lies these disorders, there is a common pattern that links them all: The immune system begins to make antibodies that attack specific cells or tissues, or cause an organ to malfunction. In diabetes, a particular organ is targeted (the pancreas); in more general autoimmune illnesses, such as lupus, the attack is spread throughout the body, causing everything from arthritis to rashes to kidney disease.

In keeping with the link between autoimmunity and hormones, most patients display their first symptoms after puberty. But the mechanism of the shift that causes symptoms to appear still baffles researchers. "Why does the immune system lose its tolerance for itself, that's the fundamental problem," says Arnett, who is searching for defects in the genes of the major histocompatibility complex (MHC), a cluster of genes that regulates the interaction of T and B cells in the immune response, that may contribute to developing lupus. Normally, the MHC genes responsible for regulating the immune response are "constantly presenting foreign invaders and components of the self" to the immune system, he says. "Presumably, it is educated to distinguish between the two. But that recognition system breaks down with these autoimmune disorders."

Arnett and other researchers suspect a virus or bacterial infection initiates this breakdown in people genetically predisposed to develop an autoimmune disease. As a partial confirmation of this idea, just a few months ago, immunologists at Duke University Medical Center triggered lupus in mice genetically predisposed to the disease by injecting them with bacterial DNA. Rather than generating a specific immune response to the foreign DNA, the mice generated antibodies to their own DNA. With this new mouse model, researchers are beginning to search for the cause of lupus—while warning patients with the disease to try to avoid bacterial infections.

Whatever differences—with the attendant advantages and disadvantages—men and women show in their immune systems begin to disappear with age (although the accompanying disorders, initiated earlier, such as lupus, do not). After menopause, when a woman's estrogen levels decrease significantly, her levels of circulating antibodies and general immune response become much more like a man's: low and steady.

Yet there is still a difference, researchers say. "Women still tend to be healthier, and they do live longer," says Grossman, adding that "everyone knows this. Even insurance companies know that with women, they're looking at a better system." Understanding in detail how that better system works may eventually offer benefits to both sexes through an improved understanding of how the immune system itself operates.

–Virginia Morell

REPRODUCTION

Attacking the Causes of "Silent" Infertility

Telling a couple they are unable to have children is a painful task. Just ask a physician who's had to do it in the line of duty. And although great strides in reproductive technology have benefited some couples, for many others the pain is extended as they try a succession of infertility treatments to no avail.

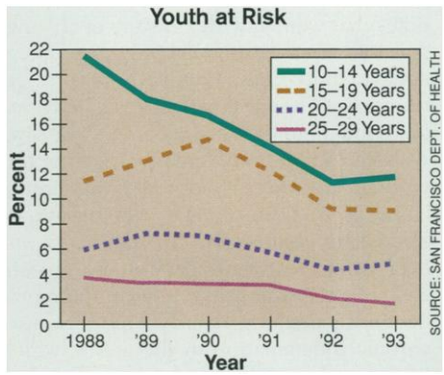
In the United States alone, researchers estimate that 15% of couples are involuntarily infertile. In the prime childbearing years, from ages 20 to 30, the causes are roughly divided between men and women. After 30, however, the balance shifts toward the female side of the equation, as the natural aging process takes its toll; at age 40, a woman's fertility plummets. Physicians can now diagnose and often treat successfully the causes of infertility in 85% of these infertile couples. But the remaining 15% are an enigma: There is as yet no scientific explanation for their infertility.

"They have what we call 'unexplained infertility,' " says Sandra Carson, a reproductive endocrinologist at Baylor College of Medicine in Houston. "Everything looks good—the woman's reproductive tract is healthy, the man's sperm count is fine—but for some unknown reason, the woman does not get pregnant." Discovering why has become a top priority among reproductive specialists.

Such researchers are pursuing a number of hot leads, from possible genetic factors involved in infertility to the silent role that low-grade inflammations caused by sexually transmitted diseases (STDs) and other disorders may play in both male and female reproductive health. In fact, the link between STDs and male infertility has never been fully investigated—yet scientists are optimistic that if the connection is confirmed, they may be able to offer possible treatments in the not-too-distant future.

Research along these lines could do much to help ease some ethical problems that have developed as infertile couples, who are often understandably desperate, turn to physicians who frequently don't have a firm basis for recommending a treatment. "Unfortunately, many things we do in infertility treatments are not scientifically based, but are done empirically," says Joseph Hill, a gynecologist and reproductive biologist at Brigham and Women's Hospital and Harvard Medical School in Boston. "There are people who will try one treatment after another without any solid reasons for doing so," he says. Some of this knowledge gap may, however, be filled by a major study, recently funded by the National Institutes of Health, at six universities to determine which therapies are most effective.

