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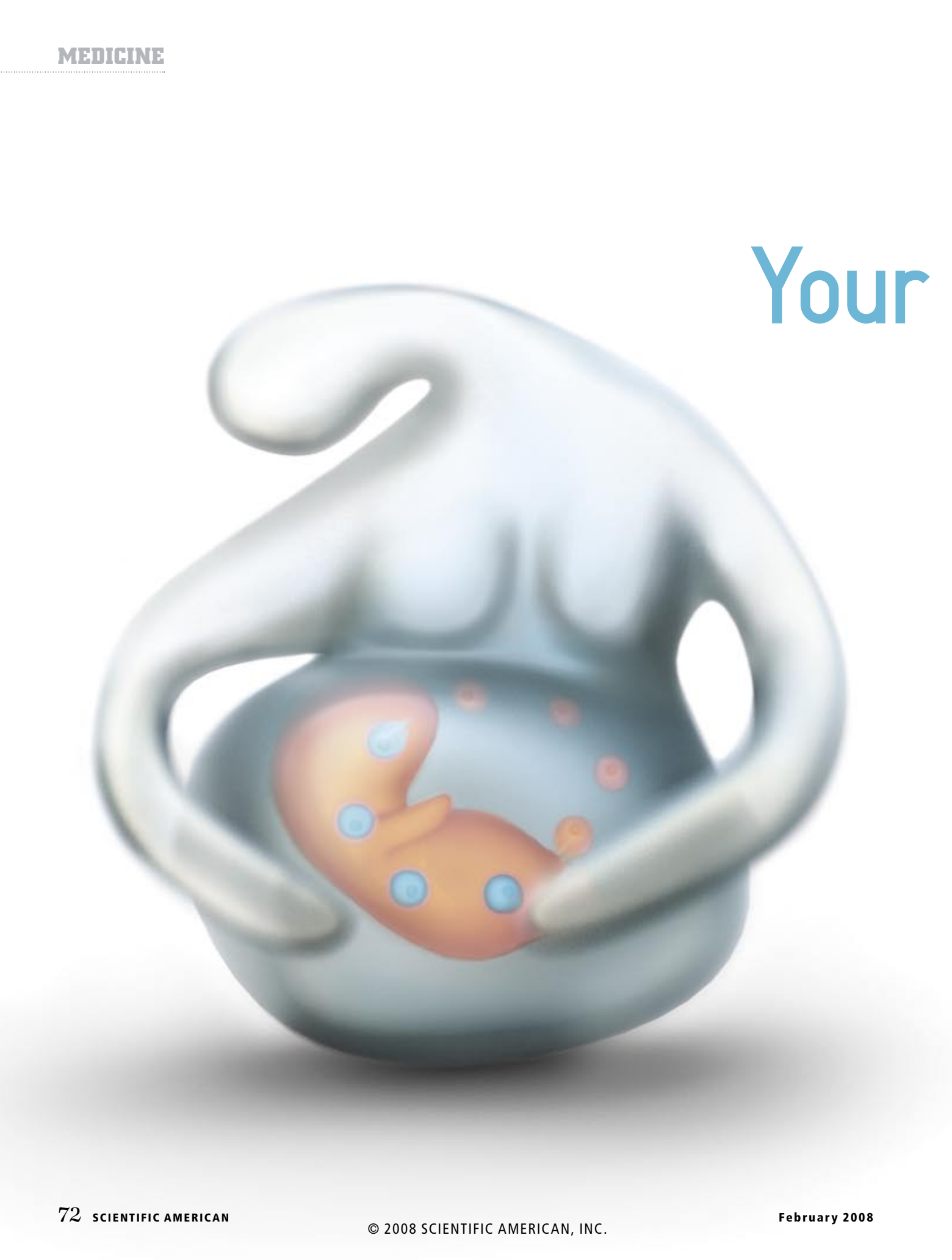


Cells Are My Cells

Many, perhaps all, people harbor a small number of cells from genetically different individuals—from their mothers and, for women who have been pregnant, from their children. What in the world do these foreigners do in the body? BY J. LEE NELSON

"I contain multitudes," says a line in Walt Whitman's poem "Song of Myself." Whitman was not thinking in biological terms, but the line has biological resonance. Recent studies suggest that each of us possesses—in addition to the trillions of cells descended from the fertilized eggs we once were—a cadre of cells we have acquired from other, genetically distinct individuals. In utero we receive an infusion of them from mom. And women who become pregnant also collect a sampling shed by the developing embryo.

