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 Morton's recent identification of a gene that is translocated in fibroids, work that is as yet unpublished, is a first step in that direction.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

begin to be made available this fall. NIAID is also collaborating with the Centers for Disease Control and Prevention (CDC) in a natural history investigation about half as large called the HIV Epidemiology and Research Study. "Most of what we're finding is reassuring the findings in men are translating pretty well to women," says CDC epidemiologist Ann Duerr, co-author of the recently published book *HIV Infection in Women*.

Regardless of whether the natural history studies show that the overall course of the disease is different in women, there are two aspects of HIV and AIDS research where the results are clearly specific to women: how the virus is transmitted from men to women and how agents such as vaginal microbicides might prevent infections. And work in those areas is also taking off.

David Phillips, a virologist at the Population Council in New York, is one of the few researchers who has studied transmission of HIV to females, and his assessment of the state of the art is blunt and downbeat: "We really don't know how transmission occurs." Researchers now trying to find out just how women become infected are focusing on two main questions: Does HIV enter the body inside a cell or as free virus? And what, exactly, is its point of entry?

Phillips has developed an elegant test tube model that may help answer both questions. Its starting point is the fact that the

Fighting Transmission of HIV to Women

The spermicide nonoxynol-9 (N9) has received a great deal of attention as a potential vaginal microbicide to block the transmission of HIV from men to women (see main text). But N9 is far from the only compound being tested for this purpose. Most of the experimental compounds, which operate by a variety of mechanisms, are selected because they work against a wide range of sexually transmitted diseases (STDs) in test tube experiments. This broad attack, researchers hope, may ultimately have both direct and indirect success against HIV: The compounds might thwart the AIDS virus while simultaneously reducing the likelihood of other STDs that cause ulcers and inflammation that pave the way for HIV infection.

Some of the new products are being tested by companies established specifically for that purpose. Biochemist David Malamud of the University of Pennsylvania, for example, started a company called Biosyn to test a new generation microbicide, C31G. Malamud says the product has spermicidal properties and is active against a broader spectrum of pathogens than N9. Like N9, C31G is a detergent that cripples microbes by disrupting their outer membranes. An initial safety test of a vaginal suppository of the compound is being tested in 10 women.

Over at the Population Council, virologist David Phillips has received approval from the U.S. Food and Drug Administration to launch initial safety studies of a vaginal microbicide that exploits Phillips' findings that male-to-female transmission begins when HIV-infected cells from the man adhere to vaginal epithelial cells. In test tube studies, Phillips has shown that compounds called sulfated polysaccharides, such as dextran sulfate, can inhibit this adhesion step. He believes sulfated polysaccharides may work by binding to HIV and fooling it into thinking that it has found a cell surface to infect. It's also possible that these molecules cause microbes to carry a negative electric charge, he says, which would repel other negatively charged biological molecules.

San Diego's Lidak Pharmaceuticals is focusing on a compound called n-Docosanol. Unlike the sulfated polysaccharides, n-Docosanol allows viruses to bind to their target cells; but it stops them from doing damage, according to immunologist and Chief Executive Officer David Katz. He and his co-workers have shown that n-Docosanol probably inhibits viral replication by interfering with uncoating, the process whereby the virus attaches to a cell and unloads its genetic material.

In a preliminary monkey experiment by Lidak researchers and Christopher Miller of the University of California, Davis, n-Docosanol protected five of six animals from a subsequent vaginal "challenge" with SIV, the monkey AIDS virus. Two untreated control animals, in contrast, became infected with SIV following the challenge. Katz says he anticipates safety trials in humans next year.

At Johns Hopkins University, biophysicist Richard Cone is trying a different strategy: developing a microbicide that exploits the vagina's natural ability to fend off pathogens. In healthy women of reproductive age, vaginal secretions are mildly acidic, with a pH ranging from 3.4 to 6 (pH 7 is neutral). Harvard University's Deborah Anderson and others have shown that HIV is inactivated in such an acidic environment. Semen is also disrupted in acidic environments, a hurdle nature has cleared by making semen a buffering agent: Within 8 seconds of ejaculation, the mildly alkaline semen raises the vagina's pH to neutral. This, explains Cone, offers STD pathogens a "window of opportunity" to cause an infection.

With his company, ReProtect, Cone is formulating a buffering gel that will maintain the low pH of the vagina even when semen is present. He says this gel, made with agents that are already used in vaginal products, will not disturb the natural flora of the vagina, nor will it irritate mucosal surfaces. He hopes to begin human tests within a year.

