Banking on Blood Conversion

New technology may change the character of the U.S. blood supply

By CORINNA WU

Eager donors arrive at a local blood drive, ready to give the gift of life. But before their blood is allowed to flow into a plastic bag through needles plunged into their forearms, they must sit down with a pen and take a test. The questionnaire—along with biochemical tests on the blood itself—is part of a rigorous screening process that has made the U.S. blood supply one of the safest in the world. As a result of this vigilance, the risks of contracting AIDS or other infectious diseases from a blood transfusion have dropped substantially.

Once that blood reaches the hospital, however, even the most careful initial screening efforts can't protect a patient from getting a fatal transfusion of the wrong blood type—a situation that occurs more often than most people think, says Harvey Klein, who is chief of transfusion medicine at the National Institutes of Health in Bethesda, Md. Sometimes, amid the chaos of an emergency room, or even in less hectic settings, a health care worker misreads a label or a chart and gives the wrong blood to a patient. If blood of type A or B is given to someone with type O blood, for example, the ensuing severe immune reaction can rapidly kill the person.

Improving blood-handling procedures and worker training can forestall such deadly accidents. Some researchers, however, think they may have found a more foolproof solution by chemically converting types A and B red blood cells to the universal type O. That way, any unit of blood cells could be transfused into any patient, removing the need to match blood types.

This innovation would have the added benefits of correcting imbalances in blood type inventories, reducing the amount of blood that gets outdated before it can be used, and cutting the costs of blood distribution. More than 15 years of research into this technique is reaching fruition; hospitals and blood centers may have blood conversion technology by next year.

In any year, as many as 1 in 12,000 units of red blood cells meant for one person is mistakenly given to another, says Klein, but "most of the time, that won't cause any harm, just by luck." Type O blood can be given to anyone, and type A blood presents no problems for someone who happens to be A or AB.

The real danger arises when, for example, a type O patient gets A or B blood or when a type A patient gets B blood. Unfamiliar molecules on the surface of the foreign blood cells trigger the immune system, which kicks into high gear and throws the patient into shock. The kidneys fail, and the depletion of blood-clotting factors causes bleeding "from the nose, ears—every orifice of the body," says Mark Popovsky, chief executive officer of the New England Region American Red Cross.

About 1 in 100,000 people who receive a transfusion dies, including most people who get incompatible blood, Klein says. Although the risk of getting the wrong blood type is fairly low, it spells almost certain death when it happens. "It's sort of like a plane crash. One in 12,000, I've always thought, is a frightening statistic," he adds. Moreover, hospitals may underreport the problem.

Some hospitals try to lessen the chance that a hurried doctor or nurse will make a fatal mistake by stocking only type O blood for emergency rooms and intensive care units, Klein says. This practice, however, can create a shortage of type O blood for the region.

On the other hand, between 5 and 10 percent of A and B blood goes to waste, says Popovsky, simply because hospitals can't use those units within their 42-day shelf life.

To minimize the waste of usable blood, hospitals sometimes ship their surplus to other institutions in the region that need more than they anticipated. Blood also travels between neighboring regional blood centers.

"No one has good data on how frequently blood is moved around," Klein says, but "we know that there is a lot of movement."

Conversion of all blood to type O can address these supply imbalances and reduce the amount of shipping necessary, says Jack Goldstein of the Kimball Research Institute at the New York Blood Center, who is one of the pioneers in the field.

The idea explored by Goldstein and other researchers is to use an enzyme to alter the chemistry of the red cell surface. Chains of sugars, which cover the cell surfaces of the four human blood types—A, B, AB, and O—all have the same basic sequence, with fucose at the end and galactose next in line.

The major distinction between types lies with the sugar that branches off from the galactose. On A cells, that sugar is *N*-acetylgalactosamine. On B cells, it's another galactose. O cells have no additional sugar at all, while AB blood cells bear a mix of A and B chains. In the United States, about 45 percent of the population has type O blood, 40 percent has type A, 11 percent has type B, and 4 percent has type AB.

A and B cells cannot be transfused into people with O blood because the extra sugar branch stimulates the immune system's antibodies to attack the foreign cells. Clipping off that additional sugar branch from A and B cells transforms them into type O, averting the immune response.