That cells cross the placenta is not surprising. After all, the tissue that connects mother and child is not an impenetrable barricade. It is more like a selective border crossing, allowing passage, for instance, of materials needed for the fetus's development. What is remarkable, however, is the extent to which migrant cells can persist in their new host, circulating in the blood and even taking up residence in various tissues. The intermingling of some cells from one person inside the body of another—a phenomenon termed microchimerism—is now drawing intense scrutiny from medical researchers, because recent work suggests it may contribute to both health and disease. Better understanding of the actions of the transferred cells could someday allow clinicians to harness the stowaways' beneficial effects while limiting their destructive potential.

Surprise after Surprise

Scientists gleaned early hints that a mother's cells could pass to her fetus almost 60 years ago, when a report described the transfer of mater-

BRYAN CHRISTIE DESIGN

TWO-WAY TRANSPORT: During pregnancy, some cells travel from mother to baby and some go from baby to mother. A fraction may persist in their new host. The condition is termed microchimerism.

KEY CONCEPTS

- Recent research suggests that each of us harbors some cells that originated in other, genetically distinct individuals—a condition called microchimerism. All of us probably save cells we have acquired from our mother during gestation, and women who have been pregnant retain cells that come from the fetus.
- The acquired cells can persist for decades and may establish residence inside tissues, becoming an integral part of the body's organs.
- Microchimerism could contribute to an immune attack in some cases but help the body heal in others. These effects make the acquired cells intriguing new targets for therapeutics that could curb autoimmunity or promote regeneration of damaged tissues.

—The Editors

nal skin cancer cells to the placenta and the infant. By the 1960s biologists began recognizing that normal maternal blood cells can also find their way to the fetus.

Data suggesting that cells flow in the other direction as well—from fetus to mother—date back even further, to 1893, when a German pathologist discovered signs of such transfer in lungs of women who had died from a hypertensive disorder of pregnancy. Yet the acquisition of fetal cells by healthy mothers was not well documented in humans until 1979, when a landmark paper by Leonard A. Herzenberg of the Stanford University School of Medicine and his colleagues reported finding male cells (those with a Y chromosome) in blood from women who were pregnant with boys.

Despite evidence of two-way cellular traffic between mother and fetus, biologists were surprised in the 1990s when they learned that small numbers of the foreign cells often survive indefinitely in healthy individuals. Earlier studies of mother-to-child transfer had shown that maternal cells could survive in children with severe combined immunodeficiency, a disorder in which afflicted individuals lack critical infection-fighting cells. But scientists had assumed that the ongoing microchimerism in these children stemmed from their disease and that a normal immune system would destroy any maternal cells lurking in a child.

That thinking changed when my colleagues and I found maternal cells in adults who had a normal immune system, including in one person aged 46. Evidence that fetal cells can likewise persist in mothers came some years earlier, when Diana W. Bianchi of Tufts University found male DNA in women who had given birth to sons decades before. (In many studies, investigators test for the presence of male cells in women and estimate the number of those cells by measuring the amount of male DNA in blood or tissue samples from the women.)

How could transferred cells survive for so long? Most cells live for a limited time and then die. An exception is stem cells, which can divide indefinitely and give rise to a panoply of specialized cell types, such as ones constituting the immune system or the tissue of an organ. The discovery of long-term microchimerism implied that some of the original émigrés were stem cells or were related descendants. Experiments later supported this assumption. I sometimes think of the transferred stem cells or stemlike cells as seeds sprinkled through the body that ultimately take root and become part of the landscape.

Microchimerism is now drawing intense scrutiny from medical researchers.

CHIMERA in mythology combines parts of different animals—a lion, a goat and a snake. A person who harbors the cells of another person is said to be microchimeric because relatively few cells are involved.

