Modern Biology for High School Classrooms

# SNAPSHOTS of Science & Medicine

Premier Issue

## Xenotransplantation

### Using Animal Organs to Save Human Lives

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NIH Office of Science Education • Office of Research on Women's Health

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## From the Editor

Welcome to *Snapshots of Science & Medicine*, a new publication dedicated to bringing cutting-edge biomedical research into high-school classrooms. The National Institutes of Health (NIH) Office of Science Education publishes *SnapShots*, with generous support from the NIH Office of Research on Women's Health.

Today, biological science is booming like nobody's business. The evening news presents a constant parade of new advances and new treatments, many of which create complex social and ethical controversies that will be difficult to sort out. It's not too much to say that biology and medicine could have as much effect on society in the coming decade as computer technology had in the decade gone by.

We created *Snapshots* to help bring the excitement of modern biology and medicine into high-school classrooms. Each issue tackles one specific area of research from four different directions. **Research in the News** provides an overview of the field. **Stories of Discovery** presents a very short history of how the field got to its current state. **People Doing Science** has a profile or two of people working in the field. **Social Impact** looks at social or ethical issues the research raises.

On top of these four core departments, each issue will have some extra features for students, as well as classroom activities for teachers. (Go to our Web site for these.) We hope the overall effect will be to reinforce key concepts in biology, illuminate how scientists actually go about their work, and give students an in-depth understanding of at least one part of the biomedical research picture.

You hold our first issue in your hands, all about the promise and perils of xenotransplantation. We hope you enjoy it. And we hope you will let us know what you think, by sending e-mail to **TaylorR1@od.nih.gov**, or hitting the "Contact Us" button on our Web site.

**Robert Taylor, Ph.D.**
Editor, *Snapshots of Science & Medicine*

RESEARCH IN THE NEWS

# Xenotransplants: Using Animal Organs to Save Human Lives

by Bruce Agnew

When surgeon Joseph Murray performed the world's first successful human organ transplant in 1954—a kidney transplant between identical twins—he had no idea what he was beginning. Today, organ transplants no longer make news: about 20,000 Americans each year receive life-saving transplants of hearts, kidneys, livers, or lungs, from people who have signed organ-donor cards or whose relatives approve the donation. But at any given moment, about 50,000 people are getting sicker and sicker while they wait for such organs—and about 4,000 die each year, still waiting.

To address the shortage of human organs, many scientists and several biotechnology companies have been working on an answer that, at first glance, might seem like science fiction: use organs from animals. The procedure is called "xenotransplantation" (from the Greek "xeno" meaning "stranger"; the "x" is pronounced like a "z," as in Xerox). And some researchers believe they are on the verge of making xenotransplantation of whole organs work—although the attempts carried out so far have not been very encouraging.

Even if it turns out that animal organs can not be successfully transplanted, researchers also have ideas for transplanting animal cells for therapeutic effect. In fact, transplants of living animal cells into people are already are being tried. For example, Suzanne Ildstad, director of the Institute for Cellular Therapeutics in Louisville, Ky., studies bone-marrow transplantation. In 1995 she transplanted baboon bone marrow into a man named Jeff Getty, who is infected with HIV and has AIDS. Bone marrow produces immune system cells. The hope was to replace Getty's crumbling immune system with an HIV-proof baboon immune system that could protect him from infection. Although the baboon cells functioned for only two weeks, Getty is still alive and the researchers learned a great deal. In another experiment, researchers at CytoTherapeutics, Inc., in Lincoln, R.I., implanted cow adrenal cells—which produce a natural painkiller—into the spinal columns of patient suffering intractable pain. The cells survived and functioned, but, unfortunately, the patients felt no pain relief.

> "If the benefits are huge, so are the barriers."

If the potential benefits are huge, so are the barriers.

The human immune system—a complex network of defenses against disease organisms and other foreign substances that evolved over millions of years—fiercely resists even human-to-human transplants. When confronted with an organ from an animal as evolutionarily distant as, say, a pig, the human immune system reacts violently. In a response known as hyperacute rejection, antibodies that seem preprimed to attack tissues from another species summon into action the so-called complement cascade, an array of proteins in the blood that attacks the internal walls of the transplant's blood vessels, rejecting the organ within hours or even minutes.

Even if hyperacute rejection can be tamped down, the human body mounts a more vigorous long-term attack on animal organs than it does against transplants of human organs. More blood cells, primarily B lymphocytes and natural killer cells, join the attack on the foreign tissue. Today, physicians can suppress many immune responses with drugs such as cyclosporine, FK506, and prednisone. These drugs are used in human-to-human transplants, known as allotransplants. In xenotransplants, heavier doses are required, and the patient's immune defenses against infectious organisms may be crippled.

This is exactly what happened when Thomas Starzl, of the University of Pittsburgh Medical Center, transplanted baboon livers into two patients with hepatitis in 1992 and 1993. Both patients died, not from a rejection response to the transplants but from runaway infections caused by microbes that are common in the environment and in the human body.

AIDS patient Jeff Getty received a baboon-bone-marrow transplant in 1995.

"There were probably some unusual rejection mechanisms that we haven't quite figured out," says John Fung, a member of Starzl's team. "But the real reason they died was from everyday bacterial and fungal infections, because their bodies were so immunosuppressed from the drugs."

The easiest way to deal with immune-system rejection of xenotransplants would be to sidestep them—to use organs from the animal that is the closest possible to human beings. That, of course, is the chimpanzee, whose genome is more than 98 percent identical to the human genome.

