Slow Going for Blood Substitutes

Solutions of modified hemoglobin could replace whole blood in many transfusions if researchers can learn how to avoid their potentially dangerous side effects

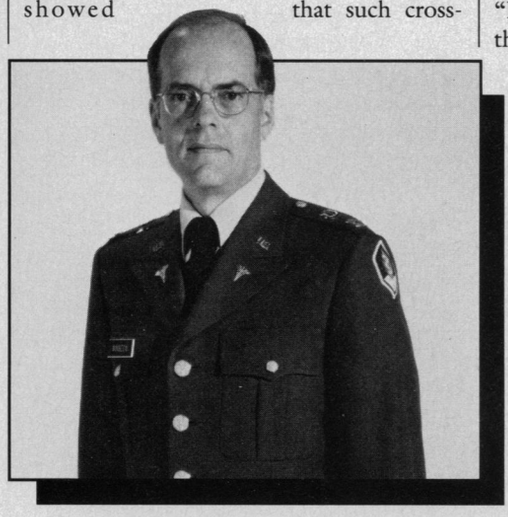
FOR 20 YEARS, A SUCCESSFUL BLOOD SUBstitute has seemed just around the corner. The medical—and commercial—rewards of such a product would be great: Patients would not be exposed to the AIDS, hepatitis, and other viruses that sometimes lurk in donated blood; doctors would not have to worry about matching blood types; and blood substitutes could be stored longer and at lower costs than whole blood, which must be kept refrigerated and has a shelf life of only a few weeks.

But developing artificial blood has proved to be more difficult than anyone expected. Several of the products, which are derivatives of hemoglobin, the oxygen-carrying protein of red blood cells, have produced unexpected side effects, including kidney failure. And progress may have been slowed by the secrecy that enshrouds much of the research on artificial blood—private companies do the majority of work in the field and keep their most important and sensitive findings under wraps.

Nonetheless, many scientists think blood substitutes may finally be getting close to market. In June, Boston-based Biopure Corporation announced that its artificial blood had been tested on ten human volunteers in Guatemala with no side effects. And a recent move by the U.S. Army's Letterman Institute of Research in San Francisco may open up the field to researchers without ties to drug companies. The Army lab has pledged to produce relatively large amounts of artificial blood, and provide samples to "anyone who wants to work with it," says Col. Robert Winslow, chief of blood research at the Letterman lab. "We're trying to make this into a legitimate, open field."

Researchers have known for decades that simply purifying hemoglobin from red blood cells and infusing it into the bloodstream doesn't work. Outside the relaxing influence of the red cells, hemoglobin holds onto oxygen molecules much more tightly—so tightly that it will take oxygen from the lungs but release little of it into the body's tissues. Furthermore, although the intact hemoglobin molecule is too big to be screened out of the blood by the kidneys, once hemoglobin is removed from the red cells it breaks down into two equal-sized halves that are filtered out—often causing major kidney damage.

Over the past 20 years, researchers have tried to avoid these difficulties by modifying the hemoglobin molecule. In 1968, Franklin Bunn at the U.S. Army Medical Research Laboratory at Fort Knox used chemical reactions to tie the two halves of the hemoglobin molecule together and avoid the problem of filtration by the kidneys. Later, Ruth and Reinhold Benesch at Columbia University showed that such cross-linking could also lower the hemoglobin's affinity for oxygen. In the mid 1970s, the German scientist M. E. Laver discovered a way to join individual hemoglobin molecules together into a hemoglobin polymer that performed much as the single, cross-linked hemoglobin molecules.



New blood. *The Army's Winslow would like to open the field to more researchers.*

Animal tests of the modified hemoglobin products were encouraging. Researchers were able to replace successfully all the blood of lab animals with blood substitutes. Even more promising was the work in reviving test animals that had been put into hemorrhagic shock. "The hemoglobin solutions worked even better than whole blood," Winslow says, because the blood substitutes had lower viscosity and could make their way through tissue faster to deliver oxygen. "This made the production of a blood substitute seem automatic—whoever could manufacture it first would get rich," he says.

But there were serious problems. Lab animals exhibited various side effects, and one of the first human trials nearly turned into tragedy. In the early 1980s, Konrad Messmer, a professor of surgery at Heidelberg University, gave a carefully prepared and tested solution to two volunteers. Although Messmer has revealed few details publicly, researchers who have spoken with him say that the two subjects suffered kidney failure and almost had to undergo dialysis. "It scared him so much that he got out of the field," one scientist says.

When researchers began seeing these toxic side effects, they could not agree about their cause—and indeed, they still cannot. Some maintain that the side effects are due to impurities in the hemoglobin preparations, such as pieces of red blood cell membranes that aren't completely filtered out or perhaps bacterially produced endotoxins. "Hemoglobin is thought to be a very potent binder of endotoxin," explains Thomas Zuck, blood center director at the University of Cincinnati Medical School. To avoid contamination by endotoxins, which can cause cardiovascular shock and other potentially fatal reactions, "You have to have a very meticulous system."

Other researchers suggest, however, that the problems might lie within the modified hemoglobin itself. "One worry is that when hemoglobin is not completely cross-linked, the kidneys may pass a lot of it and could cause problems," Winslow says. This could be a particular problem for soldiers injured in a war. "In dehydrated rats, injecting hemoglobin always produces renal failure," Winslow says, and "the military worries about this because soldiers in battle are always dehydrated."

Even if the modified hemoglobin is completely cross-linked, it may cause other problems. For instance, several of the modified hemoglobins under development are purified from cow's blood, and some researchers worry that infusing large amounts of a foreign protein into a human might trigger allergic reactions in some patients. This has made some researchers cautious about Biopure's product, which is based on

bovine hemoglobin, despite the apparent success of its Guatemalan trials.

