"This is the most exciting paper that has come out in the last year," says Thomas Jefferson's Artlett. "To me it says these cells are definitively involved." Ann Reed's team at the Mayo Clinic has similar results; her group isolated persistent maternal cells from dermatomyositis patients and showed that they react against the patient's tissues.

Even if foreign cells are shown to respond to the patients' tissues, however, most researchers agree that they can't be carrying out the entire attack themselves; there just aren't enough of them. "Scleroderma looks a lot like graft-versus-host disease," says William Reed, "but the levels of cells you find in those patients is nothing like what you have in graft versus host. Something is missing."

"My premise is that they aren't doing the bulk of the destruction," says Ann Reed; "I think they are the initiator." Once the foreign cells have started an inflammatory reaction, she suggests, the patient's own immune cells are attracted to the scene, where they do much of the damage. Ann Reed is among those who believe that these intruding cells might play an important role in a number of autoimmune diseases. "People said, 'Prove it. Prove they are there, prove that they mean something.' We are slowly doing that. But it takes time."

Lest microchimerism get a particularly nasty reputation, Nelson points out that the majority of people who harbor foreign cells—whether from their children, twin, mother, or blood donor—are healthy. "This is likely to be a broad-based biological phenomenon," she says. "And the best guess, since it is common, is that it may have beneficial roles, it may have neutral roles, and just in selected situations such as a particular lineup of *HLA* genes across generations, it can become bad."

In her talk at the recent meeting, Bianchi of Tufts mentioned two bizarre cases that suggest that microchimeric cells can build tissues as well as attack them. One subject in Bianchi's thyroid study was a 48-year-old mother who had a goiter removed. To her surprise upon examining the removed goiter tissue, Bianchi discovered that one whole section of the woman's thyroid was predominantly male, presumably from her son. Bianchi cites another case, of a woman with hepatitis C who had a liver biopsy. "Part of her liver was entirely male," Bianchi says, "and it was surrounded by female tissue."

Bianchi suggests that, in cases like that of the woman with hepatitis C, circulating fetal stem cells might help repair damaged or diseased tissue. In some cases, rather than cause the disease, she suggests, "maybe the cells are responding to the disease. Wouldn't it be amazing if one of the benefits of being pregnant is that you get, as a reward, a second population of stem cells?" If so, that would be just one more way that mothers and children continue to take care of each other.

–MARCIA BARINAGA

NEWS

Research on Contraception Still in the Doldrums

A billion young people are heading toward their reproductive years, but few new birth control methods are on the horizon

While scientists are beavering away at improving human reproduction, commensurate efforts are lacking on how to curb the process. By 2020, about 1.2 billion people, or 16% of the world's population, will be entering their childbearing years. "We are about to have the biggest proportion of young people the world has ever seen; reproductive health services are about to be inundated by a tidal wave of teenagers," says population expert Felicia Stewart of the University of California, San Francisco (UCSF). "Frankly, I think we're not ready at all." Some 90% of those entering reproductive age will be in the developing world, where there's a particularly pressing need for new forms of fertility control that are cheap, safe, reliable, convenient, reversible, and culturally acceptable.

This should be "a major time for investment" in new forms of contraception, says Stewart, who was formerly in charge of population affairs at the Department of Health and Human Services. But contraception research, which had its heyday in the 1950s and 1960s, hasn't produced a major breakthrough since the introduction of the birth control pill. And there are still only two choices for men: condoms and vasectomy.

Only a handful of companies are engaged in research on new contraceptive methods. One is Schering in Berlin; another is Organon in West Orange, New Jersey, which has just launched a hormone-releasing vaginal ring (NuvaRing), approved in November.

Few options. A Gambian health care worker discusses contraceptive devices, demand for which is expected to grow.

CREDIT: LIBA TAYLOR/CORBIS

But very few others are striving for new breakthroughs. Big pharmaceutical companies left the field in droves in the 1970s, says Carl Djerassi of Stanford University, the father of the birth control pill. Now, he says, "of the 20 largest pharmas in the world, only two have any commitment" to new contraceptives: Wyeth, and Ortho, a branch of Johnson & Johnson. "The only work most are doing is minor modifications" of existing products, he says.

Most companies have been driven away by the same forces at work 2 decades ago: liability worries, tough government regulations in the United States and other countries, and concerns about profitability, a big problem for products where the greatest demand is in poor countries. That leaves governments, international agencies, and private foundations to pick up the tab—with the U.S. government being the number one provider.

Funding has been stagnant for decades. Tellingly, there are no up-to-date figures on global expenditures for contraceptive R&D, and no one has attempted a statistical roundup since the mid-1990s. As a result, there are no more current figures than those in a 1996 report by the Institute of Medicine,* which reported that, in terms of constant dollars, worldwide funding peaked in 1972. And a new report from Johns Hopkins University relates that donors would have to quadruple their efforts to fill the same proportion of contraceptive needs in 2015 as they do now.

Nonetheless, a trickle of products continues to flow into the market, such as the vaginal ring and a new skin patch for women. And a couple of promising new approaches

* *Contraceptive Research and Development: Looking to the Future*, 1996.

are coming down the pike, both carrying benefits beyond fertility control.

Microbicides

The AIDS epidemic has spurred new initiatives to develop spermicides that also act as microbicides against sexually transmitted diseases. The U.S. National Institute of Child Health and Human Development (NICHD) is currently running a seven-center clinical trial on BufferGel, a vaginal microbicide that is used with a diaphragm. Although compounds that kill germs almost always attack sperm, too, "it's hard to find something that's both that doesn't irritate the vaginal lining," says Diana Blithe of NICHD's Center for Population Studies, which is spending about $16.2 million a year on the project. Ironically, though, the nearby National Institute of Allergy and Infectious Diseases (NIAID) is spending far more—$44 million—on developing a microbicide that kills germs but does not disable sperm.