But chimpanzees are an endangered species. They are costly to raise, and they grow slowly to adulthood. Chimpanzees may also harbor unknown viruses that do them no harm but that might cause devastating diseases in humans—diseases that might be transmitted to other people. For example, researchers have strong evidence that HIV crossed into humans from chimps during the first half of this century. The term for such a species leap is zoonosis, and the term that is becoming accepted for an animal-to-human leap because of a xenotransplant is, naturally, xenozoonosis.

Most xenotransplantation researchers agree that chimpanzees are not suitable organ donors. Researchers also agree that other "higher" nonhuman primates such as baboons are out, too. Although organs from these animals are less likely than those of more distant species to set off hyperacute rejection, they, too, harbor microorganisms that might leap to humans easily and with dangerous consequences. And like chimpanzees, baboons are costly to raise and, in some cases, suffer from population decline.

Strange as it may sound, the animal that is emerging as the most likely source of transplantable organs is the pig. Pigs' organs are the right size. The

**Too much like us?** Kanzi, a pigmy chimpanzee (Bonobo), has been taught to communicate with humans using lexigrams on a computer keyboard. Even if chimpanzees were not an endangered species, their close relationship to humans makes them an unlikely source for xenotransplant organs.

animals are highly domesticated, they have large litters, and they grow quickly to maturity. They can be raised in sterile environments, which would reduce the likelihood of transmission of at least some pig diseases to humans. Many researchers, however, still worry about viruses that are unknown or that have become part of the animals' genome and cannot be dislodged.

Unfortunately, pig organs have molecular characteristics that make the human immune system attack mercilessly. But there may be ways around that, and researchers are exploring at least two quite different approaches.

One way is to change the pig, through genetic engineering. Using existing laboratory techniques, several research teams have deleted specific pig genes—and added specific human genes—to make pig cells seem, as John Fung, of the University of Pittsburgh Medical Center, puts it, "less piggish." For example, Imutran, a biotechnology company in Cambridge, England, and Nextran Inc. in Princeton, N.J., have developed pigs that carry human genes that block activation of the complement system—and thus presumably will prevent hyperacute rejection.

Other researchers have modified a sugar molecule that appears on cell surfaces in most mammals—but not in humans and their close primate relatives. This molecule, galactose alpha-(1-3) galactose, is apparently the target for the "xenoreactive antibodies" that all adult humans have, says Jeffrey Platt, of the Mayo Clinic in Rochester, Minn. So researchers are trying to insert into pigs a human gene that will replace the pig molecule with a human sugar residue, fucosyl transferase. Whether the transgenic pigs will function normally—and whether their organs won't provoke the human immune system—is not yet known.

Suzanne Ildstad, director of the Institute for Cellular Therapeutics of the University of Louisville, and other researchers are taking a very different approach. They are trying to alter the immune system of the transplant recipient so that the person will more easily tolerate a xeno—or, for that matter, a human—transplant. Ildstad induces "tolerance" by giving the transplant recipient an infusion of specially purified bone-marrow cells from the donor. If the donor's marrow cells

*continued on page 11*

STORIES OF DISCOVERY

# Doctors Have Tried to Use Animal Parts for Centuries

by Karen Hopkin, Ph.D.

They're the stuff of mythology: satyrs, free-spirited critters with the head of a man and the body of a goat, that prance through the woods, cracking wise and looking for trouble. Or the Minotaur, a nasty beast with a man's body and a bull's head. Or mermaids, sweet ladies with fish tails and a fondness for song.

Now, we know better. There's no such thing as people who are part human, part animal. Right?

In fact, more than a few people today are walking around with a bit of the beast in them. Over the past five years, some 200 people have received transplants of animal cells or tissues to replace or assist their own failing organs.

How did this strange arrangement come to pass?

Doctors have been experimenting with xenotranplantation—the practice of transplanting parts from animals to humans—for a long time, with precious little success. But that may soon change.

Physicians and researchers are looking to xenotransplantation as a possible solution to the chronic shortage of donor organs for people with failing kidneys, livers, or hearts, and they hope to battle chronic diseases such as diabetes and Parkinson's with implants of animal cells.

But the road toward successful xenotransplantation has not been smooth, nor is it complete. So far, few whole-organ transplants from animals have worked for very long, because the human immune system is quick to destroy foreign tissue. Despite these failures, researchers doggedly press on in the hope that learning more about how the immune system recognizes and attacks foreign cells and organs will reveal how physicians can put the brakes on transplant rejection.

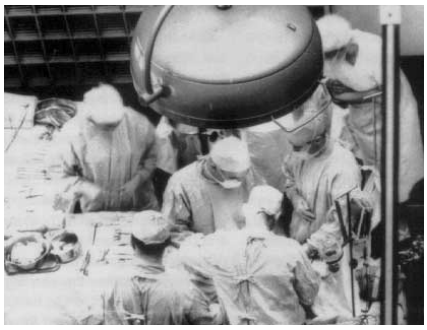
Sir Peter Medawar, Nobel larueate and the "father of transplantation biology."

**1682** Doctors repair the damaged skull of an injured Russian nobleman using a bit of bone taken from the skull of a dog. The surgery is said to be successful, but the Russian church threatens the nobleman with excommunication. So he has the dog bone removed.

**1905** The pace of xenotransplantation picks up, and physicians begin to graft animal tissues into humans with some regularity. For example, a French surgeon transplants slices of a rabbit kidney into a 16-year-old boy suffering from kidney failure. "The immediate results were excellent," he declares. But the patient dies two weeks later.

Over the next 20 years, doctors try to transplant organs from pigs, goats, lambs, and monkeys into various patients. All the grafts fail, but no one understands why.

**1953** Peter Medawar of the University of London finds that animals exposed to foreign tissues while they're young—still embryos—don't reject them. MacFarlane Burnet of Melbourne University postulates that this is because the immune cells that patrol the bloodstream in search of foreign invaders somehow learn very early on to accept whatever tissues are there as part of the body, and only attack things that show up later. In 1960, Medawar and Burnet win a Nobel Prize for their discoveries.