Leonard Jacob, CEO of Pennsylvania's Magainin, says his company is also developing a vaginal microbicide that alters pH—but not that of the vagina itself. Magainin is working with squalamine, a steroid-based molecule that inhibits a "sodium-hydrogen exchanger" on a cell's surface, a system that determines the cell's pH. "When you inhibit that system, you temporarily stop cell growth," Jacob says. Squalamine is an attractive microbicide because, he says, preliminary evidence suggests that altering the cellular pH prevents HIV's ability to infect the cell—without harming the cell. If all goes well, Magainin hopes to start clinical trials of squalamine next year, too.

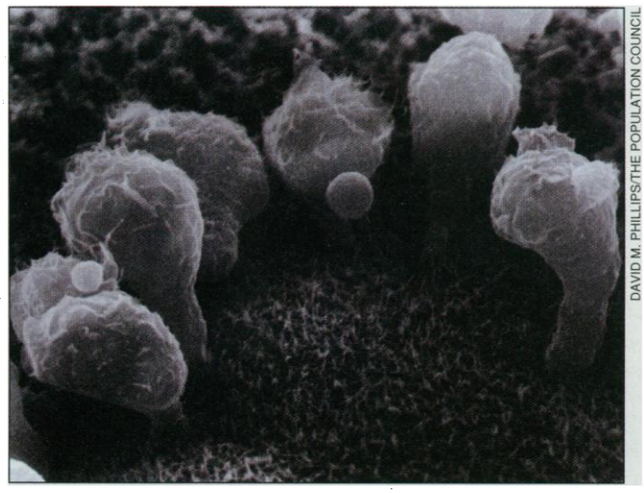
As these examples show, there's plenty of activity centering on developing new compounds to kill harmful microbes. But some researchers are more concerned about how to deliver a vaginal microbicide than they are about developing new compounds. "Drug delivery is really the crux of the matter," argues George A. Digenis, a medicinal chemist at the University of Kentucky. Digenis is working on a tablet or capsule that can release a variation of N9 within 3 minutes of being inserted into the vagina—and can continue delivering the compound for as long as 6 hours. Digenis says clinical trials of this microbicide are slated to begin in about 3 months.

Pediatrician and STD expert Lawrence Stanberry at the Children's Hospital in Cincinnati stresses that vaginal microbicides are urgently needed to counteract the one-two punch of STDs and HIV. "Even if [vaginal microbicides] are only 50% effective and don't work on HIV, from a public health point of view, a modest investment can have a major public health impact," he says. And that is why, finally, more and more researchers are beginning to bank on them as a potentially simple way to slow an epidemic that is dauntingly complex.

–J.C.

cells on the surface of the female genital tract, the epithelial cells, lack a receptor called CD4.

AIDS is characterized by the slow, steady depletion of white blood cells, or T lymphocytes, that have CD4 receptors. HIV readily infects CD4 cells because its envelope has a protein that dovetails with the CD4 receptor. Because vaginal epithelial cells lack CD4s, many researchers believe that women primarily become infected when they have lesions or inflammation of their vaginal or cervical epithelia (which attract T cells). Support for this notion comes from studies showing that women who have STDs, which cause lesions and inflammation, are at a much higher risk of HIV infection.



DAVID M. PHILLIPS/THE POPULATION COUNCIL

Deadly contact. HIV-infected T cells adhering to an epithelium, where they bud AIDS virus particles onto the epithelial surfaces.

Phillips questions the common wisdom that women are infected only via CD4-bearing cells, however. Using epithelial cell lines derived from the cervix, Phillips and his co-workers have shown, by means of electron micrographs (EMs), that HIV can infect CD4-negative cells and that HIV inside cells is much more transmissible to the epithelial cells than free virus is. Their EMs dramatically show a sequence of events that begins when HIV-infected T cells attach to epithelial cells. HIV is then shunted down to the bottom of the T cells and migrates into the gap between the T cells and the epithelial cells. Next, the epithelial cells effectively swallow the HIVs by a variety of different mechanisms—all without benefit of the CD4 receptor.

Deborah Anderson, who specializes in the immunology of the reproductive tract at Harvard's Brigham and Women's Hospital in Boston, says Phillips's work "is probably the most innovative and exciting research on this subject of HIV transmission." And her lab has now corroborated many of his studies using cells and tissues freshly taken from patients, a more true-to-life approach than the cell lines he relied on.

Although many researchers in the field join Anderson in praise of Phillips's work, others remain skeptical. Virologist Christopher Miller, a primate researcher at the University of California (UC), Davis, says he doesn't think the evidence for epithelial cell infection is strong. "I'm a believer in CD4-positive cells," says Miller, "so you have to look at CD4s at the site of infection."