BRIDGEMAN ART LIBRARY/GETTY IMAGES

My Mother, Myself

The presence of a mother's cells in her offspring—termed maternal microchimerism—is probably a double-edged sword, harmful in some cases but helpful in others. On the negative side, maternal cells may contribute to diseases typically classified as autoimmune, meaning that the immune system unleashes its fire against the body's own tissues. Cells derived from the mother appear to play a part, for instance, in juvenile dermatomyositis, an autoimmune disorder that affects primarily the skin and muscles. Research reported in 2004 by Ann M. Reed of the Mayo Clinic showed that maternal immune cells isolated from the blood of patients reacted to other cells from those same patients. Reed and her co-workers suggest, therefore, that the disease may arise when transferred maternal immune cells take swipes at a child's tissues.

Maternal microchimerism also seems to contribute, albeit in a different way, to neonatal lupus syndrome, believed to arise in part from the destructive activity of certain antibodies that travel from the mother's circulation into her developing baby's. These antibodies apparently home in on fetal tissue and thereby place the newborn at risk for a variety of problems, the most serious of which is a life-threatening inflammation in the heart.

Even though the mothers of affected infants have the disease-causing antibody in their circulation, they themselves are often healthy, and infants born later on to the same woman generally are not affected. That pattern led my co-workers and me to suspect that although the antibodies are important in the disease, they are not the whole story. Indeed, when Anne M. Stevens in my group examined cardiac tissue from boys with neonatal lupus who had died from heart failure, she discovered that it contained female cells, which we presume came from the mother. Such cells were absent or rare in fetuses that died from other causes. More than 80 percent of these maternal cells produced

proteins indicating that they were not circulating blood cells but were constituents of heart muscle.

These observations, reported in 2003, implied that the immune attack in neonatal lupus could be targeted to maternally derived cardiac muscle cells in the fetus. The findings also provided evidence for the idea that cells transferred from mother to fetus are stem cells or related cells, because the cells in the affected offspring had apparently differentiated and integrated themselves into the heart. Further, the results add to other findings indicating that some diseases considered to be autoimmune might instead occur when the host immune system reacts badly, not to native tissues but to acquired cells that have made a home in those tissues.

Other work reveals, however, that in some cases, differentiation and integration might not invite immune attack; instead cells integrated into tissues could help repair damaged organs. In 2002 my co-workers and I began to investigate whether maternal microchimerism plays a role in type 1 (insulin-dependent) diabetes. This autoimmune disorder, which strikes primarily children and young adults, erases beta cells (the insulin producers) from the pancreas. We hypothesized that during pregnancy, maternal cells could embed themselves in the fetal pancreas, differentiate into beta cells and, later, become the target of immune attack.

We were only half right. We did find maternal microchimerism more often, and in greater amounts, in the blood of type 1 diabetics than in their unaffected siblings or in unrelated healthy individuals. And we found maternal insulin-producing cells in the pancreas of a diabetic obtained from autopsy. But then we were in for a surprise: we also discovered maternal insulin-producing cells in pancreases from nondiabetics, and we saw no evidence that such cells serve as targets of the immune barrage in diabetics. Instead our results support the conclusion that the maternal cells in the pancreases of diabetics try to regenerate the diseased organ. This finding, published last year, suggests that microchimerism might one day be exploited for therapeutic benefit—if a way could be found to induce the nonnative cells to multiply and differentiate to restore damaged tissues.

