The Nine-Month Arthritis 'Cure'

Why do symptoms of rheumatoid arthritis abate during pregnancy?

By KATHY FACKELMANN

In the 1930s, Philip Hench of the Mayo Clinic encountered a medical mystery: case after case in which women with rheumatoid arthritis claimed their joint pain and swelling had completely vanished during pregnancy.

Hench listened carefully to his patients and wrote up several of their histories for the March 16, 1938 PROCEEDINGS OF THE STAFF MEETINGS OF THE MAYO CLINIC, including this description of a 33-year-old woman with the disorder:

> "Many joints were red and swollen, housework was very painful, and walking was too difficult for her to leave the house. About five weeks later she became pregnant. . . . 'Almost overnight all swelling, redness, and pain left rapidly' [the patient reported]. She was 'completely well,' and thought she was cured."

"It struck me that it was a very important biological observation," J. Lee Nelson, a rheumatologist at the Fred Hutchinson Cancer Research Center in Seattle says now. Nelson knew that in the years following the 1938 report, some scientists had tried to find out what caused this temporary reprieve. Many believed that hormonal changes explained the temporary cessation of joint pain experienced by some women during pregnancy.

However, studies of hormone concentrations during pregnancy failed to account for the temporary "cure" of rheumatoid arthritis. Indeed, scientists could find no explanation for the phenomenon.

Now, more than 50 years after Hench first published his account, Nelson and her colleagues have found a clue to that unsolved mystery: The team recently published findings suggesting that the remarkable improvement in some arthritis cases appears to result from the genetic differences between a mother and her fetus. Their study relied on powerful molecular techniques as well as on the same time-honored observations of patients that Hench had used.

"Lee Nelson has a very strong argument that she has found the key to remission," comments Michael Lockshin of the National Institute of Arthritis and Musculoskeletal and Skin Diseases in Bethesda, Md. "The new finding may give us clues as to what goes wrong in rheumatoid arthritis," adds J. Bruce Smith, a researcher at Jefferson Medical College in Philadelphia.

Nelson's interest in this mysterious phenomenon began in 1982. At the time, she was a rheumatology fellow treating patients at the University of Washington's arthritis clinic.

Enter Teri Rowe, a woman whose own experience of remission was similar to the case reports outlined by Hench. Rowe vividly recalls talking to Nelson. Rowe explained that she had developed rheumatoid arthritis at the age of 27, after the birth of her second child. She was in the middle of a flare-up when she became pregnant with her third child.

"It was like a miracle," Rowe says now of the complete relief that occurred two months into the pregnancy. Unfortunately, the reprieve didn't last. The severe joint pain, fatigue, and swelling all returned two months after her son was born.

For Nelson, the chat with Rowe proved pivotal: It swung her toward a career as an arthritis researcher.

"I wanted to work in an area that might lead to a difference for my patients in my lifetime," she says.

Nelson began studying pregnancy's relationship to rheumatoid arthritis. She recalls that she kept coming back to this puzzle: If hormones weren't the answer, then what was responsible for the cease-fire in arthritis symptoms often seen during pregnancy?

Nelson felt that if she could find the answer to that riddle, she'd find something very close to a cure — an antidote that could provide relief to the 2.1 million Americans who suffer from this painful joint disease.

Suddenly, a novel explanation occurred to her: Was it possible that the mother's immune system, which is affected during pregnancy, had something to do with the nine-month remission? Nelson finally had a working theory, but one it would take her years to test.

The word "arthritis" comes from the Greek words "arthron," or joint, and "itis," inflammation. It is a general term used to refer to a host of joint diseases, including osteoarthritis, a common condition brought on by the wear and tear of old age.

Nelson focused her attention on rheumatoid arthritis, an autoimmune disease that often strikes in midlife. Nobody knows what triggers this self-destructive process, but some scientists believe that an infectious agent, such as a virus, sets off a healthy immune response that later runs amok. Scientists suspect that in certain genetically susceptible people, the immune cells remain hyperactive long after the infectious agent has been cleared from the body. Those revved up immune cells continue their blitz, in this case attacking the synovial joints, the hinged connections between many of the body's bones.

For the millions of Americans with rheumatoid arthritis, that assault translates into soreness, stiffness, fatigue, and, in serious cases, permanent crippling of the afflicted joints. For unknown reasons, the disease may wax and wane. It eventually causes destruction of the synovial membrane (the lining inside a joint), the cartilage that cushions the bone ends, and even the bone itself. The disease can also cause a dangerous inflammation of the body's blood vessels and the lining of the heart and lungs.

From the outset, Nelson knew it would not be easy to test the hypothesis that the maternal immune system quiets joint disease during gestation. Many women who develop this autoimmune disorder have finished having children. Yet Nelson had to collect enough cases to make her study statistically significant. So she and her colleagues began the challenging task of recruiting women with rheumatoid arthritis who were pregnant or had had a child.