Surgeons perform the first human organ transplant in 1954.

**1954** Surgeon Joseph Murray performs the world's first successful human organ transplant when he transfers a kidney from one identical twin to the other. Soon after, researchers develop the first generation of drugs that suppress the immune system and prevent organ rejection. Doctors begin using these drugs routinely to inhibit organ rejection in human-to-human kidney, liver, and heart transplants.

**1963** After a lull of nearly 40 years, physicians again try their hand at xenotransplantation. Keith Reemtsma, then at Tulane University, transplants more than a dozen kidneys from chimps to humans. One woman survives for nine months, even returning for a time to her job as a school teacher. Thomas Starzl, then at the University of Colorado, performs an additional six transplants using baboon kidneys. His

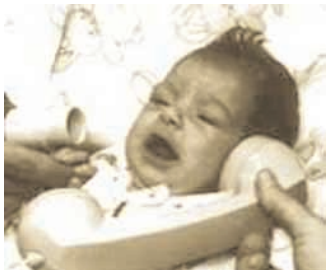
patients survive from 19 to 98 days. Although many patients now survive for weeks or months, not all the operations are such "success stories."

In one strange case, the kidneys taken from a chimp work—much too well. They produce an astonishing 54 liters of urine in one day, compared with the modest two liters considered normal for humans. The patient suffers a stroke and dies of heart failure three days later. (The surgeons had transplanted both of the chimp's kidneys, which, they later comment, "maybe we should not have done.")

**1964** James Hardy of the University of Mississippi Medical Center attempts the first cardiac xenotransplant, using a heart from a chimp. The primate heart—too small to support the patient's circulation—functions for only two hours. Two other transplants, using pig hearts, fail due to hyperacute rejection.

Outside the clinic, researchers studying animals are learning more about the causes of hyperacute rejection. They discover that human blood contains natural antibodies that can recognize cells from pigs, dogs, or other animals. When these antibodies encounter foreign tissue, they trigger a chain reaction that destroys the graft within hours.

**1979** Christian Barnaard, the surgeon famous for performing the first successful human heart transplant, tries to use baboon and chimpanzee hearts as temporary backup pumps in two patients whose hearts don't cardiac surgery. The transplants do not help the patients survive.

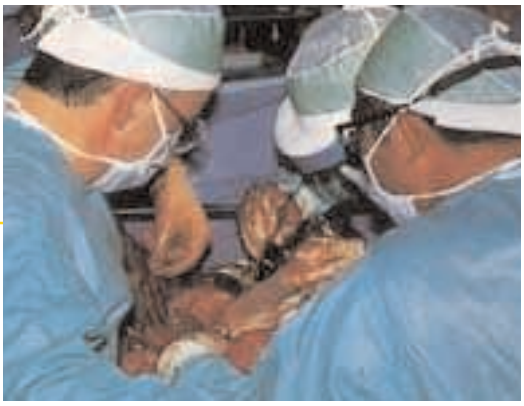


**1984** The world holds its collective breath as Baby Fae, an infant born prematurely with a malformed heart, receives a heart from a baboon. She lives for almost three weeks—longer than any other recipient of a heart xenotransplant—but then rejects the organ, due to a blood-type incompatibility (Fae was type O; the baboon, type B).

Although it didn't save Baby Fae, cyclosporine—the granddaddy of immunosuppressive drugs—is gaining widespread use for human transplants. By the end of the 1980s, newer and even more powerful immunosuppressive drugs, including FK506, come into vogue.

**1992** Xenotransplantation grabs headlines again when Starzl and his colleagues, now at the University of Pittsburgh Medical Center, perform a pair of baboon-liver transplants. One patient survives more than two months; the other, 26 days. Both die from postoperative infections that prove deadly because their immune systems are shut down by antirejection drugs. Starzl puts his xenotransplantation program on hold until the problems are better understood. Around the same time, researchers at Duke University receive permission to use a pig liver as a "bridge" to keep a critically ill woman alive as she waits for a human liver transplant. She survives only 32 hours.

Back in the lab, researchers at Massachusetts General Hospital discover that it's a particular sugar on the surface of pig cells that provokes the attack of the natural antibodies. If scientists can use genetic engineering to create pigs that no longer put this sugar on their cell surfaces, the animals' organs should be less irksome to the human immune system. Other researchers generate pigs that make proteins that can preemptively disable the very part of the immune system that would otherwise lay waste to the xenotransplant. Several biotechnology companies set out to make these "humanized" pigs and win approval for using the pig organs in humans.



Thomas Starzl and colleagues give a man a baboon liver.

**1995** Jeff Getty receives a baboon-bone-marrow transplant, in hopes that the immune cells in the baboon's marrow will replace the immune cells that Getty has lost to the AIDS virus. The baboon cells—which are naturally resistant to HIV—only function for a brief time, but Getty remains healthy (and is still alive today).

Getty's transplant may not have been a technical success, but many scientists continue to investigate how pretreating transplant recipients with marrow taken from donors might create a

"chimeric" immune system that contains cells both animal and human. Such "preconditioning" might trick the body into accepting subsequent xenografts as not really foreign after all.

**1997** Clinical studies suggest that transplants of isolated foreign cells may fare better than whole organs. In 1997, researchers report on the first clinical trial using nerve cells from fetal pigs to treat a dozen patients with Parkinson's disease. The patients show marked clinical improvement—one even takes up golf after being totally bedridden. In another recipient (who died of unrelated causes eight months after the transplant), the injected pig cells appear to survive and grow.

