that specifically affect gender differences in heart-disease risk have not yet been found, several groups are looking for them as a part of a broader investigation of genetic influences on cardiovascular disease. If defects in such gender-specific genes are found, functional copies of the genes might ultimately be administered via one of a number of forms of gene therapy for heart disease that are currently under development.

Former NIH Director Healy says she is encouraged by the blossoming of all these studies into gender-specific mechanisms of heart disease—a development she believes was stimulated by the WHI project she initiated at NIH. "Let's face it, the way to get scientists to move into a certain area is to fund that area," Healy says. "And the WHI brought money to the table and attention to the issue."

But Healy isn't by any means satisfied. She calls the studies now in progress "beginnings." "But in the case of heart disease, she says, "we still have a long way to go."

–Trisha Gura

Trisha Gura is a reporter at the Chicago Tribune.

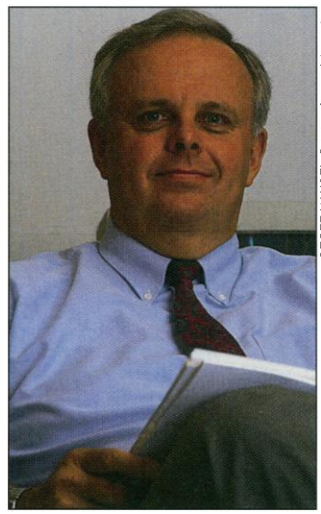
IMMUNOLOGY

Zeroing In on How Hormones Affect the Immune System

Inject an immunized male cockroach with a honeybee's venom, and chances are that cockroach will bite the dust. Do the same thing to a female cockroach, on the other hand, and she will almost certainly recover. That stark difference in outcomes, immunologists say, illustrates a basic disparity between the male and female immune systems, a difference that extends all the way from cockroaches to humans: Females are immunologically stronger than males. "In the eyes of God or biology or what have you, it is just very important to have women," quips Norman Talal, an immunologist at the University of Texas Health Science Center in San Antonio. "And so they are hyperprotected.

Adds Noel Rose, an immunologist at Johns Hopkins University: "It's a well-documented fact: Women are simply more immunologically talented than men." Yet such talent is a sword with two sharp edges. While a woman may be less susceptible to infections, she is far more likely to contract an autoimmune disease, such as systemic lupus erythematosus or multiple sclerosis—diseases in which the immune system turns against its own. Indeed, nine out of 10 lupus sufferers are women; overall, researchers estimate that 75% or more of autoimmune disease patients are women.

In seeking explanations and cures for these disorders, scientists have begun unraveling the mysteries of the female immune system itself. "By showing us what goes wrong, they give us a marvelous window on the functioning of a normal immune system," explains Joan Merrill, a protein chemist in immunologist Robert G. Lahita's lab at St. Luke's Roosevelt Hospital in New York, where several autoimmune disease studies are under way. Through that window, researchers like Merrill have come to see "that a woman's sex hormones and gonads play a central role in regulating her immune system and vice versa," she says. These studies have demonstrated that a woman's reproductive system and immune responses are so tightly interwoven that one researcher terms it "a feedback system"—but one that varies according to a woman's age, what point she is at in her monthly cycle, and whether or not she is pregnant.



GEOFF HANSEN/DARTMOUTH COLLEGE

Lack of study. Charles Wira says the female immune system has been "tremendously underinvestigated."

Although the idea that hormones affect the immune response has been around since the late 19th century, only now are researchers beginning to closely scrutinize the cyclic nature of the female immune system. "It is an area that has been tremendously underinvestigated," says Charles R. Wira, a reproductive immunologist at Dartmouth's Medical School. Investigations into this area, which are now picking up speed, are vital to understanding women's health, because they have implications for everything from drug testing to the timing of vaccinations to treating certain kinds of infertility problems to administering chemotherapy to finding treatments—and cures—for many autoimmune diseases.

The basic observation that women's immune responses are stronger than those of men has been confirmed by a host of studies. It's true in both main branches of the immune system: the cell-mediated (which controls the killer T cells) and the humoral (which controls the antibodies produced by B cells). For example: Female mice will reject a foreign skin graft faster than males will; male mice and guinea pigs that have had gonadectomies show increased resistance to infections; and in both human and animal models, females have higher circulating levels of the major immunoglobulins (IgG, IgM, and IgA). As early as age six, the levels of IgM in human females exceed those of males of comparable age.