This combination of basic research into the causes of infertility and comparative studies of treatments is taking on a new urgency, as researchers fear that the number of infertile couples in the United States will increase as a result of the explosion of STDs. Recent data show that the highest rates of



Young blood. Data from 16 San Francisco clinics show rates of chlamydia infection are highest among the youngest women.

infection with many STDs are found among the young—aged 15 to 19—and in some cases even those aged 10 to 14. "Overall, young people between 15 and 19 years old are at the greatest risk of contracting an STD, regardless of their socioeconomic background, race, or religion," says Penelope Hitchcock, chief of the Sexually Transmitted Diseases Branch of the National Institute of Allergy and Infectious Diseases. And because STDs caused by some agents, such as the herpes simplex virus type 2, human papillomaviruses, and human immunodeficiency viruses, are currently incurable, "a huge pool of diseases that linger forever" is being created, says Hitchcock.

STDs are one of the prime causes of infertility in women largely because they often go unnoticed until they do real damage. "Particularly with chlamydial infections there's often no pain, so the woman goes untreated," says Hitchcock. While the disease may initially infect a woman's lower genital tract, if left untreated, it can move into the fallopian tubes, causing pelvic inflammatory disease (PID), which can lead to scarring and tubal blockage. "A woman's chances of becoming pregnant are diminished with each incident of PID," says Luigi Mastroianni, director of the division of human reproduction at the

University of Pennsylvania Medical Center. "After the third incident, her chances are finished, short of in vitro fertilization."

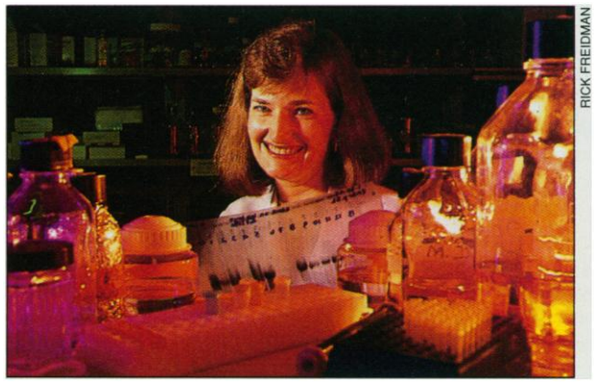
While a chlamydial infection can be diagnosed and treated, and the tubal scarring can sometimes be repaired surgically, the organism can continue to cause damage long after an apparently successful treatment. Researchers are confronting the disturbing possibility that this condition (and other STDs) may cause a low-grade, chronic infection in the uterus that creates a hostile environment for implantation of the embryo. "We usually think of tubal infertility as the major result of these diseases," says Peter Rice, a physician and immunologist at Boston University School of Medicine. "But it may be that they (and particularly chlamydia) may also cause problems with the uterus." As evidence, Rice notes that women with a history of chlamydial infections have "relatively high [pregnancy] failure rates" even with in vitro fertilization. "The egg is perfectly well fertilized and should implant, but it doesn't," he says.

Rice and Hill, who are investigating this problem together, hypothesize that initial bouts of the disease may not always be cleared up completely. "In some patients, even after treatment, part of the protein code of chlamydia still resides in the reproductive tissues," says Hill. This residue causes chronic inflammation in the uterus, which in turn brings a flood of type 1 T helper immune cells (T_H1). Hill says that recent studies by him and his colleagues have shown that T_H1 is a "bad actor" when it comes to pregnancy, probably because of the chemical signals, or cytokines, that T_H1 generates.

Under other circumstances, production of T_H1 cytokines would be a welcome event—something like the cavalry coming to the rescue. T_H1 cytokines drive the cellular arm of the immune system, producing interferon gamma and tumor necrosis factor (TNF)—good agents for fighting disease, says Hill, but often lethal to the embryo. "They interfere with implantation events and the development of the embryo and may cause spontaneous abortion." Hill's preliminary research indicates that 50% of women with unexplained recurrent miscarriages appear to generate a T_H1 cytokine response to placental tissue.

And while some researchers do not regard spontaneous abortion as part of the spectrum of infertility, Hill and others do, especially in women who have had multiple miscarriages. "As physicians, we often divide fertility into pre-conception, postconception issues," says Robert N. Taylor, a reproductive endocrinologist at the University of California, San Francisco, who is investigating the role of endometriosis in miscarriages. "But for women with recurrent pregnancy loss, the outcome is the same: They fail to have a family."

