wonder, did the doctors expect me to get pregnant if I couldn't have sex? What if I had said, 'Okay, fine, I'll have a baby—but how, pray tell, shall I go about it when sex is excruciatingly painful and I can't tolerate penetration long enough to be fertilized?' Why wasn't it enough that I was a young woman who wanted to be sexually active, but couldn't be?"

The presumption that her end goal was to be a mother was so deeply entrenched that at times, her doctors didn't even bother to ask. In her first exploratory surgery for endometriosis, a surgeon found a large cyst that had displaced her ovary and twisted the adjoining Fallopian tube. Rather than remove it, the surgeon only drained it, so as not to threaten her fertility. The pain came back within weeks. Norman was not overly concerned about her fertility; she just wanted to be free of pain. Her disease had wrecked relationships, stopped her from going to college, and made her feel constantly ashamed. Yet medical professionals made her feel like she'd brought it upon herself—for wanting a career, for wanting sex, for not wanting children. For not, as Freud would have said, adapting to her role as a woman.

There's a reason some scholars have deemed endometriosis "the new hysteria."

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from Iran, in a 2012 paper. "The number of lives that may have been affected by such centuries-long misdiagnoses is staggering to consider."

From the outside, Dr. Linda Griffith was unstoppable. A fast-talking dynamo who showed up to campus riding a Kawasaki motorcycle and sporting a leather jacket, she cut a memorable figure in the minds of her colleagues.* "Bountiful amounts of energy, totally brilliant, preternaturally young-looking, and just a phenomenon," remembers Harvard geneticist Pardis Sabeti. "Like a thunderstorm. She's the most highly energized person I think I ever met," says MIT toxicologist Steven Tannenbaum. "She's just supercharged."

None of her colleagues knew, however, what was going on under that energetic exterior. Throughout the '90s, Griffith underwent one invasive surgery after another. Yet her rogue uterine tissue kept growing back. It surrounded her bowels and ureters, squeezing them down. By the fifth surgery she could no longer tolerate crossing the Charles River. A knot would form in her stomach as she remembered all the painful hours spent in the hospital. At the same time, she was taking strong drugs, like Lupron, a hormone blocker that gave her short-term memory loss. While teaching a class on thermodynamics, she would be forget terms like "heat transfer."

She still hadn't given up on her dream of having children. In 1994, she helped recruit Lauffenburger, a systems biologist at the University of Wisconsin, to work alongside her as the head of MIT's new biological engineering department. After working together in the lab, the pair fell in love and quietly got married.† In 1997, they went through several rounds of IVF in the hopes of conceiving a child, but none of the embryos took, probably because her disease was already so advanced. Today, three carved stone cherubs hang above the doorway to her

* Today, when she isn't running the six miles to the Cambridge reservoir and back, she can be found bouncing on her hydraulic pogo stick, which she taught herself how to use during the pandemic.

† Some of their lab students are still taken aback to find out they are a couple.

kitchen: a gift from Griffith's mother, to commemorate the embryos that never were.

In September 2001, the day after her fortieth birthday, Griffith woke up with an attack of stabbing abdominal pain. Her doctor gave her an opioid, but it barely masked the agony; she had to mix it with two glasses of wine. The following morning was September 11. While the nation looked on in horror as the Twin Towers fell, Griffith rushed to the hospital in a fog of painkillers and underwent a hysterectomy with her surgeon, Dr. Keith Isaacson. The choice had been made for her: She had to get rid of her uterus, the center of her pain but also her hope for children. "There was no decision. It was hysterectomy or death," she says.

Finally, she thought, she could close the chapter on her endometriosis and move on with her life. But her uterus wasn't done with her yet. In 2005, the disease came back, requiring two more surgeries.* Afterward, she tried her best to avoid the thought of motherhood. She would come up with excuses not to attend a work dinner where a colleague's wife would be bringing her newborn. She knew that to stay on top of her career and keep herself sane, she had to keep the darkness out. "The hellmouth will open at the dinner," she says, "and you've got to keep the hellmouth closed."