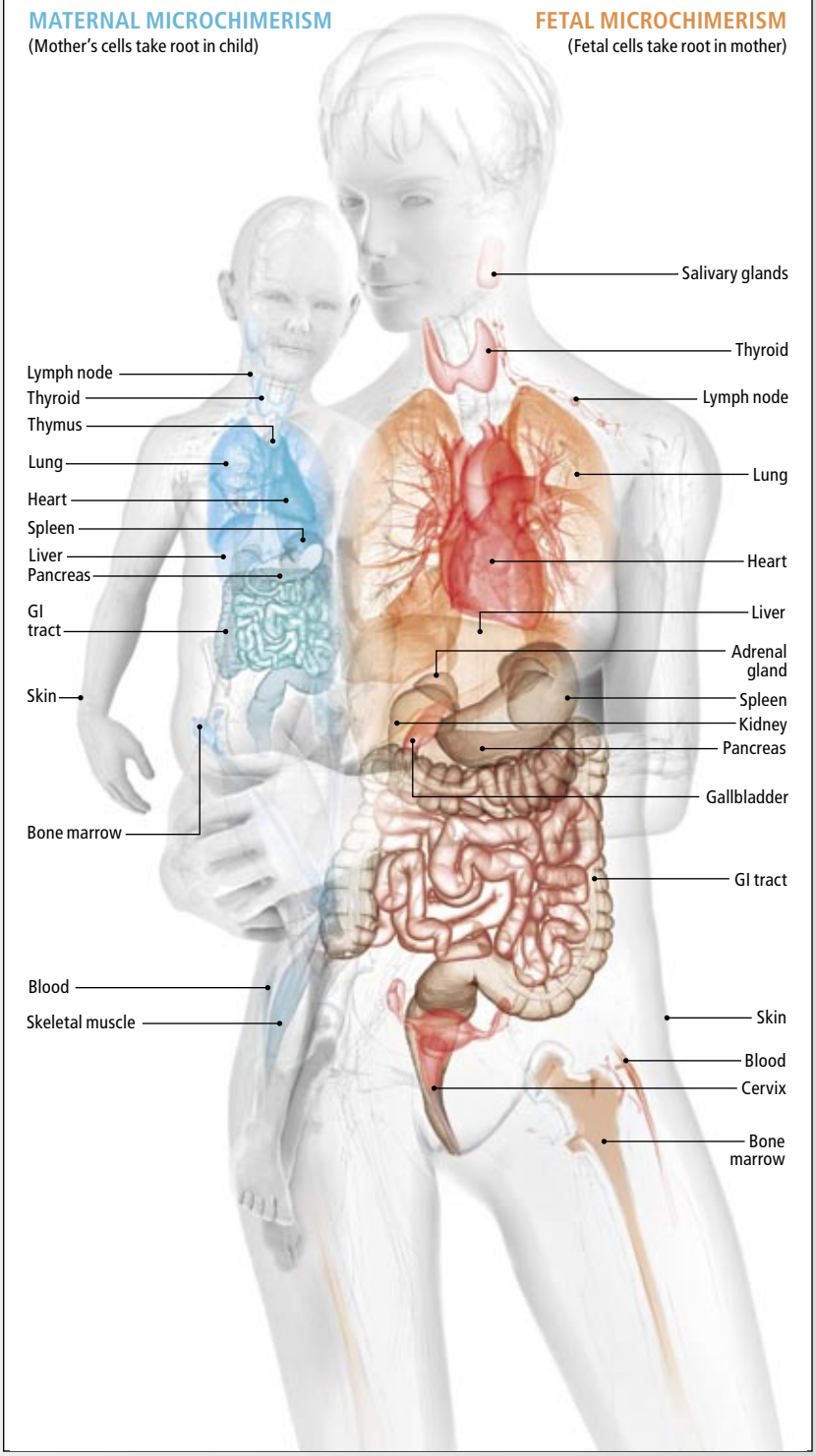
Mixed Blessings from Baby

Like maternal microchimerism, fetal microchimerism—the presence of fetal cells in the mother—appears to be something of a Jekyll-and-

[FINDINGS]

WHERE THE CELLS SETTLE

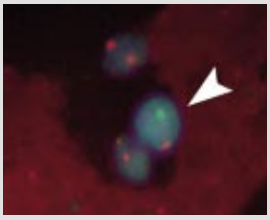
Microchimerism has been found in many human tissues, including those listed below. It can be detected by looking for female cells in a male (for maternal microchimerism) or male cells in a female (for fetal microchimerism). It can also be noted by analyzing DNA. The presence of Y chromosomes in a woman, for example, signifies that she has acquired cells from a male, most likely from a son during pregnancy.



BRYAN CHRISTIE DESIGN; SOURCE: ANNE M. STEVENS *Fred Hutchinson Cancer Research Center*

Hyde phenomenon. I uncovered the unwelcome side in the mid-1990s. Even before my team discovered long-lasting maternal microchimerism in healthy individuals, I was struck by an observation made by Jeff Hall of CellPro, a biotechnology firm, then in Seattle, who was working in prenatal diagnosis. I learned in a phone call one evening in 1994 that a technician in his laboratory had been found to have fetal cells in her blood a full year after the birth of her son. The conversation caused me to wonder what the consequences of indefinitely harboring cells from one's child might be. And these thoughts led me to ask whether disorders usually viewed as autoimmune might at times involve an interaction between a mother's own cells and those acquired from her fetus.

