Survival of the Fetus

In order for a woman to bear a child, for nine months her body must play host to a parasite

By JOANNE SILBERNER

In being the flesh of its parents' flesh and the blood of their blood, a fetus presents a problem. By containing paternal as well as maternal genes, the fetus is essentially an organ graft to the mother and therefore should provoke the same sort of rejection a foreign kidney or heart would. But our forebears did not dine on cyclosporine or other immune-suppressing drugs, and yet we're here.

Explaining the paradox has been a goal of immunologists, and was a topic of several presentations in Toronto at the recent Sixth International Congress of Immunology. What has been learned so far is already being applied as a treatment for women who repeatedly and spontaneously abort; what remains to be learned ultimately could be used to help in cancer treatment and organ transplantation.

The current scenario for how the fetus avoids being rejected by its mother involves some careful timing and cooperation between the host and guest. The immunity lapse in the mother is for the most part localized in the uterus, a fact first established in the late 1950s in an experiment not likely to be approved by ethics committees today. Researchers gave pregnant women skin grafts of their husbands' skin. The women's bodies rejected the foreign skin yet they carried the pregnancies to term and delivered normal children. Experiments in animals have since substantiated the unique status of the uterus – in rat experiments, for example, fetal material implanted anywhere else besides the womb is rejected.

The mother's uterus doesn't do all the work itself. The fetus cuts down the rejection potential by limiting how much of its father's influence it "shows" to its mother.

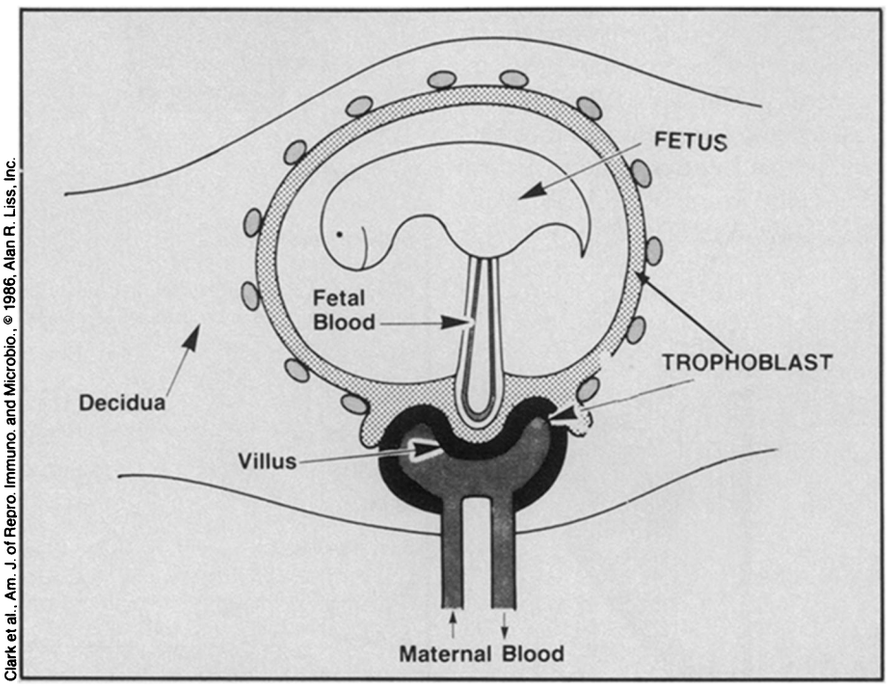
Human cells are studded with proteins known as transplantation antigens, which let the body distinguish "self" from "nonself." Some of the proteins are constructed by genes from the individual's father, and some by genes from the mother. From the mother's point of view, her cells are uniquely hers while the cells of her fetus are recognizably foreign.

To limit the provocation, the fetal cells facing the maternal cells in the placenta do not have paternal transplantation antigens on their surface, though the fetally derived cells surrounding the rest of the growing embryo, in the "privileged," less immunologically sensitive uterus do.

Early studies at first indicated that the entire fetal covering, or trophoblast, lacked paternal antigens. But the discovery at several laboratories in the early 1980s of antigens on part of the trophoblast meant that something was somehow limiting the mother's reaction to these antigens.