The turning point came in 2007, when a member of the MIT Corporation's board of trustees, Susan Whitehead, asked Griffith to speak at a Women in Science and Engineering luncheon about how her work on tissue engineering could benefit women. At first, Griffith was annoyed. "I was super not into the women thing," she says. "I

* Given that endometriosis is, by definition, a disease that occurs outside the uterus, removing the uterus rarely solves the problem for good. Often, more lesions are hiding in other parts of the pelvis, sometimes burrowed deeply into tissues. More than half of women who undergo hysterectomies for endometriosis have recurrent pain, and many have to undergo further procedures.

just tried to stay out of it because I wasn't part of the narrative." But Whitehead was a friend, so she agreed.

Toward the end of the event, the moderator asked Griffith where she saw herself and her work in ten years. She found herself thinking about her niece, Caitlin, who had just been diagnosed with endometriosis after years of being told that her symptoms stemmed from stress.

She found herself blurting it out: "I have a chronic disease called endometriosis," she began. "My niece who's sixteen was just diagnosed. And there's no better treatment for her—thirty years younger than me—than there was for me when I was sixteen." She herself had just had her eighth surgery for the disease. But it was her niece who "made lava shoot out of my head," she says.

When it came to making liver and bone, "so many other people could do them. But there was this one thing only I could do." She had recently been awarded a prestigious MacArthur "genius" grant, which came with half a million dollars for any research project. Now she knew what she was going to do with it. In 2009, she used it toward opening the Center for Gynepathology Research at MIT, the only engineering lab in the nation to focus on endometriosis and a related yet even less known condition, adenomyosis, in which similar tissues grow within the muscular walls of the uterus.

During the launch event for the center, Padma Lakshmi, host of *Top Chef* and co-founder of the Endometriosis Foundation of America, lamented the lack of research on such a devastating disease. "I have to say, I'm really shocked that it's the first research center of its kind in America," she said. "That is stunningly bad news on the one hand, that she's the first one doing it. On the other hand, better late than never. Thank God for Dr. Linda Griffith."

Most labs devoted to women's diseases are accompanied by obvious symbols of womanhood: a rose, a tulip, an hourglass silhouette. Not

Griffith's. Tucked away in the building for biological engineering, the Center for Gynepathology Research is marked only by the letters CGR in red and black, the *G* formed from a curved arrow representing the hand of the engineer. "We needed something that wasn't all pink and flowers," Griffith says, in her slight Georgia drawl. "We really thought it should be, like, 'This is science.'"

Like Griffith herself, her lab speaks the genderless (some would say masculine) language of science and engineering. It's part of her push to change the conversation around endometriosis from one of women's pain to one of biomarkers, genetics, and molecular networks. "I don't want to make endometriosis a women's issue," she told the *MIT Technology Review* in 2014. "I want to make it an MIT issue."

In her lab, she has begun growing uterine organoids—tiny domed droplets, with glands that look like swirling craters—from the uterine cells of endometriosis patients. Placed in a gel made to mimic the uterine environment and fed the right nutrients, these cells spontaneously form structures that resemble the human uterine lining, growing and shedding in response to hormones. These "patient avatars" are ideal tools for testing potential new treatments for the disease: Biologically, they are closer to human uterine cells than those of mice, as mice don't naturally menstruate. And they enable researchers to sidestep some of the ethical issues that arise with human trials.

Her research highlights what a remarkable organ the uterus truly is—and not just during its signature function, pregnancy. Humans, unlike almost every other mammal, grow their entire endometrium—the womb's inner lining—once a month, whether or not a fertilized egg takes hold. If no egg appears, they shed it.

Picture the womb as a small orange, and the pith would be its lining—a plush, living bedding for a potential embryo. Each month or so, triggered by a drop in the hormone progesterone, this lining sloughs itself off and builds itself anew. Immune cells rush to the site to heal the wound. Connective cells that line the uterus differentiate into new lining, complete with delicate, spiraling blood vessels. The pro-

cess repeats itself, swiftly, scarlessly, without a trace of injury, again and again, up to five hundred times in a woman's life. "How the body can coordinate that is extraordinary," says Dr. Hilary Critchley, a reproductive biologist at the University of Edinburgh.