At the heart of the female cycle—and the yin-yang of male and female immune responsiveness—lies that key biological difference: reproduction. "Women have to make the offspring to carry on the species," says Charles J. Grossman, an immunoendocrinologist at Cincinnati's Veterans Administration Medical Center. "So it's not surprising that they have a better [immune] system." To become pregnant in the first place, he adds, a woman must be healthy, which may explain why her immune responses are stronger than a man's. And once pregnant, she must "overcome the stresses of a long gestation; then after the child is born, she has to face the stresses of nursing and protecting that child. A man doesn't have to do any of these things."

Indeed, while a woman's estrogens keep her immune response "revved up," as Grossman puts it, a man's androgens tend to suppress his immune system. The male's system is also subject to little variation after puberty, while the woman's spikes up at puberty, is depressed during pregnancy, returns to its previous high level after pregnancy, and is lowered again at the onset of menopause.

Yet, paradoxically, the mother's revved-up immune system places the fetus at risk, because it is in a sense a foreign body and therefore liable to be attacked. And that, Grossman and others say, is where the cycling sex hormones come into play. "Studies have shown that prior to ovulation, the sex hormones up-regulate the immune system," says Grossman. Estrogen, he suggests, acts to increase secretions of both prolactin and growth hormones, which, in turn, increase the production of T and B immune cells—thus giving the woman an added boost in fighting off viruses or bacteria.

But in the second half of a woman's cycle, after ovulation, the level of estrogen drops, while progesterone is increased, regulating her immune response. "The immune system

has been tailored so that it protects against invading bacteria and viruses," explains Wira, "but does not destroy sperm—or the fetus." Thus, the increase of progesterone, the dominant hormone during pregnancy, along with other immunoregulatory factors, suppresses the immune system's functions so that the fetus is not rejected.

So suppressed is a woman's immune system during pregnancy that she is at great risk of contracting a variety of viruses, including rubella, varicella zoster, influenza, and viral hepatitis. But after she delivers the baby, the woman's immune system rebounds to its normal level, giving her the added protection she needs while nursing and caring for a newborn. During nursing, the mother is also "transferring some of her antibodies to her baby," notes Grossman, "so she needs that higher level to protect herself and her infant" until the baby is able to fight off infections on its own.

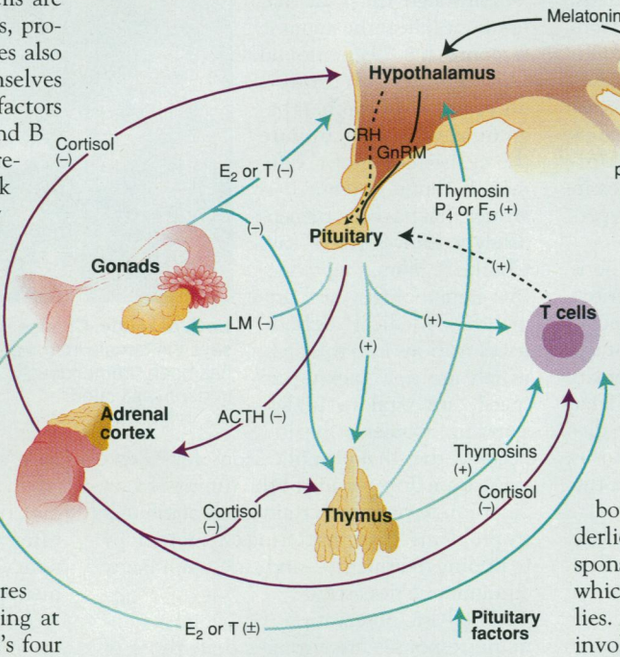
While researchers have yet to work out all the pathways and mechanisms sex hormones use to accomplish these varied tasks, they do know that some immune cells are equipped with receptors for estrogens, progestins, and androgens. Recent studies also suggest that the female gonads themselves may be involved in the production of factors that regulate the immune cells (T and B cells, and macrophages) found in the reproductive tract. "People used to think of the uterus in a rigid way as basically a muscle—just a safe container for babies," says Sara E. Walker, a rheumatologist at the Veterans Administration Medical Center in Columbia, Missouri. "It is that, but there is also evidence that the uterus is producing cytokines and other immune factors. Whether it does this independently of the brain, we don't know."

Wira's studies of the reproductive tract in female rats show just how finely tuned are the correlations between female reproductive structures and immune responses. "We're looking at the mucosal secretions of the female's four major reproductive organs—the vagina, cervix, uterus, and fallopian tubes," he explains. "Each of these has a different biological function, and we think they are immunologically distinct as well." For example, his research has shown that 24 hours before ovulation, levels of estradiol (the primary estrogen) in the rat's blood are elevated, pushing the antibodies in uterine secretions to their highest level. "That's probably important for cleansing the uterus, to destroy any bacteria that might be present so that it is prepared for fertilization and implantation," he says.