And, in fact, Miller has evidence to support his belief in the importance of CD4-positive cells. In the November 1992 issue of *Laboratory Investigation*, he and his colleagues reported taking tissue samples from the vaginal and cervical mucosa of 14 rhesus macaques at necropsy and analyzing the cell types. In the tissue directly under the epithelial cells, they found many CD4-bearing macrophages and Langerhans cells, both key immune system actors. And they showed that at different phases of the menstrual cycle, the epithelial layer can swell or thin. Theoretically, a microlesion in the epithelial layer at the right time of the month might open a path for HIV to reach CD4-bearing cells. Miller says both Langerhans and macrophages make "good candidates" for being the target cells.

Unlike Phillips and Anderson, Miller thinks infected cells may have a far smaller role in infecting females than does virus simply floating free in blood or semen. "I don't think it's clear at all that infected cells are the things causing infection," he says. Miller cites an experiment of his in female macaques in which free SIV, the simian cousin of HIV, easily infected the monkeys when small doses were placed in their vaginas. In contrast, when Miller put whopping doses of cells infected with the same virus into monkey vaginas, no animals became infected. Miller says he knows of no researcher who has vaginally infected a monkey using cell-associated SIV.

In addition to analyzing cells and their role in HIV transmission, researchers are attempting to clarify which region of the female reproductive tract is the likely point of entry. Epidemiologic studies have shown that women who have what is known as cervical ectopy—a natural state common in puberty and pregnancy that exposes fragile epithelial cells—are particularly vulnerable to HIV infection. This has led some researchers to conclude that the cervix is one of the primary sites for infection.

Yet Miller again has data contradicting that view. Although he doesn't rule out a role for the cervix, he has shown that he can completely remove the cervix and uterus of a monkey and still infect the animal vaginally. "The cervix isn't required for transmission to occur," Miller says flatly.

The kinds of questions Miller and others are wrestling with aren't merely theoretical, because the study of male-to-female transmission of HIV is one of those rare areas where the boundaries of basic and applied research blur. "If we understood more about transmission we could possibly prevent disease, which is what medical research is all about," says Phillips.

Perhaps the most tangible application—and one that's being tested now—is the development of vaginal microbicides that specifically target HIV. "We feel it's critical that chemical methods [to prevent HIV infection] be made available for women," says physiologist Nancy Alexander, chief of the contraceptive development branch at the National Institute of Child Health and Human Development (NICHD).

Although studies have proven that condoms are an effective way to prevent male-to-female transmission of HIV, many scientists have noted that women cannot control whether condoms are actually used. "Millions of women can't negotiate their partner's use of a condom," says Malcolm Potts, a family planning specialist at UC Berkeley, who for 12 years headed Family Health International and has long advocated the use of topical microbicides. A female condom is on the market, but researchers note that many women find it bulky and awkward to use. "It doesn't matter if it works if it isn't acceptable," says the CDC's Duerr.

The limitations of these approaches have led researchers to study a host of chemicals that might prevent HIV transmission if applied in the vagina (see box). The most famous is nonoxynol-9 (N9), a commercially available spermicide. Although some researchers are convinced N9 can prevent HIV transmission, others insist there are scant data supporting its efficacy, and still others point to data showing that N9 might increase the risk of transmission.

Much of the controversy surrounding N9 stems from a trial in Kenyan prostitutes suggesting that N9, in a vaginal sponge, caused genital ulcers that might have led to increased HIV transmission. To some researchers, the controversial study, reported in the 22 July 1992 *Journal of the American Medical Association*, tarnished N9's reputation wrongly, because either the sponge itself or the dose of N9 might have been the problem. "It's a detergent that will provide significant protection against many STD pathogens, and there's every reason to believe it will work against HIV," says Richard Coné, a biophysicist at Johns Hopkins University who in the June 1993 issue of the journal *AIDS* reported a study in cats showing that N9 can block

vaginal transmission of FIV, the feline version of the AIDS virus.

Epidemiologist Joan Kreiss of the University of Washington, who led the Kenyan study, is more circumspect. "The importance of [the Kenyan] study is that it made us all aware that N9 has potential adverse effects on women, and it emphasized the importance of doing randomized clinical trials before setting public health policy," she says.

Cone acknowledges that N9 has drawbacks, including destroying normal vaginal flora and leading to irritation. "You can look at N9 and see all of its difficulties—and we do," says Cone, who like a dozen other researchers is now working on developing new microbicides. "But in terms of women and the next decade, what should we be telling them? N9." NIAID's Hitchcock disagrees. "The data aren't there," she says. To obtain more data, an efficacy trial of condoms with and without N9 delivered to the vagina on a piece of film is being conducted in Cameroon by Ron Roddy and his colleagues at Family Health International; Kreiss is about to launch another efficacy study in Kenyan prostitutes using N9 in a gel.