Although infertility is often deemed a woman's problem, "silent" infections by STD agents may play a significant role in unexplained male infertility. Normally, both a man's immature and mature sperm cells are largely protected from cells of the immune system, which can kill sperm. It is not unusual, however, for many reproductively healthy men to have some white blood cells in their semen. But problems occur when there are more than 1 million white blood cells per milliliter of semen, a condition known as leukocytospermia, says Deborah Anderson, an immunologist at Brigham and Women's Hospital and Harvard Medical School and Hill's colleague and wife. "The incidence of this disorder varies around the world," says Anderson, with the condition being particularly prevalent in Europe, and North and South America. "In Boston, as many as 20% of all infertile men have this condition, while in China, it's about 2%. We think that reflects the incidence of STDs."



RICK FREIDMAN

Black-and-white issue. Cynthia Morton is pursuing a gene that causes uterine fibroid tumors, which can cause infertility and are three times as likely to strike black women as they are whites.

Anderson hypothesizes that the male reproductive tract may serve as a harbor for a variety of such pathogens. As in women, these may be clinically silent, but in fact cause a low-grade inflammation that leads to infertility. "This is an overlooked, sleeper cause of male infertility," she says. "But there is a direct association between the presence of elevated levels of white blood cells in the semen and poor semen parameters, such as motility and failed egg penetration tests." Some men also harbor T cells and macrophages (immune cells that attack bacteria, fungi, and certain viruses) in their semen. "These leukocytes are full of bioactive products, such as free oxygen radicals and cytokines, which are used to kill invading organisms," Anderson explains. "But they have a bad effect on sperm as well."

Anderson recently launched a 3-year study of men with low-grade reproductive tract inflammations and infertility to determine whether there is a correlation. Specifically, her team is extracting DNA and RNA from the men's semen and searching the extracts via the polymerase chain reaction for the presence of any pathogens: "We want to see if a disease-causing micro-organism is there and at what levels." It may be that even a low-grade infection is sufficient to trigger an immune response lethal to sperm, Anderson thinks. Because antibiotics may not be effective in treating these reactions, particularly if the infection is latent or of viral origin, Anderson and her colleagues say an alternative is to try anti-inflammatories or immunosuppressants to see whether that might help restore normal levels of fertility.

STDs may not be the only trigger of silent inflammations—and subsequent infertility—particularly in women. Taylor suspects that endometriosis, a condition in which the mucosal membrane of the uterus grows abnormally, causing lesions, ovarian cysts, and sometimes scarring on the fallopian tubes, may do the same. "There is still some debate about whether endometriosis is a cause of infertility or something that just goes along with it," Taylor notes. "But most of us in the field think there is more than a casual connection."

Taylor thinks endometriosis starts early in a woman's life—in late adolescence—as a result of "retrograde menstruation," where the flow backs up through the uterus and fallopian tubes. "This is fairly universal," he says, "but it seems that in some women, the immune system cannot adequately cope with the spillage of cells into the peritoneal cavity, leading to the lesions." The lesions themselves then initiate a low-grade inflammatory response, Taylor hypothesizes, which somehow impairs ovum-sperm interactions: "We think that once the endometriosis has become established, it starts secreting signaling molecules that attract inflammatory cells, such as macrophages. As these accumulate, the macrophages secrete chemical factors, such as interleukin-1 [IL-1] and [TNF], that could interfere with fertilization." In studies on rodent models, both IL-1 and TNF proved toxic to embryonic development, Taylor notes. "This research is in its infancy," he adds, "but if we could identify the factors the endometriosis cells make that cause inflammatory reactions, we might be able to develop inhibitors to those factors," and so treat this cause of infertility.

Genetics may also play a significant role in the silent infertility caused by STDs and endometriosis—a role that some researchers are now investigating with increased urgency. "There's growing evidence that women with a certain type of HLA [human leukocyte antigen] are at higher risk for contracting STDs," explains Hitchcock. In other words, their immune response is not strong enough

either to fend off the invading virus or to kill it completely, subsequently leading to a low-grade inflammation and infertility. Researchers hope to eventually be able to identify such genetically predisposed women and offer advice and counseling before they become sexually active.

A genetic predisposition may also play a role in endometriosis, says Taylor, causing certain women to have the disorder while sparing others. And defective genes appear to be linked to uterine fibroid tumors, another possible cause of infertility, says Cynthia Morton, a molecular cytogeneticist at Harvard Medical School. "It may be that as many as 80% of all women have these in their reproductive years," she notes. "But no one knows if a woman is born with this predisposition, although there is some indication that they [the tumors] run in families." African-American women, for example, are at least three times more likely to develop fibroid tumors than are white women.