Meanwhile, other researchers try wrapping animal cells in a capsule that prevents immune cells from getting at them. The capsule—made of material containing very tiny pores—still admits nutrients and allows the cells to deliver their molecular products to the patient. For example, researchers at a biotech company in California encapsulate pancreatic islet cells from pigs for use in treating people with diabetes. The cells secrete insulin (which diabetics can't make themselves) and could help control patients' blood sugar levels. And about 100 cancer patients receive encapsulated adrenal cells—from fetal calves—that secrete natural painkillers called enkephalins and other neurotransmitter molecules that help ease their pain.

**"The road toward successful xenotransplantation has not been smooth, nor is it complete."**

**Tomorrow** The future of xenotransplantation is still uncertain—technical difficulties and the possibility of accidentally introducing animal pathogens into people may yet prove to be show-stoppers. But one thing seems clear. As society debates the ethics of transplanting animal tissues into humans, scientists will probe the secrets of the human immune system. And their discoveries will undoubtedly boost the success of transplantation, whether the organs come from a caring relative or an engineered pig. •

## On the Web

If you only have the print version of SnapShots of Science & Medicine, you aren't playing with a full deck. For the rest of the story come to our Web site http://science-education.nih.gov/snapshots

For our xenotransplantation issue, we have:

- Our "Junior Science Journalist" contest, giving you an opportunity to become rich and famous by writing a short news article. The winner gets a prize, and we'll publish the best entries.
- All the articles you see here, but in flashy color and optimized for the Web.
- Audio versions of all our articles. Eyes tired? We'll read to you.
- Activities to help students better understand both the science and ethics of xenotransplantation.
- A compendium of further Web resources about xenotransplantation.
- A feedback page. We really, truly want to know what you think. That goes for the topics we write about—we publish representative Letters to the Editor—as well as any ideas you have for making SnapShots better.

# Researcher Suzanne Ildstad Facilitates Xenotransplants

by Bruce Agnew

Suzanne Ildstad, M.D.

As a medical student in the mid-1970s, Suzanne Ildstad didn't have much good to say about research. Her professors at Mayo Medical School in Rochester, Minn., "remember me saying that I thought research was a waste of time and money," she says, chuckling. "At that point, I had decided to be a surgeon, and I thought operating was the be-all and the end-all."

Live and learn. Suzanne T. Ildstad, M.D., director of the Institute for Cellular Therapeutics—and professor of surgery—at the University of Louisville, is now a star of medical research. She's the discoverer of a type of bone-marrow cell that may significantly lower immune-system barriers to organ transplantation—including the transplantation of animal organs into humans, known as xenotransplantation. She's the developer of a procedure for "conditioning" transplant recipients that may transform bone-marrow transplantation from a last-resort treatment in fatal diseases like leukemia into a routine cure for a whole host of diseases, ranging from diabetes to sickle cell anemia. And in 1997, she was elected to the prestigious Institute of Medicine—an arm of the National Academy of Sciences—1 of only about 1,200 scientists, chosen by their peers as the leaders of their profession.

She changed her mind about research while doing her surgical residency at Massachusetts General Hospital in Boston. She kept asking questions of the head of Mass General's transplant program, Paul Russell, "and he would say to me, 'You know, you really ought to think about going into the lab for a couple of years.' " So she did, and got hooked.

Growing up in Minnesota, "I always wanted to be a doctor, as far back as I can remember," Ildstad says. That may run in her family: Her grandmother was a scrub nurse for Will and Charlie Mayo, the pioneering brothers who founded the Mayo Clinic in Rochester, Minn., early in this century. Her mother is also a nurse—and trained at the Mayo Clinic. "I tell my mom she might have brainwashed me, but it was something I always wanted to do," she says.

In fact, she got an early start. When she was in high school, "one of the neighbors—I used to baby-sit for their children—was a psychiatrist, and he knew I was interested in medicine." So the neighbor helped her get a summer job at an inpatient adolescent psychiatric facility.

Partially as a result of that experience, she has always opened her institute to summer volunteers, ranging from high school to medical school students. "I think the key time for students to be exposed to science, and starting to think about what career they might want to pursue, is when they're in junior high and high school," Ildstad says.

In the other important facet of her life, Ildstad, 47, has been married for 27 years to a fellow physician-professor whom she met at age 19 and married after her first year of college (and his third year). They have two children—a 16-year-old son and a 14-year-old daughter—who may or may not go into medicine themselves. "I think they're still deciding—trying all the possibilities," she says.

Many young women who are interested in scientific careers worry that they may have to postpone marriage and a family. According to the scientific stereotype, researchers put in their longest hours, do their best work, and establish themselves (or not) before the age of 35. Ildstad disagrees—although she doesn't exactly counsel impulsiveness, either.

"I don't think you have to [postpone things]," she says. "I think the key thing, though, is finding the right person. You've got to find someone who respects you. It always takes compromise on both sides, but in my opinion, you've got to have respect."

She does say, however, that combining a family with a top-echelon research career "takes a lot of planning, and it takes setting priorities." She and her husband try to avoid professional commitments on weekends—physicians can't always do that, of course—and they spend their free time with the children. "So we don't have a very active social life," Ildstad says. "We do activities with the family, and we make sure that we eat dinner together every night and breakfast every morning. I think that's really important."

Recently, one family activity involved a hunt through the attic. "One of my son's friends is into music—he composes songs—and a lot of his favorite songs are the ones from my generation, when I was growing up. We went up to the attic not too long ago and pulled out these ancient records that my son never knew I had—like the Beatles and Herman's Hermits and the Rolling Stones and Jethro Tull. Now they're antiques, right?"