Goldstein found the right enzymes for the job in what might seem to be some unlikely places. He isolated the enzyme for B conversion, α-galactosidase, from coffee beans. "It's not so far-fetched," he says. Beans and seeds use the enzyme to break down large molecules into individual sugars, which provide energy.

The enzyme for A conversion, α-*N*-acetylgalactosaminidase, came from chicken livers. These digestive enzymes, Goldstein says, are "ubiquitous in nature, but you have to use the right ones." In the beginning, he needed 50-pound batches of both coffee beans and chicken livers to get the necessary quantities of enzyme for experiments. "I think Mr. Perdue [the chicken magnate] was happy for a few years," Goldstein says. "We used a lot of chicken livers. [It was] so traumatic, I put them out of my mind."

Researchers don't need to wallow in vats of chicken innards or mounds of coffee beans anymore. With the techniques of biotechnology, the enzymes have been cloned and are now synthesized in bulk.

The large number of sugar chains and their different orientations on cell surfaces made finding the right conditions for conversion a real challenge, says Goldstein.

Type B cells have over half a million sugar chains on their surface, while type A cells have twice that amount. Some are perpendicular to the surface; others lie parallel.

"This is what fascinated me," says Goldstein, "to get enzymes and conditions where the enzymes would work." For example, the enzyme for B conversion works best at a high acidity, but blood cells do their job of carrying oxygen in neutral conditions. Goldstein had to strike a balance that allowed the enzyme to efficiently clip off the extra galactose without destroying the red cell's function. Eventually, he determined that the reaction could take place at 26°C, rather than the higher temperature the blood cells are accustomed to, and at a slightly acidic pH of 5.5 or 5.6.

"When I started this work, no one had really treated red cells at such a low pH," he says. "It was thought that they would just become nonviable." That turned out not to be the case. Not every sugar chain on every cell gets changed, he says, but as long as enough are clipped, the body accepts the cells.

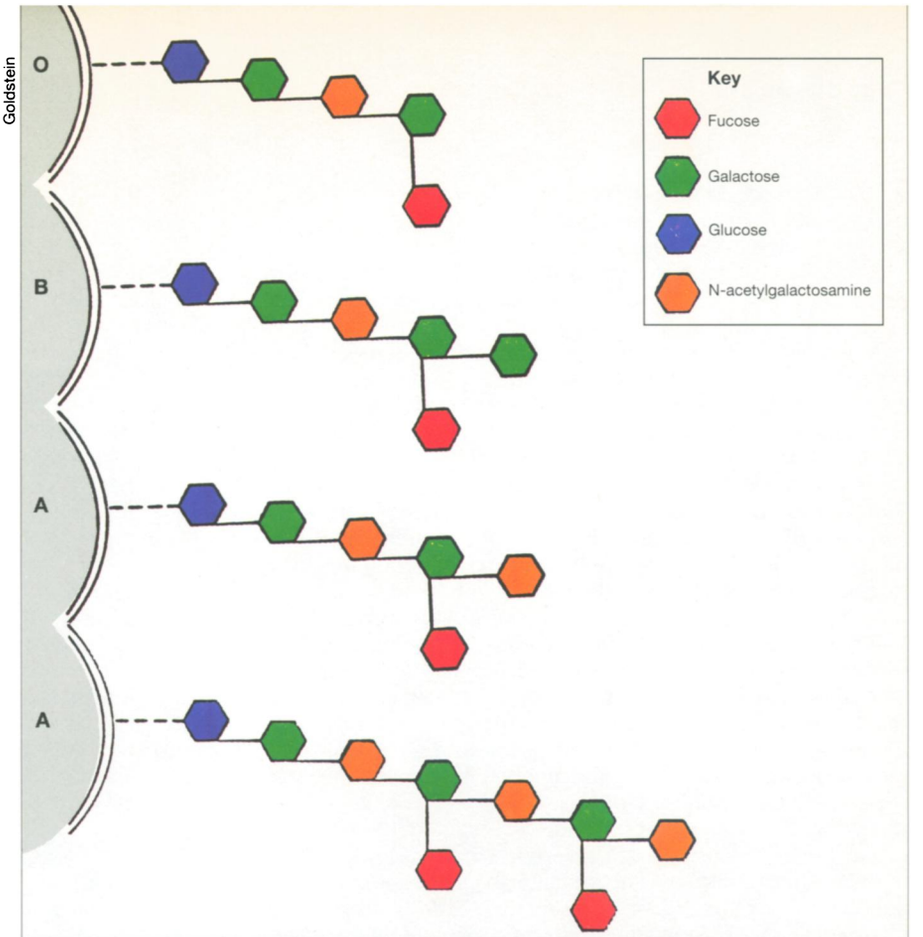
A company called ZymeQuest in North Andover, Mass., is currently conducting clinical trials to determine whether converted B cells have the same medical utility as unconverted O cells. So far, studies have shown that converted B cells behave like normal O cells and don't trigger any immune reaction.