"Everybody worries about the second infusion from Biopure," Zuck says. "Is there going to be an allergic reaction [now that the body may have become sensitized to a foreign substance]?" There are still too many unknowns, adds Kim Vandegriff, a researcher at the Letterman lab. "It's not clear how long you want this stuff to stay in the blood, for instance. We may not want it to stay a long time."

The concerns may be justified since even the use of a polymerized human hemoglobin preparation may not prevent allergic reactions. In 1987, for example, Northfield Laboratories of Illinois became the first company in the United States to obtain FDA permission to conduct human tests of a modified hemoglobin blood substitute. The first phase of tests on six healthy volunteers came off with only a slight hitch—one subject had a minor tightness in the chest—but problems arose early last year when the company began injecting small amounts of their blood substitute into post-operative patients. The first two patients to receive the artificial blood suffered allergic reactions stronger than had appeared in the earlier test—flu-like symptoms and a tightness in the chest that both lasted about 2 hours, the company says. The trial was canceled.

Northfield has said publicly that contaminants in the solution were to blame for the reactions, but other researchers are not so sure. "I don't think we know," says Winslow, who was at a 14 March hearing of the FDA where Northfield and seven other companies presented data on modified hemoglobin products. That meeting was called, says Joseph Fratantoni, chief medical reviewer for blood substitutes at the FDA, because the Northfield tests revealed that "we didn't have a handle on the question of potential toxicity of hemoglobin."

After the hearing, the FDA released a comprehensive list of requirements that will have to be met before it grants requests for future clinical studies. Although the FDA does not reveal when a company has received permission to perform human trials, researchers familiar with the field say that they know of no company doing such work in the United States at this time.

What is really needed, argue many scientists outside the private drug companies, is more open research. "When [the drug companies] do research, they do it under cover, and in order not to discourage investors, only positive data are propagandized," says Enrico Bucci, a biochemist at the University of Maryland who studies modified hemoglobin. "This kind of partial information has sometimes produced misinformation." Philip Russell, who recently retired from the Army's Medical Research and Development Command, says, "The field has not moved as well as it should, and it's partly because of the way these companies have behaved."

It was in response to these concerns that the Letterman lab made its offer to supply modified hemoglobin to interested researchers, Winslow says. Although he predicts it will be 5 or 6 years before a blood substitute is on the market in the United States, Winslow does think that day is coming. Eventually, he says, the Army hopes to have a blood substitute that can be freeze-dried for storage and transport. Then, when it's needed, just add water and stir—instant blood. ■ ROBERT POOL

Blood, Money, and the Pentagon

Before a single blood substitute product has appeared on the market, they are already big business. Two weeks ago, Boston-based Biopure announced that it had sold rights to its modified hemoglobin product to the Upjohn Company; the pharmaceutical giant paid $25 million and promised to put in an additional $154 million if the product passes certain milestones in the development process. And Upjohn may well have gotten a bargain—*Business Week* estimates that the total market for artificial blood could reach $10 billion worldwide. With this much at stake, the scramble to be the first to put a blood substitute on the market becomes much more than a scientific contest.

"There is a lot of politicking going on," says Harvey Klein, chief of transfusion medicine at the National Institutes of Health in Bethesda, Maryland. Indeed, he says, a 14 March meeting held by the Food and Drug Administration to review progress in the field was apparently "brought about by companies pushing the FDA to be more lenient in allowing clinical trials." This type of pressure from drug companies may be nothing new to the FDA, but some companies developing artificial blood have turned their attention to the Pentagon, and some of the military's own experts on blood substitutes aren't too happy about that.

"The Army has always been interested in blood substitutes," says Robert Winslow, chief of blood research at the Letterman Army Institute of Research in San Francisco. An artificial blood that is easy to transport and to store could mean the difference between life and death for men seriously injured in combat, he says, and studies with lab animals indicate that some blood substitutes might actually be more effective than whole blood in reviving people in shock from loss of blood. (Also see story on p. 1655) But, Winslow says, Army researchers have been frustrated by the secretiveness of private companies, which do most of the research in the field, and the Army lab has not yet been convinced of the safety of any of their products.

For that reason, some Army scientists say in private that they have been irritated by attempts by at least one drug company to go over their heads and appeal to top brass in the Army and in the other armed services. According to one Army insider who insisted on anonymity, former Surgeon General C. Everett Koop met with Army officials this fall to urge them to consider the blood substitute manufactured by Biopure. Koop was recently hired by Biopure as chairman of its scientific advisory committee. "It's possible they have a good product," the source said, "but they've been so goddamned secretive that they haven't allowed enough investigation [of the product] to generate a high level of confidence in the scientific community."

Still, Koop's lobbying may have paid off for Biopure, at least giving the company ample opportunity to present its case. According to a different source, Biopure officials met 2 weeks ago with the surgeons general of the various branches of the armed services to offer information about the company's blood substitute.

When questioned about Biopure's lobbying efforts, company spokesman Andrew Plesser said, "To say that the company has been politically pressuring [anyone] is absolutely false." He said he could neither confirm nor deny that the purported meeting at the Pentagon took place. Koop was out of town and unavailable for comment.

Whether talks with Pentagon officials will help Biopure land a contract is another question altogether. In Winslow's opinion, the Army won't consider any artificial blood before approval by the FDA, and at least seven other companies in the United States, Canada, and Japan are competing with Biopure. Which will be the first on the market is anybody's guess, but workers in the field hope it will be the company with the best research and the best product, not the best lobbyists. ■ R.P.