Clinical trials on BufferGel show why companies shy away from such research. It costs several million dollars a year to test its efficacy as a contraceptive, says Blithe. And, she notes, separate tests of its efficacy as a microbicide—being conducted at NIAID—are particularly difficult. Researchers have to target a population at high risk for sexually transmitted diseases, and to satisfy ethics requirements, couples must be advised to use condoms in addition to the gel. Huge numbers of subjects are needed because the only useful data come from women whose partners failed to don condoms. Blithe says that although diaphragms don't enjoy great popularity anywhere, the hope is that women might reconsider the method if the gel gains a reputation as an effective dual-purpose product.

Twofer for men

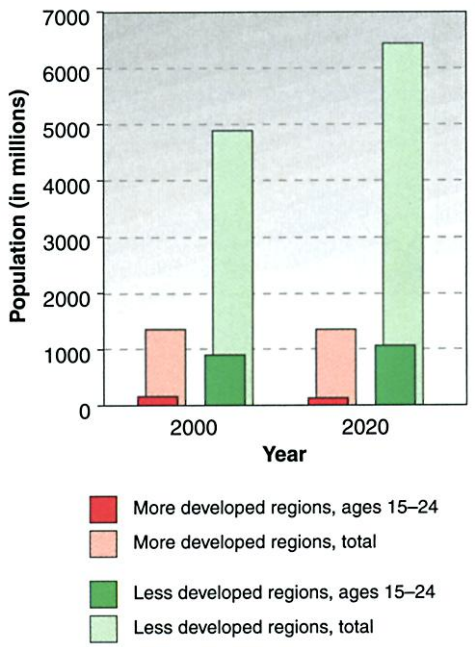
Spearheaded by the Population Council in New York City, work is also picking up on a hormone-based male contraceptive. One obstacle to the decades-old vision of a long-acting male contraceptive, says James Catterall, director of research in reproductive physiology at the Population Council, is that some kinds of hormonal intervention can stimulate prostate growth and potentially contribute to cancer.

But sugar-coating this pill might make a difference. Scientists at the Population Council and at Schering in Berlin, the company that has licensed the product, are working on a patch or implant that can suppress sperm production while at the same time supplying desirable hormone supplements. It would shut down testosterone—and therefore sperm—production by stimulating the immune system to create antibodies to a hormone called GnRH.

Supplementary hormone is needed to replace the missing testosterone. So the key to the product is a potent synthetic androgen, called MENT, developed by the Population Council, that does not stimulate the prostate but does keep muscle mass and libido at desirable levels. In addition to providing contraception, says Catterall, the therapy could furnish androgen supplements for aging men. Such a product might override some males' resistance to contraception and feed into the growing interest in male hormone replacement therapy—an "explosive area," according to Robert Spirtas, chief of contraceptive research at NICHD.

Unrealized promise

But contraceptives for the 21st century are yet to materialize. Stanford's Djerassi says there are a number of technologies—such as a reversible vasectomy or a contraceptive vaccine—that have been scientifically obtainable for more than a decade but that are at the moment dead in the water. Hopes for vaccines, for example, have been pretty thoroughly dampened due to worries about reversibility and side effects. And the fruits of recent advances in biology "haven't even yet begun to be addressed in contraceptive research," says UCSF's Stewart. Few researchers are working on interventions that can block a specific phase of sperm or egg development, for instance, without affecting the whole body as do hormone-based contraceptives.



Oh, babies. The newly fertile population is expected to jump in the next 20 years.

SOURCE: POPULATION ACTION INTERNATIONAL

Donald Patrick McDonnell, a molecular pharmacologist at Duke University Medical Center in Durham, North Carolina, says that "probably one of the major advances in recent years" has been the development of selective estrogen receptor modulators (SERMs), such as tamoxifen. They have contributed to advances in hormone replacement therapy—where market demand is strong—but, he says, researchers have been slow to explore them for contraception. But SERM-like compounds, says McDonnell, could contribute to a generation of contraceptives that are both highly specific—acting either just on the hypothalamic-pituitary-adrenal axis or the uterus—and dual-purpose as well, providing hormone replacements that help prevent cancer or osteoporosis.

But Djerassi, for one, is not optimistic about a renaissance any time soon in contraceptive research. He says the Pill never could have been developed in the current climate. He did his pioneering work before the post-thalidomide tightening of drug regulations and before the arrival of the "litigation explosion," whose beginning was marked by a suit over an intrauterine device, the Dalkon Shield, which bankrupted A. H. Robins and cast a temporary pall over such devices.

Clinical trials, always expensive, are now even more so. In a typical trial, according to Regine Sitruk-Ware of the Population Council, researchers must follow 10,000 cycles including 200 women for 2 years. That means starting with 1200 women, given the dropout rate. In Europe regulations require twice that number of cycles.

Instead, companies prefer to tinker with existing products, such as pills with lower doses of hormones. Most companies are doing well with the Pill, so "if they develop something new, they're essentially competing with themselves," explains Stewart. And something new that lasts a long time is far less profitable than a pill that must be taken daily. "It's hard to find a [corporate] partner interested in a 12-month ring"—one suitable for poor women who don't visit clinics often, says Sitruk-Ware.

To reengage the private sector in contraceptive research, says Stewart, "we've got to change the rules of the game"—that is, offer financial incentives as well as measures to protect companies from liability. Allan Rosenfield, dean of Columbia University's School of Public Health, says rules to encourage public-private partnerships would help. If the government would offer a buffer against liability, as it has done with vaccines such as those for childhood diseases, "that would be a major step forward," he says. But don't hold your breath, he adds: "There's no way this government would ever do that for contraceptives."

—CONSTANCE HOLDEN