To capture these systemic interactions, her team is seeding their models with blood vessels, nerve cells, and immune cells. They hope to eventually connect them to models of the liver, bone, and gut. Clearly, Griffith sees the uterus far differently than the Greeks did: not as the center of female frailty but as a powerhouse of renewal and regeneration. Dynamic, resilient, and prone to reinvention, this organ offers a window into some of biology's greatest secrets: tissue regeneration, scarless wound healing, and immune function. "The endometrium is inherently regenerative," she says. "So studying it, you're studying a regenerative process—and how it goes wrong, in cases."

As it turns out, Griffith's in vitro models are sorely needed. When it comes to understanding endometriosis—and menstruation in general—science lacks good animal models.

The art of growing and then sloughing off the entire uterine lining is a rare quality throughout the animal kingdom, limited to a handful of primates, four species of bats, and a couple shrews. Even fewer experience menstrual disorders like endometriosis. Altogether just 84 species—1.6 percent of all placental mammals—are known to menstruate. If you look at a phylogenetic tree, they're all over the place, suggesting that uterine bleeding has evolved at least three times independently. This underscores a fundamental mystery: Menstruation, with all its requirements and regularity, is why the human uterus is so dynamic. But it is also costly, requiring an animal to shed an entire organ and regrow it every month. So why would any animal bleed?*

* Humans may not be quite as exceptional as we think. The Cairo spiny mouse, a

One of the most common explanations is the idea that the female body needs to get rid of something dirty or harmful. In the 1920s, a doctor named Béla Schick theorized that women had special toxins in their menstrual blood, which he called "menotoxins." His questionable experiments suggested that menstruating women sweated toxins from their skin that made flowers wilt and die. Although none of his findings were replicable, others latched onto the idea, arguing that menstruating women did indeed wither plants and spoil beer, wine, and pickles. Even today, many theories about menstruation come from the idea of the vagina as dirty and in need of cleansing: In 1993, a physician and mathematician named Margie Profet made waves when she suggested that menstruation's function is to "defend against pathogens transported to the uterus by sperm."*

The real explanation may be not about getting rid of something harmful but defending against harm in the first place, says Dr. Günter P. Wagner, a Yale researcher in the ecology and evolutionary biology department who studies the evolution of menstruation.

Consider that motherhood isn't all warm and fuzzy. It's a fight for resources, often waged brutally between mother and offspring. Since an offspring holds only half the genome of its mother, its evolutionary interests aren't exactly the same as hers—and sometimes, they directly conflict. Evolutionarily speaking, the goal of the fetus is to suck as many resources as possible from Mom, whom it basically sees as its personal Giving Tree. Mom's goal, by contrast, is to survive her pregnancy and limit the aggressiveness of her offspring. The evolutionary

rodent native to the Middle East, doesn't look like much—just "a little bottlebrush that has eyes and a tail," says Nadia Bellofiore, a researcher at Monash University who works with a colony of them. But it is the only rodent that we know of that bleeds. Bellofiore has found that, like us, this "humanesque rodent" ovulates spontaneously, sheds its lining, and marshals immune cells to repair the wound. Interestingly, spiny mice are also known for their regenerative powers: they regenerate skin and hair follicles.

* Though you could say that this at least shifted the blame to the penis.

tug-of-war that takes place between mother and child's genomes is called "maternal-fetal conflict."

Animals that menstruate have particularly conflict-riddled relationships with their offspring, Wagner says. They tend to have more invasive fetuses and placentas, which burrow deeply into the mother's body to gain access to her nutrients and blood supply. This poses an existential threat: In blurring the boundaries between the mother's body and her offspring's, the fetus runs the risk of siphoning off too many resources and weakening or even killing its host.

Fortunately, Mom has some tricks up her sleeve. The key event in menstruation is not bleeding, but the differentiation of the uterine lining. Over a period of about three days, uterine cells called fibroblasts transform into what are known as "decidual cells"—meaning that they eventually fall off, like the leaves of deciduous trees. While these cells are necessary for an embryo to implant, they simultaneously create a matrix that is more difficult to penetrate. They also help tamp down the inflammatory response that occurs when a fetus implants, an event akin to a wound. All of these developments make sure the embryo burrows deeply enough to stay viable, but not so deep that it harms the mother.