One frustration for many researchers interested in developing microbicides is the paucity of available funding. This spring, NIAID awarded $1.5 million to HIV microbicide research; NICHD funds some of this research as well. But industry (apart from a few small biotechnology companies) has shown little interest in developing microbicides, because they would likely be sold cheaply; in addition, their makers might be vulnerable to lawsuits from women who become infected.

Some researchers are so concerned about the lack of corporate interest that they've started companies to remedy it. David Malamud, a biochemist at the University of Pennsylvania who has formed a company to make an anti-HIV microbicide, says it's a "serious problem" that big pharmaceuticals aren't involved. "I do believe the only way this will happen is for nonprofits to make fairly substantial investments," says Malamud. "There's an awful lot of lip service pertaining to women's health in general and to microbicides in specific."

While there clearly is much more that can be done to prevent HIV infection in women and to help those women who do become infected, it is equally clear that the scientific community is focusing on questions about women and HIV with an intensity that was woefully short just a couple of years ago. That, of course, is no guarantee that answers are right around the corner, but the stepped-up pace certainly increases the chances of understanding just how HIV specifically infects—and affects—women.

–Jon Cohen

OBSTETRIC CARE

New Push to Reduce Maternal Mortality in Poor Countries

One of the bonuses of living in a wealthy country is relatively safe childbirth. For most women living in poor countries, however, being pregnant is all too often a life-threatening condition. More than half a million women in those countries die each year from disorders associated with pregnancy and childbirth.

"We have a health crisis, a real gap in health care," says public health physician Beverly Winikoff, program director of reproductive health at the Population Council in New York City. "In developing countries, women are still dying of things they were dying of 50 years ago here." A tragic aspect of this situation is that the majority of loss of life is avoidable. But although the international community made maternal health a top priority in the 1980s, it has failed to staunch the tide of death and disease. Some experts think, however, that this picture of failure might change dramatically if a campaign to promote a controversial form of maternal care in developing countries continues gathering momentum.

The key to resolving this crisis for women in developing countries, say Winikoff and some other experts, is not preventive, primary health care, which for decades has been the focus of much of the help provided to developing countries by external agencies. Instead, they argue, the only way to stem the carnage caused by childbirth is to supplement primary care with emergency curative services that are unavailable to many women in developing countries. "You can't prevent [most] obstetric complications. They happen, they happen quickly, and they happen without warning—but you can treat them by providing emergency medical care," says epidemiologist Deborah Maine, director of the Prevention of Maternal Mortality Program at Columbia University School of Public Health's Center for Population and Family Health.

EVE ARNOLD/MAGNUM PHOTOS

Ear to the future. Most funding for maternal and child health has gone to preventative care; here, a nurse in South Africa checks a pregnancy.

At first blush, the type of care Maine is talking about seems out of the reach of poor countries. In those countries, health services are often minimal, and the emergency care facilities needed to deal with an obstructed birth or hemorrhage exist only in a few cities, far from the rural majority. But although money—or rather the lack of it—is the root of some of this evil, it's not the whole story. Indeed, according to two recent World Bank analyses, not only is emergency obstetric care affordable by all but the poorest countries, it's also one of the few truly cost-effective medical interventions. It's not money that's been the barrier to preventing deaths due to childbirth, say the experts, but the twin demons of political apathy and strategic misjudgment.

"There's been an acceptance that women [in developing countries] die in childbirth. In some ways, it's been considered quaint and traditional," contends Anne Tinker, senior health specialist at the World Bank. That attitude meant that women's health—except as a route to improving infant health—was for decades low on the list of health priorities for both governments and international health agencies.

In light of the statistics, that lack of concern seems surprising. Throughout the world about 15% of pregnant women suffer life-threatening complications. A woman's chances of dying from those problems, however, vary tremendously depending on which continent she calls home. An African woman has a one in 21 lifetime risk of dying from birth complications, a woman in Asia has a one in 54 lifetime risk, and a woman in Northern Europe has an almost negligible one in 10,000 lifetime risk.

Indeed, although infant mortality in developing countries is a subject of great concern among health professionals, the discrepancy between the rich and poor countries is up to 10 times higher for maternal mortality than it is for infant mortality. And the real killer is complications of pregnancy. Diseases exacerbated by pregnancy, such as malaria, account for some maternal deaths. But the biggest hazards—accounting for up to 75% of all deaths are obstetric emergencies, predominantly hemorrhage; septic abortion; eclampsia (convulsions and coma trig-