Ildstad working in the lab

Whenever possible, she also takes one or both children with her on trips for speaking appearances or to perform operations, sometimes in foreign countries. "I involve them a lot in what I do," she says. Their travels—aided by frequent-flier miles—have included California, Texas, France, Italy, and Germany. On one particularly memorable trip, she took her daughter to a university-research retreat in Germany, hosted by the current head of the Hohenzollern family that once ruled Prussia. "She was 11 or 12 then," Ildstad recalls, "and she was seated next to the prince at a formal dinner in the castle, and it was like a fairy tale. She thought I do that routinely. I don't."

Routine or not, what Ildstad is doing now would have sounded as magical as any fairy tale just a few years ago.

Her research has centered on bone marrow, which produces blood and immune-system cells. Conventional bone-marrow transplants are very risky procedures, and are only done in patients with dire conditions such as leukemia. They involve complete destruction of the recipient's bone marrow, and require replacement with marrow from a donor who's as close a match as possible in all immune-system characteristics to the recipient. Finding suitable donors is difficult, and anything short of an identical twin is chancy. Failure is usually fatal.

But in 1994, Ildstad isolated what she calls "facilitating cells" in bone marrow that make it possible for transplanted marrow to take hold and grow even if the recipient and donor are not close matches. These facilitating cells are present only in tiny quantities—less than 0.4 percent of marrow cells. They're extremely difficult to isolate, because they're similar to workhorse immune-system cells known as T cells. Ildstad has worked out a way to remove active immune-system cells—which would attack any host they are given to—from donor marrow while leaving the facilitating cells intact.

Having facilitator-rich donor marrow opens up possibilities for transplantation. When a recipient's bone marrow is partly destroyed and marrow from a donor introduced, the recipient develops a "chimeric" immune system, bearing characteristics of both the recipient and the donor. This should make it easier for the recipient to tolerate transplants of whole organs—heart, kidney, liver—that also come from the marrow donor. Moreover, this should work whether the donor is human or animal.

Ildstad has shown that inducing such a chimeric immune system does indeed ease transplants and xenotransplants in laboratory mice and rats. Now she's demonstrating it in humans. Since early last year, she's used the technique in three heart transplants; one of the patients died from his underlying disease, but the other two are doing well. She's about to test it in human kidney transplants.

Ildstad is also about to aim her technique of induced chimerism at an entirely new class of disorders—autoimmune diseases such as diabetes and rheumatoid arthritis, in which the immune system goes awry and attacks its own body. By chance, some leukemia patients who received complete bone-marrow transplants also happened to have type I diabetes, caused by immune-system destruction of their cells that secrete insulin. In a few of these cases, the bone-marrow transplant had the unexpected benefit of curing the patients' diabetes, too. Apparently, the new immune system these patients got through the bone-marrow transplant didn't go after their insulin-secreting cells, allowing a few surviving cells to recover.

Conventional bone-marrow transplantation is far too dangerous to use against type I diabetes and other autoimmune diseases, because it, in effect, requires complete destruction of the recipient's immune system. But Ildstad has received Food and Drug Administration approval to test her much less destructive "mixed chimerism" methods against severe autoimmune diseases, as well as in patients with serious bone-marrow disorders, such as aplastic anemia.

NIH officials have recemtly provided funding to add another target: sickle cell anemia, a painful and potentially fatal disorder in which people with two copies of a defective hemoglobin gene produce misshapen red blood cells. The idea is to give sickle cell patients the ability to make the normal form of hemoglobin without completely destroying their own bone marrow. Ildstad had applied for funding to test induced chimerism against sickle cell disease six years ago, but was turned down.

"It was nerfed," she says. "They said it'll never work, can't be done, won't be done, and it was ahead of its time." But last year, an NIH official called her up, asked if she remembered the application (she did), and asked her to resubmit it. Its time, apparently, is now: She expects to operate on her first sickle cell patient this spring.

"I think it's going to work," Ildstad says. "It's still a research question, but I think it's going to work." She adds: "If we can cure that one, I think it would be really outstanding. It's a terrible disease." •

# Tracy Gunrud: Cow-Cell Engineer

by Richard Currey

According to chemical engineer Tracy Gunrud, the best thing about being a scientist is that "you can do some very cool stuff—stuff that helps people, that really makes a difference."

Chemical engineer and Ph.D. candidate Tracy Gunrud.

She ought to know. At age 29, she has several years as an industrial scientist under her belt, and is well on her way to earning a Ph.D. in chemical engineering. She has, among other things, studied how to power cars with hydrogen, constructed a computer-controlled fermenter to brew up yeast cells that have been genetically engineered to produce human hemoglobin, and helped implant cow cells into patients' spinal columns in an attempt to ease their pain.

Gunrud grew up in Tuftonboro, N. H., where she attended Kingswood Regional High School. "I was kind of a jock in high school. I ran track and played soccer and field hockey," she says. "I had no idea I'd end up being a scientist. I was more interested in being outside."

As for school, Gunrud says she enjoyed reading and writing, and even thought she might like to teach English or become a writer, an interest she attributes to the influence of her mother, a librarian. But, she says, her father, a mechanical engineer, "gave me his fascination with how things are made and how they do the job we want them to do—and how we can make them work better. That was certainly a beginning for me as a scientist."

But to get her firmly headed toward science as a career, she needed another push. As high school graduation loomed, "I didn't have a clue what I'd study in college," Gunrud recalls. At this critical point, her guidance counselor offered a simple and sensible suggestion: just keep studying what you enjoy most in high school. That, she readily admitted, was science, but she wasn't at all sure that she wanted to make a career of it. "Having fun in a high school course was one thing, but I didn't understand what scientists really do," she says. "I got the big concepts in class, but what did it all mean? What could I do with it? I worried that college science would be dry and boring."