That action takes place in the uterus. Research has shown that the mother does her part in preventing rejection initially by tempering the action of white blood cells that hover in the uterus near the placenta. During pregnancy, these cells are less responsive to the immune-stimulating chemical interleukin-2 and hence less responsive to foreign "attack." White blood cells in the mother's circulation are not a problem, since maternal blood never enters the fetus.

David A. Clark of McMaster University in Hamilton, Ontario, and his co-workers have found a potential mitigator: an agent produced by the trophoblast that stimulates development of a special type of white blood cell in the uterus. This cell in turn releases something that blocks the action of interleukin-2. Without interleukin-2 stimulation, the muscle men of



Clark et al., Am. J. of Repro. Immuno. and Microbio., © 1986, Alan R. Liss, Inc.

The fetus and most of its surrounding layer of cells, the trophoblast, contain proteins that the mother would recognize as foreign. But some of these proteins do not appear at the maternal-fetal interface (heavy black line) in the placenta. Their absence lessens the immune system "insult."

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the immune system, killer T cells, are quiet.

Paradoxically, the initial immune system provokers – the paternal antigens – have to be on the trophoblast for the system to work. The hypothesis proposed by Clark and others is that recognition by the mother's immune system of the foreign growth stimulates antibody production, which in turn prompts the protective defenses of the fetus, including the manufacture of the interleukin-2 inhibitor. Without the initial provocation, the fetus doesn't learn to defend itself, and subsequent attack by the immune system results in the fetus's abortion.

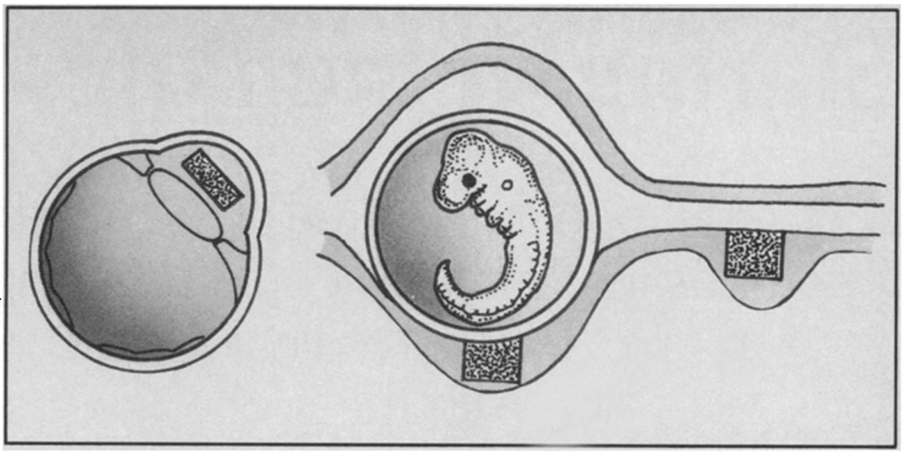
Peter M. Johnson of the University of Liverpool in England estimates that about 1 in 300 couples suffer from immune-related spontaneous abortions. "With no active protection, the fetus is afforded no special privilege and is rejected as a transplant would be," he says.

In these cases, the active protection is missing because the initial alarm wasn't sounded – the father is genetically too much like the mother for his contribution to be recognized as different. However, with a father who differed more genetically, the spontaneous abortion wouldn't occur. "The evidence is that a change of partner will ameliorate the problem of recurrent miscarriage in many of these women," Johnson says.

Since many women don't consider that a viable solution, researchers at St. Mary's Hospital Medical School in London began a study in 1982 to determine whether the mother's recalcitrant immune system could be manipulated into accepting the fetus – that is, trying at first to reject it. Their approach was to spark the crucial initial immune reaction with paternal material. "It seems as if in some way vaccinating a woman creates an immune response that generates interaction between the trophoblast and suppressor cells such that the suppressor increases," says Clark.