In most species, this crucial differentiation happens only when an embryo appears. But in menstruators, it happens about once every month, spontaneously. (Menstruating animals ovulate, or release eggs, spontaneously—as compared to animals who ovulate in response to light and temperature, like frogs, or copulation, like dogs.) "You don't want to be defenseless when this pesky embryo is coming along," says Wagner. You want to be ready for it—"sort of like a standing army." These animals get a head start by erecting their defenses with every ovulatory cycle—no fetus required.

Once that lining has differentiated, and once the body realizes there is no embryo, it has nowhere to go but down. The progesterone drop causes the blood vessels to violently die, killing the surrounding tissue and causing the rest to disintegrate and exit the body through the vagina.

So what really links animals that menstruate? Evolutionarily, they're Type-A planners. They anticipate conflict, priming the uterus and shielding themselves should an unwanted visitor happen to implant, rather than waiting until it's too late. Mom's body does this independently, regardless of whether a male, or fetus, comes along. There may be another advantage to regular menstruation: The uterine lining could play a role in sensing the "quality" of the fetus and deciding whether a prospective embryo should live or die. By taking into account chromosomal errors, aging sperm and eggs, and other quality-control issues, the mother might summarily eject an embryo that isn't worth the investment. The uterus may even learn from its mistakes and adapt to new conditions.

Many researchers argue that the remarkable dynamism of the uterine lining is a double-edged sword. In the past, Critchley points out, women menstruated only around forty times in their lifetime, and spent the rest of the time pregnant or nursing. Today, the average Western woman menstruates up to five hundred times—meaning it's statistically more probable that some step in the intricate process will go askew. Consider endometriosis: Taken out of its natural context of the womb, the dynamic nature of the uterine lining proves catastrophic, intent on executing its life cycle in places where it caused scarring, pain, and inflammation.

Others counter that this logic is just the modernized version of Hippocrates's wandering womb: it presumes that women's uteruses are set up for disease, and that pregnancy is protective. There's no reason that the frequency of menstrual cycling should be inherently pathological, says Dr. Kate Clancy, a biological anthropologist who studies reproduction at the University of Illinois Urbana-Champaign. There are other changes to modern women's bodies that deserve deeper investigation, including external factors like toxins from the environment that have been linked to endometriosis. Perhaps the problem is not in women's heads, or even their pelvises, but in the world they inhabit.

"I'm increasingly thinking that it's not a system flaw," Clancy says. "At a certain point we need to start to think about this with the same rigor we would if this was a cisgender male body that we were exploring."

That starts with understanding the basic mechanisms of menstruation. Shedding light on processes like uterine differentiation will help reveal what makes the cells of endometriosis different from other uterine cells and, ultimately, help scientists disrupt the process. It isn't a woman's lot to suffer just because she isn't pregnant. We just haven't been asking the right questions about how the uterus truly works.

Nor, it seems, have we been asking the right questions about endometriosis.

One of the first doctors to systematically probe the origins of endometriosis was Dr. John A. Sampson, a twentieth-century gynecologist who practiced in Albany, New York.* Sampson had grown fascinated by a common yet mysterious condition in about 1 in 10 of his female patients. When he opened up their pelvises, he found "chocolate cysts" attached to their ovaries and uteruses—named for their contents, which resembled chocolate syrup. To figure out what was happening, he began intentionally scheduling hysterectomy surgeries while women were on their periods. He removed their uteruses, injected the arteries and veins with red and blue dyes, and inspected them under the microscope. That's when he noticed something strange.