Worried or not, Tracy enrolled at Northeastern University in Boston as a chemical engineering major. "At first it was just what I was afraid of—dry and boring. But I hung in." But sometime in her second year, she says, "I had a light-bulb moment—you know, when the light bulb goes on over your head and you really understand something." She had always enjoyed cooking—especially creating experimental dishes to tempt her friends. "Suddenly, I realized that chemistry is just cooking on a very large scale—mixing ingredients and cooking them up, all to create something useful. Once I figured that out, I got really excited about all of science. It's not just a lot of rules and lists. It's about making things that people need or want, and whether it's cars or hiking boots or ice cream, there's a scientist in there somewhere who figures out how to make something useful—or fun."

Gunrud (left) works with her lab partner in her high school.

After she finished up at Northeastern—where she was a member of the varsity rowing team—Gunrud went to work for CytoTherapeutics, a biotechnology firm in Lincoln, R.I. There she applied her freshly minted "cooking" skills to finding new ways to relieve pain for people with cancer or other diseases. "I put cells from cows' adrenal glands—which have pain-relieving qualities—into tiny containers that look like those little coffee-stirrers," she says. "The containers were then implanted into the spinal fluid of patients. The containers protected the cow cells and kept the patient's body from rejecting the cells. We were searching for a way to stop pain without people having to take drugs all the time." As it happens, that effort didn't pan out—the cow cells survived in the patients but didn't help with the pain. But what the

researchers learned about implanting living cells will likely prove useful in the future, says Gunrud.

**"I always thought scientists were some sort of 'special people,' and then I found I could do science, too."**

After five years at CytoTherapeutics, Gunrud went back to Northeastern part-time to get a master's degree. She is currently in school full-time, working toward a Ph.D. For now, this suits her just fine. She still manages to be plenty athletic, and competes occasionally in bicycle and running events that help raise money for medical research. But best of all, "I'm not just sitting in a laboratory, repeating textbook exercises," she says. "I'm part of an effort that really matters, that makes a difference for real people. That's a great feeling. And there's always an unanswered question, a new possibility, a challenge to meet. There's not a lot of jobs around where you get paid to be creative and help people have better lives."

Although she enjoys her work in the lab, she also thinks she'd like to teach someday, either in high school or in college. "I always thought scientists were some sort of 'special people,' and then I found out I could do science, too—not only do it but have fun at it. It would be very gratifying if I could get other young people excited in the same way, and motivate them to give science a try." •

Gunrud in her Northeastern University Lab. (Courtesy James Ceavitt, Northeastern U.)

## RESEARCH IN THE NEWS continued

# Xenotransplants: Using Animal Organs to Save Human Lives

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survive and function to produce mature blood cells, the patient's immune system becomes "chimeric." It includes some blood cells that belong to the patient and some that are produced from the donor's bone marrow. And in experiments with animals, Ildstad has found that the chimeric immune system accepts both same-species transplants and xenotransplants.

Ildstad has performed three human-to-human heart transplants using this technique, and she plans to try it with kidney transplants, too. In experiments with rats and mice, she has shown that inducing a chimeric immune system also gives xenotransplants a better chance of success.

Despite the obstacles, some xenotransplantation experiments involving humans are going on today—although not whole-organ transplants. By the end of 1998, says Amy Patterson, a scientist with the NIH Office of Recombinant DNA Activities, more than 200 people in the United States had received xenografts of animal cells or tissues. These experiments included implanting fetal-pig neurons into the brains of people with Parkinson's disease and using plastic-wrapped pig liver cells to cleanse the blood of people with liver failure, keeping them alive until a human donor liver can be found.

Researchers who would transplant whole organs have another big, unanswered question: How well will the animal organs will work in the human body? "Will the pig heart, for example, or the pig kidney function in a normal way in the human, as it did in the pig?" asks Jeffrey Platt, of the Mayo Clinic in Rochester, Minn. So far, the signs have been "encouraging," he says, "but this is clearly an issue with which we need to grapple." •

SOCIAL IMPACT

# Do We Have the Right to Transplant Animal Parts?

by Bruce Agnew

Almost certainly, scientists will one day overcome the barriers to xenotransplantation, by genetically engineering "humanized" animals or devising new ways to tame the immune system, or maybe both. But once we can safely transplant animal organs into people, should we?

Xenotransplantation raises a host of ethical and practical issues. Among them: Do we have the right to take animals' organs to save human lives? Should society have new protections against diseases that might leap from animals to people—such as requiring informed-consent not just from xenotransplant patients but also from families and associates? (See related story, "Viruses Pose Problems . . .")

Perhaps the most emotional question concerns the proper use of animals. This is a subset of a debate over animals in research that, in western society, traces back to the ancient Greeks. But it's getting renewed attention now both from Ph.D.-toting bioethicists and ordinary people.

On one side, proponents of "animal rights" firmly oppose xenotransplantation or, in fact, any commercial use of animals—for research, for food, or even as pets.

The most vociferous and probably largest of these groups in the United States, People for the Ethical Treatment of Animals (PETA), declares that "animals are not ours to use—for food, clothing, entertainment, or experimentation." PETA calls xenotransplantation "Frankenstein science" and in June 1999, formally asked the U.S. Food and Drug Administration (FDA) to ban all xenotransplantation experiments.

On the other side is the argument that human needs trump animal rights.

AIDS patient Jeff Getty, who underwent an experimental xenotransplantation of baboon bone marrow in 1995, contended in a 1996 letter to the *Wall Street Journal,* "You can't be for AIDS, breast cancer and diabetes research and also support militant animal rights groups"—because animal research is essential to scientific progress against disease.

Parts store? An engineered pig.

Most Americans seem to share that view. After all, we eat about 17 billion pounds of pork each year, and more than 142 million hogs and pigs went to market in 1997, according to the U.S. Department of Agriculture.