Such tumors are hormonally influenced, sometimes appearing in late adolescence, and typically regressing when a woman enters menopause. While they are benign, they can lead to abnormal uterine bleeding and pelvic pain; the ultimate treatment is hysterectomy. "Every day, women's uteruses are being removed because of these; they are a major factor in women's health," Morton says. They can also cause infertility, although how they do so is not known. It may be, says Morton, that the tumor poses an anatomic problem, preventing the zygote from implanting in the uterus. Alternatively, she adds, the tumor may "change the biochemistry of the uterine environment so that it is not receptive."

In some women, fertility can be improved via myomectomy, which involves surgically removing the tumors. But in others, this strategy fails for reasons that remain unclear, as there has not been a controlled study to determine which infertile women benefit from such a procedure. "It's a lot like back surgery," says Morton. "Some get better; some don't."

Ultimately, by understanding the genetic background of the woman and the genetics of the tumor itself, Morton hopes to offer a better form of treatment. "The dream is to devise a way to keep tumor growth under control, or to understand the way they regress during menopause, and use that to halt their growth or eliminate them," perhaps facilitating pregnancy and avoiding hysterectomy. Morton's recent identification of a gene that is translocated in fibroids, work that is as yet unpublished, is a first step in that direction.

A simpler solution for some cases of unexplained infertility may be at hand if the hypothetical link between silent STDs and infertility is confirmed. "That's the first step," says Rice, "to ascertain if the pathogen is there at all." Physicians might then treat the condition with immunosuppressants or anti-inflammatory drugs, he and his colleagues suggest. There's no point in trying to kill the pathogen, "since it's already dead," Rice continues. "What's left is the detritus, and that's what's causing the problem. So the best thing we've thought of is to tone down the immune response" to this remnant.

Hill already has plans to test one such therapy in patients with high levels of T_H1 cells in their uteruses. "We have unpublished data that certain immunomodulating agents will block the production of T_H1 cytokines" in the lab, he says. "Now we want to test it in vivo." Such trials should begin within the year.

Although similar trials for men with silent STDs are several years away, Anderson notes that if and when they do begin, researchers will have a bounty of drugs to test: "The field of immunology therapy is progressing so rapidly that it may be that a drug that's now being developed for rheumatoid arthritis or an allergy [conditions that also involve inflammation] can also be applied to infertility." If so, it may take only a handful of pills—instead of a series of hit-or-miss therapies—for physicians to help a couple produce their bundle of joy.

–Virginia Morell

HUMAN IMMUNODEFICIENCY VIRUS

Women: Absent Term in the AIDS Research Equation

When AIDS first surfaced in the United States more than a decade ago, it was dubbed "gay-related immunodeficiency disease" (GRID) because it appeared to afflict homosexual men specifically. But as more cases were diagnosed, it became evident that the name of the disease had to change: Not everyone who developed "GRID" was a gay male—or even a male.

Yet in some ways, women have remained an unrecognized part of the AIDS equation—at least until recently. Patricia Fleming, White House AIDS policy coordinator, says she was taken aback when she first looked into HIV research regarding women while working as a congressional staffer in 1992. "It was appalling to see that while so much progress was being made in AIDS research, so little focused on women," says Fleming. "I think women were neglected from the beginning of the epidemic." Most early studies in women, for example, were largely restricted to preventing transmission of HIV from an infected mother to her child.

That neglect is all the more surprising because women's presence in the epidemic has been growing steadily. Today, gay men account for more than 50% of the total AIDS cases reported in the United States, but women are 13% of the cumulative total. And the number of women with AIDS in the United States is increasing fast: from 7% of the new cases reported in 1985 to 18% last year. And in developing countries, where heterosexual sex is far and away the main mode of transmission of HIV, the World Health Organization estimates that nearly half of AIDS cases are among women.

Some researchers argue that even these estimates understate the disease's impact on women. Penelope J. Hitchcock, chief of the sexually transmitted disease (STD) branch at the National Institute of Allergy and Infectious Diseases (NIAID), argues that globally, "we have more women infected than men." Although there is no solid census of HIV infection around the world, Hitchcock is confident her assertion is accurate. For one thing, several studies that have followed heterosexual couples in which only one partner was infected initially have shown that women are at least twice as susceptible to HIV infection as men are.

During the past 3 years, however, there has been a concerted push to change the skewed focus of AIDS research, with the launch of several major efforts to expand scientific understanding of how HIV affects women. These studies are beginning at the beginning: tracing the course of the disease through large cohorts of women. Although such "natural history" studies in gay men have revealed much about the disease, HIV may affect women differently—but whether it does is still unknown, because large natural history studies hadn't been carried out in women.

"It was appalling to see that while so much progress was being made in AIDS research, so little focused on women."

—Patricia Fleming

To address this deficiency, in 1993, NIAID launched the Women's Interagency HIV Study, a multiyear project that will follow 2000 HIV-infected women and 500 others at high risk of becoming infected. Data should