Most menstrual blood flows downward, through the vagina. But Sampson observed that some also escaped upward through the fimbriae-tipped ends of the Fallopian tubes, into the fluid-filled pelvic cavity. Like cuttings from a tree, he mused, this escaping tissue

* He has an artery named after him, Sampson's artery, otherwise known as the artery of the round ligament of the uterus.

could seed the pelvis and spread to other organs. This, he believed, was the origin of the chocolate cysts. He called them "menstruating organs," which grew and then attempted to shed in response to hormones. Some were small and superficial, but others invaded deep into the pelvic tissue, or even into the uterine wall, similar to a cancer. The result was pain, irritation, more bleeding, and, most distressingly to doctors, infertility.

Sampson's explanation for how endometriosis takes root relied on the idea of a literal wandering womb, a reproductive system gone haywire. He considered endometriosis a disorder primarily of the uterus and ovaries—a disease of menstruation, reproduction, and women. He noted that endometrial cysts "affect women in a most valuable period of their lives, usually from 30 years of age to the menopause," and was one of the first to assert that pregnancy seemed to have a beneficial effect.*

Yet this approach never yielded a definitive answer. In 1940, Sampson concluded that the disease remained "tantalizingly alluring and elusive."

It still is, today. Despite the fact that this disease has been known for more than 150 years and afflicts at least 200 million women and other menstruating people worldwide, nearly every scientific paper on endometriosis starts out with the words "mysterious," "enigmatic," or elusive." "There are few diseases in gynecology that are as enigmatic as endometriosis," begins one 2010 article in a gynecology journal. "It remains a riddle that baffles researchers and clinicians." Surgeons sometimes refer to endometriosis as "the pelvic chameleon" or "the

* Later OB/GYNs put it more baldly: "Nature (since the beginning of time) has employed an efficient prophylactic and curative measure for endometriosis, i.e., pregnancy," wrote Dr. Clayton T. Beecham in 1949. "It is noteworthy that the frequency with which the diagnosis of endometriosis is made parallels the increased use of contraception, the emancipation or rise of womankind to careers and/or late marriage with late childbearing."

great pretender"—phrases that invoke the dissembling language of hysteria itself.

But is the disease really so elusive—or have we just been looking at it the wrong way?

A narrow focus on fertility may be one reason so little has changed when it comes to managing endometriosis. Getting a diagnosis usually requires a surgical procedure to confirm the presence of lesions, meaning that women wait years, if not decades, for an official diagnosis. Once they have a diagnosis, the two main options are still surgery to cut or burn away the lesions—which often grow back—or shutting down the reproductive system by depriving it of hormones. Newer drugs like Orilissa, a partial estrogen suppressant released in 2018, still rely on these same mechanisms, says Dr. Linda Giudice, a reproductive endocrinologist at UC San Francisco who studies the biology of the uterine lining. "It's not something super novel," she says. "It's a variation on a theme."

Endometriosis patients—like the nineteenth-century women who had their ovaries cut out—were once considered victims of their own delicate, flawed reproductive systems. Increasingly, researchers like Griffith are seeing it differently. To them, endometriosis is far larger than a "women's disease": it is a systemic disease of inflammation, affecting nearly every organ system. "We need to address this as a disease that affects many aspects of the body, whether it's inflammation, a dysfunctional immune system, inflammatory bowel syndrome," says Elise Courtois, a researcher who studies the genetics of endometriosis at the Jackson Laboratory. "As women, we are not only made for reproduction."

One enduring mystery of endometriosis is how lesions can appear in places as far-flung as the lungs, eyes, spine, and even the brain. The answer may have to do less with the uterus and more with regenerative

processes happening throughout the entire body, notes Dr. Hugh Taylor, chair of the department of obstetrics, gynecology, and reproductive sciences at Yale School of Medicine. Taylor investigates whether stem cells, which are plentiful in the uterine lining, could contribute to the spread of the disease by circulating throughout the body. Stem cells outside the uterus may also play a role: in women with uterine damage, stem cells from bone marrow flow in to repair the damage.*

Chronic, low-level inflammation of the uterus may also contribute to the origins of the disease. Dr. Peter Gregersen, a rheumatologist, and Dr. Christine Metz, an immunologist, both at Northwell Health's Feinstein Institutes, have spent five years developing a simple diagnostic test for endometriosis using menstrual blood. When looking for a biomarker to base their test around, the pair put regular uterine cells into an inflamed environment and found that they transformed. They became stickier, more invasive, and worse at decidualizing—exactly like the uterine cells in women with endometriosis. These invasive cells, Gregersen noted, were similar to the ones he had previously studied in inflammatory diseases like rheumatoid arthritis and lupus.