Australian philosopher Peter Singer condemns this attitude as "speciesism." Animals deserve "equal consideration of interests," Singer said in a 1992 speech. "Pain is pain, whatever the species of being that experiences it."

Singer, now at Princeton University, acknowledged that if forced to choose between the life of an animal and the life of a child, "it seems defensible" to choose the child. But, he went on, such a choice "reinforces the attitude that animals are just things for us to use—and this is an attitude that we should strive to change."

Singer's is a minority view. In 1996, prestigious study groups sponsored by the U.S. National Academy of Sciences (NAS) and England's Nuffield Council on Bioethics examined ethical and other issues raised by xenotransplantation and recommended that the research go forward. Key factors for both groups, along with most bioethicists, were animals' phylogenetic relatedness to humans and their "sentience"—the degree to which they appear to share such human traits as intelligence, consciousness, self-awareness, the ability to form intentions, and the ability to feel emotions such as sympathy.

Both panels signaled opposition to the use of nonhuman primates—particularly chimpanzees—as xenotransplant donors, both because of their close relatedness to humans and for fear of driving them to extinction. But this is now a dead issue. Chimpanzees and baboons are simply not going to be used as xenotransplant donors.

"The people who think that apes and primates are going to be used as organ sources are just wrong," says Harold Vanderpool, a professor of history and the philosophy of medicine at the University of Texas Medical Branch in Galveston. "It's not going to happen, because of the worries that we rightly have over infectious disease from primates . . . and also because we could decimate the entire primate population and we still wouldn't have enough organs." But Vanderpool says primates could still be used in the short run—ethically—as researchers develop xenotransplant methodology.

The Nuffield and NAS panels found less objection to the use of other animals such as pigs. "While the pig is an animal of sufficient intelligence and sociability to make welfare considerations paramount, there is less evidence that it shares capacities with human beings to the extent that primates do," the Nuffield working group said. The NAS panel observed that most people would accept the use of pigs "because these animals are traditionally used as a source of food, are distant from humans phylogenetically, and fall much lower on the personhood scale." As bioethicist Carl Cohen of the University of Michigan has said, "One cannot coherently object to the killing of animals in biomedical investigations while continuing to eat them."

Singer would agree at least with this point. "If anyone thinks that it is wrong to attempt to use the body parts of animals for transplantation purposes, but all right to use them for breakfast, then their way of thinking has nothing in common with mine," he said.

Not everyone who is concerned about animal welfare adopts an absolutist position. The Humane Society of the United States, for example, acknowledges that "biomedical research has advanced the health of both people and animals," and recognizes that "the research community is concerned about the welfare of the animals they use," says Andrew Rowan, the Humane Society's senior vice president for research, education, and international issues.

John McArdle, director of the Alternatives Research and Development Foundation in Eden Prairie, Minn., says there's an even better way to solve organ shortages. He contends that if the United States made a serious effort to spur organ donation, there would be sufficient human organs for transplant, except possibly kidneys. He notes that several European countries have enacted "presumed consent" laws, which make all organs available upon a person's death unless that person or his or her survivors has objected. "A major ethical issue is, can we justify xenotransplants when we've got such a poor record of actually trying to get human organs?" McArdle says.

In the end, the issue boils down to the same question that arises over the use of laboratory animals. And the tradeoff is the same. "The argument," says Vanderpool, "comes down to whether we think that a responsible use of animals is ethically permissible—not an irresponsible use, but very targeted, using as few animals as possible, using pain-free methods."

"Whether that's ethically permissible," he adds, "depends very much on whether one wants to side for better health for human beings or one is willing to say that the rights of animals trump desperate human needs on a very large scale." •

# Viruses Pose Problems for Xenotransplants

by Robert Taylor, Ph.D.

The use of animal organs, tissues, and cells for human transplantation is promising, says Amy Patterson, a scientist in the Office of Recombinant DNA Activities at the National Institutes of Health (NIH) in Bethesda, Md. If researchers can solve problems with immune-system rejection of tissue from other species, animal organs may end the acute shortage of useable human organs and save human lives, she says. Unfortunately, animal organs may bring with them unwanted viruses and other infectious organisms, which could potentially harm not only the patient getting the animal organ, but other people as well. "We need to know more about these risks so we can carefully assess the transition from the research laboratory bench to human patients," says Patterson.

Researchers don't yet know how dangerous any viruses carried along with a transplanted animal organ or tissue might be. They do know, however, that animal viruses can sometimes cross the species barrier and cause human disease. Most researchers agree that the risk of such an animal-to-human viral jump is greatest from closely related primate species such as baboons, but viruses have also come into the human population from other species, including horses and birds.

The risk that animal viruses might infect transplant recipients greatly complicates future prospects for xenotransplants, as animal-to-human transplants

**Unlikely organ donor.** In the wild, baboons don't eat peaches. But at the University of Washington Regional Primate Research Center, this baboon sometimes gets a treat

are called. But that danger would be weighed against the potential benefit of the transplant.

Unfortunately, potential dangers from animal viruses don't stop with the transplant recipient, says Patterson. An animal virus could conceivably go on to infect others—someone in a nearby hospital bed, for example, or even people with whom the transplant recipient has contact long after he or she recovers. In fact, the nightmare scenario some researchers worry about is a xenotransplant that introduces a deadly but unrecognized virus into the human population that spreads widely before the danger is discovered. Risks to people not involved with the transplant—who, after all, don't directly benefit from the operation—must also be taken into account when considering how to proceed with xenotransplant research, says Patterson.