The St. Mary's group immunized spontaneous aborters, in whom no apparent cause for abortion could be found, with white blood cells from the fathers. They recently reported that 17 of the 22 women immunized with their husbands' cells became pregnant and bore children, compared with 10 of the 27 women in a control group who were given their own cells.

Last year a 26-center international study was begun to test the process further. Spontaneous aborters – some of whom have aborted as many as 20 times – are being enrolled. Of about 400 women treated so far, more than 150 have achieved live births, Johnson said at the immunology meeting. The success rate of maintaining a fetus beyond the early stages is around 70 to 80 percent. Instead of using paternal cells to stimulate the immune system, Johnson's center is vaccinating with placental material from uncomplicated pregnancies.



Gardiner Morse, adapted from D. Clark et al.

Immune system cells have difficulty reaching the anterior chamber of the eye. Even so, a fetal tissue transplant (dark blocks) there will be rejected (left). The same tissue can persist in the uterus (center) by taking advantage of the localized immune suppression induced by the outer covering of the fetus, unless the implanted material is placed too far away (right).

One center, the University of Michigan in Ann Arbor, has reported several babies born smaller than normal because of slowed intrauterine growth. Whether this growth retardation was a statistical fluke or a result of the procedure is unknown. Johnson says this problem has not been reported elsewhere. A second concern sparked by the human trials is that if the immunized women ever need organ transplants in the future, their 'already educated' immune systems may react more strongly against even a closely matched transplant.

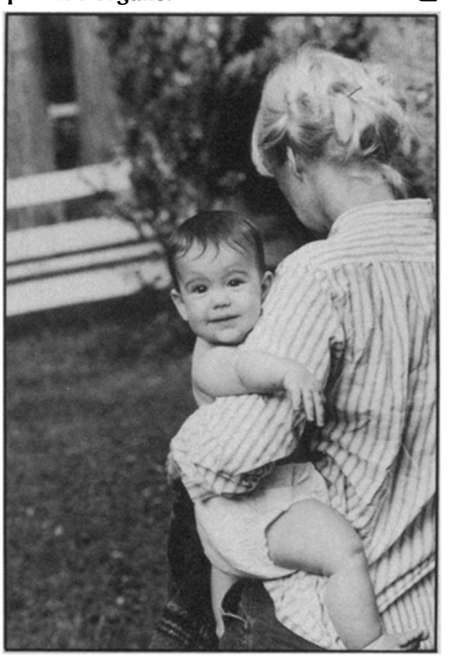
The human trials followed cross-species fetal implants in animals, in which maternal immunization similarly enabled threatened fetuses to survive. In one instance, scientists from Cornell University in Ithaca, N.Y., and Cambridge University in England artificially implanted donkey fetuses into six horses primed by injection with donkey white blood cells. Three of the mares bore live donkeys. Without immunization, 90 percent spontaneously abort (SN:7/6/85, p.8).

Figuring out the specifics of toleration as well as those of rejection could suggest ways to intercede in other situations. Clark was originally doing cancer research, and became curious about how fetal cells, like cancer cells, avoid rejection.

"There are many similarities between tumor cells and cells of the fetal-placental unit," he says. Both tumor and fetal cells are invasive, he notes. Tumor cells sometimes display proteins seen on the fetus and nowhere else. Genes that become active when normal cells become tumor cells are active in the fetus as well as part of normal development, then they turn off. The migration of cells within the fetus is typical of what can happen in the spread of cancer.

Like the fetus, tumor cells escape rejection. "It occurred to me that perhaps tumors exploit methods of evading rejection normally used by fetuses," Clark says. So far, one similarity has been found: Certain brain tumors produce interleukin-2-blocking factors similar to those associated with successful pregnancies. Practical applications of this finding in the treatement of cancer, he says, "are still a matter for research."

Theoretically, in addition to suggesting a successful point-of-attack for cancer treatment, the fetal rejection-protection system could be promoted in order to prevent the rejection of transplanted organs. Says Johnson, "If the laws of [organ] transplantation were to be obeyed, the conceptus in early pregnancy would be rejected." The trick, he suggests, would be to figure out just how the fetus gets away with breaking the law, and to "teach" the method to transplanted organs. □



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