If Gregersen and Metz's hunch is right, it could mean that anti-inflammatory drugs currently used for rheumatoid arthritis might be repurposed to prevent endo from taking hold in some women in the first place. "The endo community is very dominated by people who think this is an abnormality of hormonal regulation," said Gregersen. "And I mean, it may well be. But I don't think that's the whole story."

As for where all that inflammation might come from: Dr. Kevin Osteen, an obstetrics and gynecology researcher at Vanderbilt who has worked with Griffith, studies how early exposure to environmental toxins might lead to uterine inflammation and, ultimately,

* Because uterine stem cells are relatively accessible, they could also be a boon to regenerative medicine. Taylor has shown that, like other stem cells, uterine stem cells can be grown into new neurons and insulin-making cells to treat diseases like Parkinson's and diabetes.

endometriosis. Osteen began focusing on the disease in the 1980s, when he was leading Vanderbilt's fledgling IVF program and realized that many of his patients suffered from it. Since then, he has come to believe that the key to halting endo is tackling the inflammation associated with its early stages, long before it progresses to infertility. "In my mind, understanding the immunological origins of endometriosis opens the window to prevent the disease from even developing," he says.

Osteen has also found that the pollutants he studies, dioxins, lead to similar inflammatory pathways in both men and women. Though they don't lead to endometriosis in men, they can cause other problems with fertility and testicle function, and can be passed down to daughters. "It's not at all just a woman's problem," he says. "It needs to be looked at much more broadly than that."

Meanwhile, Griffith brings something else to this conversation besides in vitro models: her unique perspective as both patient advocate and researcher. Her vantage point has helped her see what her colleagues miss—for instance, the way medical language contributes to keeping endometriosis siloed and overlooked. In 2009, she started noticing something in her lab: physicians like Dr. Isaacson often referred to her disease as "benign." She knew what they meant, of course: non-cancerous. But the word made her wince. As a patient, it felt dismissive. More importantly, the word was signaling the wrong thing to funding entities like the NIH. "If I write that I'm studying a benign disease, who's going to give me money?" she says. "It's not a disease. It's just like: live with it." In 2019, she began campaigning to remove the word "benign" from endometriosis research. Today it has virtually disappeared from conferences and medical papers in the field.*

* In case anyone forgets, she reminds them in her email signature: *Please don't refer to endometriosis, adenomyosis, or fibroids as "benign disease"—they are not benign, they are "common and morbid."*

Once, Griffith thought of endometriosis as her cross to bear. Today, she is embracing both halves of her identity to bridge the divide between medicine and the public. "Everybody has their little piece of the puzzle," she said one evening at her home in Cambridge. "It's all a giant mosaic. We put our tiles in, and the picture emerges."

There is a second meaning to the idea that endometriosis is more than a "women's disease." It isn't just about the disease physically reaching beyond the uterus. It's the fact that endometriosis is far from a disease of neurotic white women, as it was thought of in the days when Griffith was diagnosed.

In 2019, Maisha Johnson was in bed with a heating pad on her midriff. Scrolling through Facebook, she came across a video in which actress Tia Mowry talked about living with endometriosis, and mentioned that the first doctor to take her condition seriously was Black. Maisha was thrilled to see another Black woman sharing her story—but then she scrolled down to the comments. White women, she recalls, were commenting that stories like these create division within the endometriosis community. Many were saying, essentially: "Why do you have to make it about race? Endo affects all of us the same way!"