One way doctors can reduce risk is to screen animals for any known viruses and reject infected animals as donors. This is not always possible, however. For example, all pigs carry multiple copies of a retrovirus in each cell's DNA. In 1998, scientists at the Institute of Cancer Research in London showed that this virus, called PERV (for porcine endogenous rertrovirus) can infect human cells in laboratory culture. It would be extremely difficult, if not impossible, to rid pigs of these retroviruses—and pigs genetically engineered to avoid provoking the human immune system are currently front-running candidates to be sources for xenografts.

Other unknowns face xenotransplantation researchers. Patterson notes that screening for viruses only takes you so far, because you can't screen for what you don't know, and animals sometimes silently harbor viruses that scientists have not yet discovered. Moreover, the kind of exposure that occurs with xenotransplantation is not like anything that occurs naturally, in that a xenograft is placed permanently inside the patient, whose immune system is often partially shut down to prevent rejection. Researchers aren't yet sure how animal

viruses, known or unknown, might behave under these circumstances.

Xenotransplant researchers recently got some reassurance that PERV won't be a show-stopper for the use of pig organs. In August 1999, a study published in the journal *Science* showed that of 160 people exposed to living pig cells in one form or another, none showed any evidence of a PERV infection.

Despite that encouraging result, all the uncertainty gives policy makers reason to worry, and they are studying the problem. The Department of Health and Human Services (HHS) has issued guidelines to govern screening of donor animals and long-term follow up of xenotransplant recipients. Researchers are still looking for signs of infection in people who have already received animal tissues. And HHS has formed a national advisory committee to study policy questions for many aspects of xenotransplantation, including the danger from animal viruses.

**"Policy makers must find the right balance between the risks, and benefits."**

"There are many unanswered questions that concern all of us, and policy makers must find the right balance between the risks and benefits," says Patterson. "The risk of introducing new viruses into the human population through xenotransplantation is not something that we can just dismiss." •

## Summary Guide: Xenotransplantation

by Robert Taylor, Ph.D.

Here are some basic facts you need to understand before you can begin to talk sensibly about xenotransplantation. **Don't memorize this list,** but read through it. After reading the articles in this issue of Snapshots, you will (we hope) be able to say, "OK, I knew that," about each point.

- An organ or tissue transplanted from a member of one species (such as a pig, baboon, or chimp) into another (such as a human) is a xenotransplant. An organ or tissue transplanted between two members of the same species (such as two humans) is an allotransplant. (*Xeno* is Greek for foreign; *allo* is Greek for different).
- Pathogens are microscopic creatures that make you sick. These include both bacteria and viruses.
- Bacteria are single-celled microorganisms that multiply on their own.
- Viruses are bits of DNA or RNA surrounded by a protein coat. They must take over a host cell's replication machinery in order to multiply.
- Your immune system attacks foreign pathogens without mercy. This is great for protecting you from infection and sickness. This is not good if you get a transplanted organ. Your immune system sees the transplant as a foreign invader and tries to kill it. This is called transplant rejection.
- The more closely related the transplant donor is to you, the transplant recipient, the less violently your immune system reacts.
- If the donor is your identical twin, your immune system won't attack the transplant at all. If the donor is not your identical twin, your immune system will attack the transplant to some extent. Some people are good transplant matches, and rejection hardly occurs. Others are bad matches, and rejection is very vigorous.
- If the donor is from a completely different species (such as a pig or a chimp) your immune system goes all

# Summary Guide: Xenotransplantation

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out to kill the transplant. The more distant the species, the more vigorous the attack.

- For human-to-human transplants, doctors have become very good at using drugs to suppress the immune system just enough to prevent rejection without leaving people completely open to attack by pathogens. Most transplant recipients have to take antirejection drugs for the rest of their lives.
- More than 20,000 human-to-human transplants are performed each year in the United States. Most transplant recipients would soon die without the transplant.
- Donor organs mostly come from people who have died in accidents or violence. Either donors agreed ahead of time to donate their organs when they die, or relatives agree to donate a loved one's organs around the time of death.
- There are not enough donor organs to fill the need. 50,000 people are on waiting lists for donor organs. About 4,000 of these people die from their illnesses each year, still waiting.
- Xenotransplantation is still very experimental, but many researchers have high hopes that the scientific problems posed by rejection can be solved.

## Next Time in SnapShots . . .

### Really Tiny Laboratories: DNA meets the Microchip.

**RESEARCH IN THE NEWS**

The massive effort to sequence the entire human genome has given researchers a huge mass of raw data. Fortunately, a new tool is coming on line to help them make sense of it all. DNA microarrays, a.k.a. DNA chips, allow scientists to get information in an afternoon that would have taken an army of technicians months to gather with older techniques. These devices look set to play a key role in connecting human genetic variations with health and disease, and to let researchers understand how genes work together to produce whatever critter they encode. And because DNA chips can be mass-produced, genetic analysis may soon find a place in routine medical care.

**STORIES OF DISCOVERY**

The DNA chip is a marvel of modern technology, but its intellectual roots go clear back to a 19th century Austrian monk's patient study of pea plant reproduction. The technology even shares an ancestor or two with the desktop computer.

**PEOPLE DOING SCIENCE**

Molecular biologist **Archana Nair** went to high school in Bombay, India, her first home town. Now she designs DNA microarrays at a company called Genometrix, headquartered near Houston, Texas.

**SOCIAL IMPACT**

As DNA Chip technology improves, it will get easier for researchers to get genetic information from a collection of individuals, each of whom must give explicit, informed consent before anyone tests their DNA. But information about the incidence of specific genetic variations in an identifiable group might reflect for good or ill on group members who weren't tested. Researchers and ethicists are trying to figure out how consent can be sought, and granted, from entire communities before data gathering begins.

**Plus classroom activities**, computer animations, a guided Web search, lesson plans, opportunities for fame and glory, and more.