It took them almost a decade.

In the end, the researchers had gathered information on 57 pregnancies in 41 women with rheumatoid arthritis. In 18

cases, the researchers followed the woman through a pregnancy. In 39 others, the team asked the woman to recall details of a previous pregnancy. In every case, they asked the woman whether her joint pain and other symptoms subsided during gestation.

To make sure these self-reports were accurate, the team also scrutinized the medical records for each pregnancy and noted whether physicians had seen signs of improvement.

Their analysis revealed significant improvement or remission of joint disease in 34 cases. In 12 others the arthritis remained active throughout pregnancy, and in 11 cases there were not enough data to assess the status of the disease. The team didn't study those 11 cases any further.

Next, the researchers used molecular techniques to study genetic material from each mother and her offspring, whether a newborn or a child from a previous pregnancy. They obtained fetal blood from the umbilical cord after delivery and maternal and older children's blood from a vein. From children too young for a needlestick, researchers snipped a lock of hair for the study.

Nelson and her co-workers analyzed the DNA in each blood or hair sample and homed in on genes that are part of the human leukocyte antigen (HLA) system.

From her search of the literature on pregnancy and the immune system, Nelson concluded that HLA genes might shed some light on the remission of arthritis during pregnancy. These genes carry the blueprint for manufacturing so-called HLA proteins, which sit on the surface of certain immune cells, including white blood cells called lymphocytes. These proteins enable the immune system to differentiate between the body's own cells and foreign cells, such as those of the fetus.

Many years ago, scientists believed a mother's immune system didn't recognize the fetus, which is attached to her via the umbilical cord. While it's true that there is no direct blood-to-blood connection between mother and child, scientists today believe that fetal cells do escape into the maternal bloodstream.

Some of those fetal cells carry HLA proteins coded for by genes inherited from the father. Researchers have long wondered why the mother's immune system doesn't mount an attack against those paternally derived HLA proteins.

There are a slew of HLA genes, and each comes in a variety of forms, or alleles. Thus, a person's HLA profile is as individual as a fingerprint.

Nelson decided to compare each mother's genes with her child's in order to determine whether the stock of HLA genes a child inherits is similar or dissimilar to its mother's HLA profile in cases of remission.

Using polymerase chain reaction, a technique that amplifies target bits of DNA, the Seattle team first looked at the 34 pregnancies in which women had reported improvement in their arthritis symptoms. The researchers found marked differences in mother-child HLA in 26 of those pregnancies (76 percent).

Of the remaining 12 pregnancies — those with no remission — only three (25 percent) exhibited marked HLA differences. In the other nine cases, the fetus had inherited HLA types similar to the mother's, Nelson says.

The researchers could find no other factor to explain the difference between mothers who got better and those who remained the same during pregnancy. The team presented their findings in the Aug. 12 NEW ENGLAND JOURNAL OF MEDICINE (NEJM).

Nelson's team also documented two cases in which women had very different experiences from one pregnancy to the next.

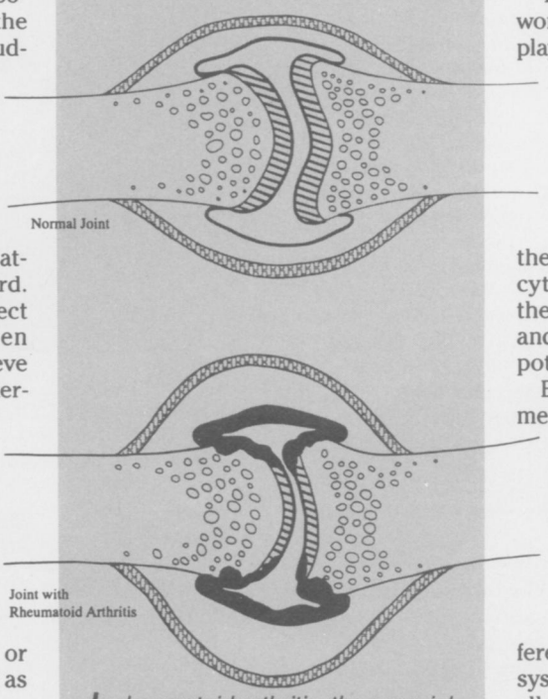
In the first, a Minnesota woman experienced a dramatic improvement during her first pregnancy but painful joint symptoms during her second. It turns out that the child in the second pregnancy had an HLA profile that resembled the mother's, Nelson says.

In the second case, a Washington State woman reported having active rheumatoid arthritis during her first pregnancy but relief from arthritis pain during her second pregnancy. The researchers found that the second child had a genetic profile very different from the mother's.