MALE CELL in the liver of a woman is evidence of fetus-to-mother cell transfer. The cell was identified by the one Y chromosome (*green dot*) and one X (*red dot*) in the cell's nucleus (*blue*). The woman's own cells contain two Xs.



[EFFECTS]

DISEASE LINKS

Microchimerism is more common or more pronounced in people with certain disorders (such as those listed below) than in healthy individuals. Sometimes the transferred cells seem to contribute to illness; other times they may combat disease or result from it. For instance, maternal cells have been proposed to attack tissue in those with juvenile dermatomyositis, to be the targets of attack in neonatal lupus and to be trying to come to the rescue in type 1 diabetes. Often the cells' activity is unclear. More research is needed to clarify their roles in specific diseases.

Mother-to-child transfer has been found in:

- **Biliary atresia** (fetal liver disorder)
- **Juvenile dermatomyositis** (immune attack on skin and muscle)
- **Neonatal lupus** (immune attack on various tissues in fetus)
- **Scleroderma** (immune attack that thickens skin and can damage other tissues)
- **Type 1 (insulin-dependent) diabetes** (immune attack on pancreas)
- **Pityriasis lichenoides** (inflammatory skin condition)

Fetus-to-mother transfer has been found in:

- **Breast cancer**
- **Cervical cancer**
- **Multiple sclerosis** (immune attack on neurons of central nervous system)
- **Preeclampsia** (pregnancy-induced hypertensive disorder)
- **Polymorphic eruption of pregnancy** (inflammatory skin condition)
- **Rheumatoid arthritis** (immune attack on joints)
- **Scleroderma**
- **Systemic lupus erythematosus** (immune attack on multiple organs)
- **Thyroid diseases** (Hashimoto's, Graves' and other diseases)

The idea was too exciting to keep to myself, and in a 1996 hypothesis paper I laid out a constellation of observations derived from very different areas of medicine that led me to question the traditional picture of autoimmune diseases. First, most such disorders affect more females than males and usually strike women in their 40s, 50s and 60s—after many have had pregnancies and often after the time when cyclical hormonal fluctuations might be to blame. If long-lasting cells derived from a fetus have a role to play, one would expect to see such diseases most often in women and in those who have passed their child-bearing years.

A second line of thinking came from the field of transplantation. Transplant surgeons generally attempt to genetically "match" donors and recipients; that is, they try to make sure that certain molecules—called human leukocyte antigens, or HLAs—on the surface of a donor's cells are very similar or identical to those of the recipient. If a donor's HLAs differ significantly, the recipient's immune system will reject the graft, destroying it as if it were a disease-causing agent. Conversely, if cells that come from a donor who is not perfectly matched manage to survive, the transplant can trigger a condition called graft-versus-host disease. In this situation, immune cells in the donated organ attack the recipient's tissue. The reaction causes hardening of the skin, destruction of the gut lining and eventually damage to the lungs.

This constellation of symptoms looks much like what happens to patients with a disease called scleroderma, which is considered to be autoimmune. The similarity suggested to me that fetal cells in the mother might be integral to the process that leads to scleroderma in women. So I proposed to Bianchi that our labs collaborate on investigating that idea. We decided to focus on mothers of males because it is relatively easy to demonstrate the existence of a few male cells within a sea of female cells: we could take blood or tissue samples from women with scleroderma and from healthy women and search for Y chromosome DNA.

Like maternal microchimerism, fetal microchimerism appears to be something of a Jekyll-and-Hyde phenomenon.

In our study, the first to look at microchimerism in an autoimmune disease, we found evi-

ANNE M. STEVENS *Fred Hutchinson Cancer Research Center (liver micrograph)*

dence for the involvement of adopted fetal cells in scleroderma. As a group, patients with the condition had higher levels of fetal microchimerism in their blood than healthy individuals showed. And in other studies, our teams—and, separately, that of Sergio A. Jimenez of Thomas Jefferson University—found fetal microchimerism in the skin and other disease-affected tissues.