Yet in the cervix and vagina, "estradiol does exactly the opposite; it inhibits the immune response," says Wira, "presumably so that the sperm are not killed." As to why the same hormone could have opposite effects in different organs, Wira says, "That's the $64 question." He suspects the varying function is controlled by genes—and has some evidence that proteins and mRNA are involved as well. In any event, he adds, "it's a highly orchestrated series of events." Wira is now leading a National Institutes of Health–funded 4-year study to see whether this symphony of effects also takes place in humans.

If it does—as Wira suspects—then the varying levels of mucosal immune responsiveness can greatly affect a woman's health. "Depending on the stage of the cycle, a woman may be more susceptible to sexually transmitted diseases [STDs], including HIV," notes Wira, "while at other times she may be more protected." Such immune vagaries could also influence a woman's response to drugs or vaccines, Wira suggests, particularly those under development for STDs. "There may be optimal times for giving a vaccine to a woman, when you would get a better immune response," he says.

Gordian knot. Recent research has detailed the very complex interactions between hormones and the immune system; (+) indicates stimulatory effect; (–), inhibitory; (±), variable.



In addition, because of a woman's cyclic endocrinological nature, Wira and other researchers emphasize that pharmaceutical trials should always include separate studies for women within the same trial—something that was not done, even on female rats, until about 5 years ago. "Women metabolize drugs differently than do men," says Arlene Bardeguez, an obstetrician and gynecologist at the New Jersey Medical School, "and frequently drugs, such as AZT, are more toxic in women than in men." Women, for example, have a different distribution of body fat; in addition, women tend to be smaller and to have less muscle mass relative to men. Thus, the concentration of the drug might be too high if a physician used the same dosage in a woman as he does in a man.

The strong influence of hormones on a woman's immune system doesn't just have a bearing on drug trials. It also helps explain why women are more susceptible to autoimmune disease. "If you start with an immune system that is normally revved up [because of the hormones involved], and then you get some kind of [hormonal] imbalance," you're likely to develop some type of autoimmunity, according to St. Luke's Lahita. As an illustration of this point, women with lupus have increased levels of estradiol, which in turn leads to increased levels of circulating antibodies. "Women with lupus have very low levels of male hormones and very high levels of estrogens; they are, in a sense, superwomen," says Lahita. But the result is that the "rheostat for controlling the immune system doesn't work; it's like a light that's left on bright all the time. A normal woman's system can turn the lights down." Very few men suffer from lupus, presumably because of the protective effects of testosterone, which keeps the male immune system humming at a steady, if lower, level. "Testosterone is very protective of men when it comes to these autoimmune diseases," says Lahita. So it puzzles him and other researchers why any males develop lupus—as some do. "The men who do get lupus aren't at all feminized; they are hirsute and very fertile. I haven't a clue just now."

Lahita and others suspect that in both men and women a genetic defect underlies the malfunctioning immune response, because autoimmune diseases (of which there are at least 80 types) run in families. Because a variety of genes seems to be involved—and any number of defects—not every member of a family is necessarily afflicted with the same autoimmune disorder.

For example, a mother may have lupus, while her daughter has rheumatoid arthritis or endometriosis (some forms of which are suspected of being caused by an autoimmune response), and a son has Coxsackie myocarditis (an often deadly inflammation of the heart muscle). "When you put all the family members together and get histories on how many relatives have autoimmune diseases or simply abnormal antibodies in their blood, then it looks like there is an autoimmune gene or genes," says Frank Arnett, a rheumatologist at the University of Texas.

But if a variety of genetic defects under-

ILLUSTRATION: K. SUTLIFF
SOURCE: CHARLES J. GROSSMAN

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.

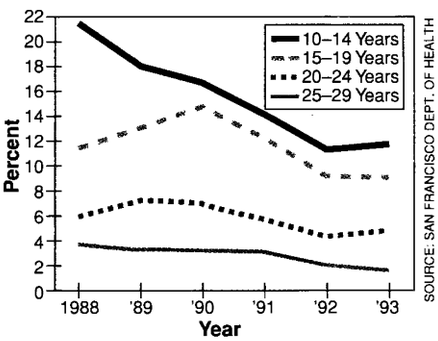
In the United States alone, researchers estimate that 15% of couples are involuntarily infertile. In the prime childbearing years, from ages 20 to 30, the causes are roughly divided between men and women. After 30, however, the balance shifts toward the female side of the equation, as the natural aging 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 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.



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

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