The new study provides some "very intriguing observations," comments David S. Pisetsky of the Duke University Medical Center in Durham, N.C. "I think this report will lead to some quite interesting work," he adds.

"Lee Nelson has a very strong argument that she has found the key to remission."

— Michael Lockshin



In rheumatoid arthritis, the synovial membrane (outlined in black) is the target of an autoimmune attack. Inflammatory cells then release an enzyme that chews up bone and cartilage.

How do genetic differences between maternal and fetal HLA genes lead to temporary remission of arthritis symptoms? One possibility is that when a mother's HLA genes are very different from those of the fetus, some sort of protective mechanism kicks in to shield the developing child from its mother's immune cells.

To understand how that protection works, consider the role HLA proteins play in a mother's normal immune response. HLA proteins help the immune cells guard against invaders, such as viruses. In some cases, a roaming B lymphocyte in the mother's immune system will hook onto a viral fragment and display that foreign material in the jaws of the HLA proteins that sit on the lymphocyte's surface. That presentation sounds the alarm, telling helper T lymphocytes and other immune cells to gear up for a potentially nasty fight.

But HLA proteins also display fragments of proteins produced by the body — perhaps to stamp the cells as "self" and prevent an immune system attack. In rheumatoid arthritis, something goes awry in that system, and the immune cells start bombarding the cartilage, bones, and linings of the joints.

When mother and child carry different HLA types, the mother's immune system may turn down its activity to allow the fetus to develop undisturbed in the womb. At the same time, the immune system scales back its attack on the mother's joints.

How does this come about? One theory is that a fragment of a fetal HLA protein, a

peptide, floats into the mother's bloodstream. There, it may draw the attention of a B lymphocyte. That B cell snatches up the fetal peptide for display. But rather than trigger an attack, Nelson speculates, this fetal fragment somehow gives a signal that dampens the maternal immune system – an action that protects the baby and gives the mother some sorely needed pain relief.

An alternative explanation for the remission is that the mother's immune system, noting the potential danger for the genetically different fetus, actually manufactures a substance that quiets the immune response, Pisetsky suggests.

Researchers don't understand what goes wrong in people who suffer from rheumatoid arthritis, so speculation about what is going right during pregnancy is just that – speculation – Nelson warns.

"Whatever the mechanism of remission of arthritis during pregnancy, it is likely to be complex and multifactorial," the team writes.

If scientists can identify the link between remission and the immune system, they may eventually be able to develop an antidote to rheumatoid arthritis, Pisetsky points out. After all, the relief provided by pregnancy, although limited, is quite dramatic.

"Pregnancy is a powerful drug," Lockshin says.

Nelson's former patient, Teri Rowe, agrees. Her rheumatoid arthritis symptoms disappeared during her pregnancy but returned in full force afterwards. Although Rowe's pain can be modulated by drugs, many patients with this autoimmune disease suffer from aching that cannot be controlled with medication.

Today, doctors rely on aspirin, nonsteroidal anti-inflammatory drugs, and powerful corticosteroids to treat the disorder. Although Hench's 1938 report never solved the pregnancy mystery, it did lead to the discovery that cortisone, a hormone produced by the adrenal glands, could deliver great relief to patients with rheumatoid arthritis. Indeed, Hench, Edward Kendall, and Tadeus Reichstein together won a Nobel Prize for their work with cortisone.

During the 1950s, cortisone and synthetic hormone-like drugs were thought to produce near-miraculous cures in people who had been crippled by rheumatoid arthritis. Yet such drugs could keep the disease at bay for only limited periods, and severe side effects curtailed their use. "Over the years, [cortisone] has not proven to be the cure for rheumatoid arthritis by a long shot," Lockshin says.

The new research suggests that rheumatologists may one day rely on a whole new class of substances to provide their patients with joint relief. Indeed, Smith's team plans to take Nelson's theory one step further. He and his colleagues will give people with rheumatoid arthritis white cells bearing HLA proteins that are different from the patients' own. That therapy may coax the patients to secrete a chemical that blocks the attack on joints, they speculate.

Many scientists hope that research to elucidate this enigmatic phenomenon will have broad implications. Lockshin believes such studies will shed light on the causes of other autoimmune disorders, such as systemic lupus erythematosus, multiple sclerosis, and even type I diabetes.

And if scientists can unravel the mechanism by which the fetus gains protection during pregnancy, they may be able to devise better treatments for infertility, Pisetsky adds. Women who suffer from numerous miscarriages may have a defect in the way their body shields the fetus from the maternal immune system, he says.

As for people who are actually suffering from rheumatoid arthritis, the new findings provide the expectation of good news in the future.

"The hope is that this will give us another medication," says Rowe, who still wakes up in the middle of the night with aching joints. "And it will buy us more time," she adds. □