ZymeQuest, which holds the license to develop Goldstein's technology, has designed an automated machine that performs the B-to-O conversion. Able to convert many units of blood with little human intervention, such machines could easily be incorporated into the daily routine of regional blood centers, says president Douglas Clibourn. He estimates that the company should have a salable product by the end of 1998, pending approval by the Food and Drug Administration.

A similar technique could be used for A-to-O conversion, but that project is about a year behind. Effectively converting A cells is trickier than altering B cells, because about 75 percent of people with type A blood have two kinds of sugar chains on their cells. Out of the million or so structures on each A cell, about 50,000 have a second copy of the final three-sugar sequence, which includes an *N*-acetylgalactosamine. "It's not that far in, but it means that one has to use a different approach to remove it," Goldstein says. "We're very close to solving this problem."

Starting experiments with type B blood turned out to be a good choice, he says. "If we had started with A, maybe I would have dropped this project earlier."

Once conversion technology for A and B blood is established, altering the AB cells should be straightforward. "The cost of converting all the A, B, and AB blood to O," Clibourn says, "is less than the current cost of all of that blood shipping."



Different sugar chains on the surface of red blood cells distinguish the four main blood types. On O cells, the chain ends in fucose. On B and A cells, galactose and N-acetylgalactosamine, respectively, branch off the penultimate sugar. Three-fourths of people with A blood have an additional sugar chain—one that contains a repeat of the final three-sugar sequence—on their red blood cells. Red blood cells of type AB have both A and B sugar chains.

Any technology that would convert blood to a true universal donor type must take another characteristic, Rh factor, into account. A cell surface protein first discovered in the blood of Rhesus monkeys, the Rh factor can provoke an immune reaction in people whose blood doesn't normally carry it. People who have the protein on their red blood cells are deemed Rh-positive; those who don't are Rh-negative.

Rh incompatibility is less of a problem than ABO incompatibility, says Klein. A majority of people in the United States, about 84 percent, have Rh-positive blood.

Moreover, an Rh-negative person can withstand one accidental transfusion of Rh-positive blood because the Rh-negative person doesn't develop anti-Rh antibodies until 3 or 4 months later, Klein says. "The second transfusion, after they already have that antibody they made as a result of the first transfusion, could be very serious." An Rh-negative woman who develops antibodies from bearing an Rh-positive child faces that risk if she conceives a second Rh-positive child or receives an Rh-positive blood transfusion.

Several labs have cloned the Rh factor, Goldstein says, but no one fully understands its three-dimensional structure. Therefore, researchers are only beginning to explore techniques for Rh conversion. If researchers can identify which part of the protein stimulates the immune response, then perhaps they can alter that portion to make the blood cell effectively Rh-negative. Eventually they want to produce type O, Rh-negative blood—the kind any person can receive without fear.

Despite the promise this technology holds, it doesn't produce a limitless supply of blood, Popovsky says. The key factor in maintaining the blood supply is still sufficient donation.

"Today, the demand for blood is very great," Popovsky says. "We need healthy people to donate so that they support the blood system of this country. Without them, it would collapse." Although there is talk about artificial blood substitutes, he adds, humans still cannot chemically synthesize molecules that can do everything a red blood cell does. "The human red cell is a fantastic structure—there's nothing like it." □