Maisha was frustrated that those who see the systemic problem of gender bias within medicine couldn't recognize that racial bias, too, is systemic and often compounds the problem. In her own journey as a Black woman with endo, she recalls instances where doctors assumed she was seeking opiates, and instances where her pain was ignored. "If I'm seen as a woman who's prone to hysteria, and then also a Black woman who's not as affected by pain, then obviously if I'm talking about being in pain, then I'm just exaggerating and it can't possibly be that bad," says Maisha, a thirty-four-year-old content writer for *Healthline Media* who writes about chronic conditions and mental

health. This is particularly vexing when it comes to a disease that requires surgical evidence to get a definitive diagnosis—yet doctors are often reluctant or unwilling to provide that surgery. Seeing those comments motivated her to write a blog post on her experience with race and endometriosis for *Healthline*.

Jaipreet Virdi, who is deaf and Southeast Asian, told me about a similar experience. Virdi was thirty-five and working as an adjunct history professor of medicine in Toronto, researching disability and gender, when she felt what she would later learn was a nine-inch mass in her abdomen. Time after time, her husband would accompany her to the ER and she would spend hours in the waiting room screaming in pain, only to be sent home. "After the third time it became really apparent they were looking at me like I was a drug-seeker," she says. That was the first instance she experienced "very subtle racism, class bias as well" in a medical setting. Eventually, she began demanding that her medical files reflect that she was a historian of medicine, so that doctors would respect her expertise.

Only after three more emergency room visits did a doctor actually feel her mass and investigate further. All of the doctors involved in her eventual diagnosis, she remembers, were people of color. She was finally sent in for surgery, where surgeons tried to remove as much endometrial tissue as possible from her ovaries, intestines, and bladder. Now forty, Jaipreet has come to terms with the fact that children may not be in her future. What frustrates her is that if doctors had taken her pain seriously earlier—when she had painful periods, when she was fainting in the bathroom—she may have had options.

Finally, associating endometriosis only with those who look stereotypically feminine means that many LGBTQ people—particularly trans men, masculine-presenting women, and nonbinary people—have an even harder time getting doctors to recognize and treat their disease. Gender-diverse patients report that doctors often lack knowledge of how hormones or other treatments can affect the disease in different bodies. "Many clinicians are unable to disentangle gender from

anatomy when it comes to providing care," Dr. Frances Grimstad, a gynecologist at Boston Children's Hospital, told *VICE* in 2020. Worse, doctors often lack basic respect for their gender identity, leading them to feel discomfort around sharing their true concerns.

That was the experience of Cori Smith, a twenty-eight-year-old trans man from Rochester, New York, who has endometriosis. Cori's first period, at thirteen, was excruciating. Six months later, he was in the emergency room for a burst ovarian cyst. After being diagnosed with endometriosis at seventeen, he underwent several surgeries to remove endometrial tissue. At the same time, he was figuring out his gender identity. From an early age, he felt sure that he was a boy; at age twelve or thirteen he saw the word "transgender" on the cover of *People* magazine, and knew that was what he was. Still, he put off transitioning because he was constantly dealing with his health problems. When he was twenty-two, he finally went on testosterone and got top surgery to remove his breast tissue. Eventually, knowing he wanted to have biological children someday, he froze his eggs and had his ovaries and uterus removed due to complications with his disease.

Despite his lower levels of estrogen and lack of female reproductive organs, his disease returned, baffling his doctors. "As a girl, they thought I was just a hormonal teenager that just wanted attention," he said in a video interview with *NowThis News* in 2018. "No matter which version of my life, they still ignored it." His experience echoes that of thousands of women who are prescribed hysterectomies to deal with their disease, yet continue to suffer. Six years after transitioning, Cori still finds himself in the OB/GYN office more than most women. "Because of all that, I'm more aware and in tune with the problems that women face in the medical system," he says. For him, endometriosis "is so rooted in who I am and what I've been through that for me it's my story. I don't walk away from it, I kind of walk towards it."

After sharing his story with *NowThis News,* Cori says he's received hundreds of personal emails and messages from others in the endo community. His experience has led him to believe that the numbers of trans and nonbinary people with endo are likely far higher than documented, and that the compounding barriers of having a stigmatized "women's disease" and not identifying as a woman conspire to keep them silent. Continuing to speak about endometriosis as a "women's disease," to him, obscures the reality of this condition, and makes the trans and nonbinary people who suffer invisible. "Breast cancer happens to men," says Cori. "I just don't think it should be gendered."