We also made another interesting discovery, relating to a certain subset of HLAs called class IIs. HLA IIs on fetal cells in women with scleroderma tend to be more similar to the mother's class IIs than is usual. (Because a fetus inherits half of its genes from the father, up to half of the child's HLA genes, and thus half of its HLA molecules, could differ from the mother's.) Our explanation for this pattern might sound counterintuitive, but we believe that harboring fetal cells whose HLAs differ markedly from a mother's own HLAs is unlikely to be a problem, because the mother's immune system will easily "see" that those cells are foreign and will eliminate them. But cells that look extremely similar in terms of their HLAs might well slip past the mother's first line of immune defense and go unrecognized.

Trouble could occur later on in several ways. If, for example, something causes the mother's immune system to wake up to the interloper's presence, an attempt to then eliminate the cells could cause collateral damage to the mother's own tissues and might even trigger an autoimmune attack. Or perhaps the masqueraders could interfere with the delicate checks and balances that are part of the mother's normal immune system.

Because this area of research is very new, no one knows yet why fetal cells that a mother's immune system has lived with since pregnancy would suddenly be perceived as undesirable aliens decades later, nor how a mother's body comes to tolerate the interlopers in the first place. These intriguing questions will be addressed in the next phase of studies.

Pregnancy Brings Relief

As is true of maternal microchimerism, the fetal type may have good as well as bad effects. In what ways might it be beneficial? In theory, immune cells obtained from a baby could react strongly to disease-causing organisms that the mother's immune system handles poorly; in that situation, the fetal cells might help shore up the mother's immune response. They might also

[THE AUTHOR]

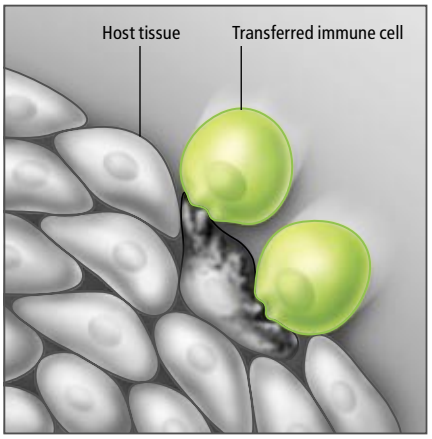
J. Lee Nelson is a member of the Fred Hutchinson Cancer Research Center and a professor of medicine at the University of Washington, both in Seattle. She has been studying the role that microchimerism plays in the initiation and remission of autoimmune diseases since 1986, the year she joined the Hutchinson center. She is also investigating microchimerism's involvement in transplantation, cancer and reproduction. Nelson earned her undergraduate degree from Stanford University and her medical degree from the University of California, Davis, and went on to train in rheumatology at U.W.

[MECHANISMS]

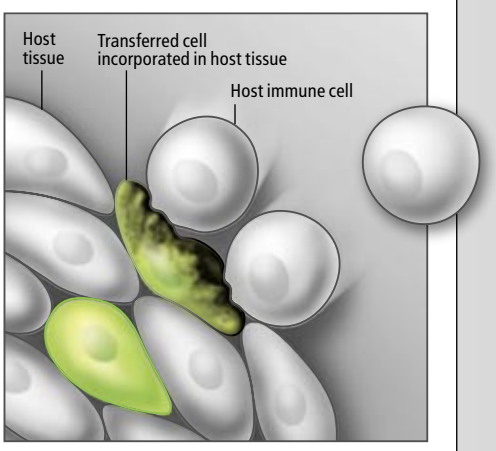
HELP OR HURT?

These are some of the effects that have been posited for cells transferred from one individual to another:

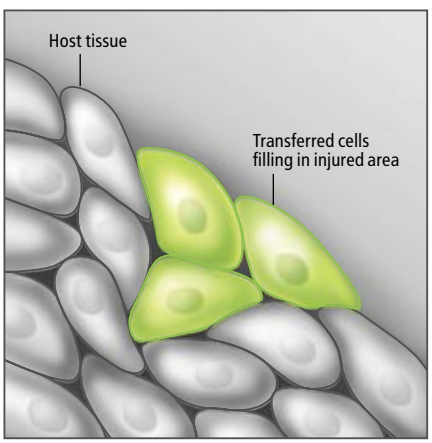
HARMFUL: Transferred immune cells attack host tissue



HARMFUL: Host immune cells attack transferred cells in tissue



PROTECTIVE: Transferred cells attempt to regenerate host tissue that has been damaged



DEAN FORBES *Fred Hutchinson Cancer Research Center (Nelson)*; JEN CHRISTIANSEN *(illustration)*

repair some tissues. And although transfer of fetal cells to the mother might contribute to certain autoimmune diseases, we have some indirect evidence that it can actually benefit women afflicted by at least one autoimmune condition: rheumatoid arthritis, which is marked by chronic, often painful joint inflammation.

Seventy years ago American Nobelist Philip S. Hench observed that rheumatoid arthritis often improves—and sometimes vanishes entirely—during pregnancy and then returns within a few months after delivery. At first doctors invoked hormones, particularly cortisol, which doubles or triples in concentration during pregnancy. But hormones cannot fully account for the phenomenon, because some women with low cortisol enjoy a remission, whereas others with high cortisol do not.

Because pregnancy challenges the immune system (the child is, after all, genetically half-foreign), my colleagues and I sought an immunological explanation for the remission and later reemergence of the disorder. We had discovered in 1993 that the amelioration of rheumatoid arthritis during pregnancy was more likely to occur when the child's set of HLA IIs differed greatly from the mother's. This finding suggested that a disparity in class II HLAs between mother and child could somehow account for the improvement during pregnancy. Later, we found that higher levels of fetal microchimerism in the mother's blood correlated with greater

MICROCHIMERISM FAQs

Is everyone microchimeric?
Each of us probably harbors some maternally derived cells. When my co-workers and I took a single blood draw from healthy adults and tested the equivalent of about 100,000 cells, we found maternal microchimerism in about 20 percent of subjects. But that is a minuscule portion of blood and does not take into account cells that could be in tissues—something that is possible, but challenging, to examine in humans.

How many cells in the body come from our mothers—or our children?
In the circulation maternal or fetal microchimerism is minimal. Calculations based on measuring DNA in healthy individuals indicate that generally fewer than one in 10^5 to 10^6 cells are foreign. But we know that counts can be much higher in tissues than in the circulation. In one study, we were able to obtain a variety of tissue samples from a woman who died of scleroderma. In her case, the numbers varied by organ and cell source. For example, although the DNA measures indicated she harbored about 190 maternal cells and 105 fetal cells for every million of her own cells in a lymph node, in her lungs she had about 760 maternal cells and 3,750 fetal cells per million of her cells.

Aside from two-way transmission between mother and fetus, can microchimerism arise from other natural processes?
Exchange of cells is known to occur between twins in utero, an observation first made in cows. And some twins are lost before being detected by an obstetrician, so microchimerism could derive from a "vanished twin." Also, though not yet proved, microchimerism could be acquired from an older sibling: in this case, the older child, while still a fetus, would have passed some cells to the mother, and mom would pass these cells to a second child during a later pregnancy. Whether microchimerism can occur through sexual intercourse is not known. But indirect evidence indicates that maternal cells can pass to an infant during breast-feeding.

Can blood donation and organ transplantation lead to microchimerism?
Yes. When caused by medical interventions, the phenomenon is termed iatrogenic microchimerism. Donated blood is usually irradiated before it is given to a recipient, which should prevent engraftment. Studies of trauma patients have shown, however, that some who receive multiple unirradiated transfusions retain donor cells years later. Organ recipients likewise may collect and retain cells from the donor, and of course hematopoietic cell (bone marrow) recipients become chimeric.

If alien cells are lodging and living in tissues, why is it that they do not take over a tissue entirely?
This is another open question. It would be a biological disaster if microchimerism were allowed to run rampant. Although this issue has not yet been specifically investigated, researchers feel sure that HLA molecules—the molecules that transplant surgeons generally aim to match in donors and recipients—play a major role in keeping the cells' proliferation in check.

Adopted cells bear HLA molecules that differ from the host's, so why does the immune system fail to recognize and eliminate all such cells?
Perhaps the cells somehow mask their HLA molecules. Or they may "teach" the host's immune system to tolerate them in spite of the differences. But these are speculations. Insight into this question could also shed light on why fetuses, which differ genetically from their mothers, are not eliminated by the mother's body. Interestingly, data suggest that too much HLA sharing during pregnancy is actually bad; fetuses that are miscarried often have more HLAs just like the mother's than do babies that go to term. Nobody knows why that is, although the phenomenon makes evolutionary sense: HLA variance would promote genetic diversity in a population. Such diversity is advantageous because it increases the likelihood that at least some members of the group will have traits enabling them to survive a sudden change in conditions. ***—J.L.N.***

BARBARA PENOYAR *Getty Images*

WHAT'S NEXT?

Beyond continuing to investigate immune-mediated diseases, my colleagues and I are beginning to explore the roles (both good and bad) that microchimerism might play in cancer, reproduction and neurobiology. Some of our questions are:

- Preliminary data suggest that persisting fetal cells could contribute to the decrease in breast cancer risk enjoyed by women who have given birth. But what might they do, exactly, to help?
- It seems reasonable to expect that the maternal cells we harbor—which are, of course, older than we are—could be prone to becoming malignant. If they are not, uncovering the mechanisms that guard against such adversity could suggest new ways to prevent cancer.
- Human reproduction has a high failure rate, with frequent miscarriages. Do the cells that adult women harbor from their own mothers influence the fate of their pregnancies? In other words, when it comes to grandchildren does the maternal grandmother have an extra input?
- Finally, can cells acquired from a mother or a fetus defy the blood-brain barrier and work their way into the brain and spinal cord? If so, do maternal cells influence brain development?

—***J.L.N.***

dampening of arthritis symptoms during pregnancy, and plummeting levels correlated with the characteristic postpartum arthritis flare. We do not yet know why more fetal microchimerism or greater HLA II disparity would cause more pronounced improvement of rheumatoid arthritis in pregnant women.

So far investigators have detected fetal microchimerism in such organs as the thyroid, intestines and liver of mothers with a variety of diseases. Some of the cells showed characteristics of the tissues in which they resided. Fetal microchimerism has also been confirmed in circulating immune cells of mothers. Whether these fetal cells are helpful or hurtful may vary in different people or circumstances.

A New View of "Self"

Overall, then, it appears that microchimerism can affect the body in several ways. For instance, transferred immune cells could mount an attack on body tissues, as may occur in juvenile dermatomyositis. Or adopted cells that differentiate into body tissues could elicit attack by the host's immune system, as we believe happens in scleroderma and neonatal lupus. Another possibility is that stowaway cells could be deployed as a relief team, traveling to body tissues that have suffered damage to help with regeneration and restoration of function, as appears to be the case in type 1 diabetes.

Each scenario brings forth the possibility of new therapeutic strategies to consider. If acquired cells are attackers, they could be selectively pinpointed for removal or inhibition. If they are targets of attack, strategies that induce the immune system to tolerate them could be developed. And if they can help regenerate damaged tissues, they might be stimulated to ease diseases marked by tissue destruction.

Although only women are subject to fetal microchimerism, anyone could harbor cells from the mother, including men, children and women who have never been pregnant. Because maternal microchimerism becomes established during development (when the fetus's immune system is forming) and fetal microchimerism occurs when the mother's immune system is mature, the contribution of the two processes to the "self" may differ—just as immigrants who arrive as a nation is being formed may assimilate differently than those who arrive later. We do not yet know very much about those differences. And we understand very little about another intriguing frontier: whether women face unique consequences from harboring cells across generations, both from their own mothers and from one or more of their children.

The discovery that a mother's cells can turn up in her adult progeny and that fetal cells can occur in women who were once pregnant heralds the emergence of microchimerism as an important new theme in biology. The work also challenges the traditional view of self in immunology. Our findings and those of others in this new field support a redefinition that embraces the naturally acquired microchimerism that is probably always with us—from the earliest moments of life well into our adulthood. Also thought-provoking are recent reports of maternal and fetal microchimerism in the brains of mice. These discoveries raise a host of fascinating questions—among them, do maternal cells influence brain development, might fetal microchimerism be harnessed for treating neurodegenerative diseases, and what constitutes our psychological self if our brains are not entirely our own? ■

Anyone could harbor cells from the mother, including men, children and women who have never been pregnant.

MORE TO EXPLORE

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