

Lifeline

in a Bottle

Inorganic blood substitute developed

Every cell in your body depends on it for survival. So in times of trauma—a shattering car collision, a shooting, a stabbing—stabilizing the flow of blood can mean the difference between life and death.

Researchers in the UB School of Medicine and Biomedical Sciences are working to improve the odds for trauma victims by testing an inorganic blood substitute that could be administered anywhere from an ambulance to a battlefield. The goal is to enable the body's remaining blood to circulate life-giving oxygen more effectively. This lengthens the window of time for the patient until he or she can be rushed to a hospital for whole-blood infusions.

THE WIDER THAT WINDOW, the better the chance that someone will make it through the ordeal.

The substance in question is DDFPe, short for dodecafluoropentane emulsion. It doesn't look like much—a milky-white liquid stored in glass bottles half the size of a roll of Lifesavers. But researchers, working under a new four-year \$1.5 million grant from the National Institutes of Health, hope it will become a lifesaver.

"Just five little bottles can replace the loss of half the blood volume, which if untreated may be lethal," says physiology and biophysics department professor Claes

Lundgren, MD, PhD, director of the UB Center for Research and Education in Special Environments (CRESE) in the School of Medicine and Biomedical Sciences and principal researcher on the project. "What's very interesting to us is that, if you treat the loss of oxygen supply, you may get away without giving any additional fluid."

That's important logistically, he says, because other attempts to develop emergency blood substitutes have resulted in bulky liquid compounds that are too cumbersome for jam-packed emergency medical services vehicles

or for other uses. With DDFPe, Lundgren says, “you could imagine a soldier carrying his own blood supply in his pocket.”

It’s all about getting oxygen to tissues, including sensitive brain cells that would rapidly die without it. In a healthy body, the blood-borne iron compound hemoglobin chemically latches onto oxygen in tiny capillaries on the interior surface of the lungs, then releases the oxygen to the cells as it circulates throughout the body. But in a traumatized person who has lost a lot of blood, there isn’t enough hemoglobin to perform this task effectively. Shock, and death, can come quickly.

Standard practice for emergency services workers is to try to replace the volume of the lost blood by infusing saline solution or Ringer’s lactate, a similar benign liquid. That provides enough volume for the circulatory system to keep the blood moving, but doesn’t solve the problem of too little oxygen being carried.



PHOTO BY ERIC FRICK

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Lundgren and colleagues Ingvold Tyssebotn, MD, PhD, professor of physiology and biophysics at UB, and Guri Bergoe, PhD, senior research scientist in CRESE, are working with one of the few blood substitutes being developed that does not depend on hemoglobin. Instead, DDFPe is a fluorocarbon-based compound that was originally used as a contrast medium for taking ultrasound images; its tiny bubbles reflected the sound waves to enhance the image.

How a photo-enhancing chemical became a promising medical advance, familiarly called “bubble blood,” is a tale

of nimble scientific minds at work.

Lundgren’s research group, under the umbrella of CRESE, studies the effects of such endeavors as diving, flying and space travel. Researcher Hugh Van Liew, PhD, now professor emeritus of physiology, working earlier with his student assistant at the time, Mark Burkard, did some computer modeling of the tiny bubbles that form in the bloodstream during “the bends,” the painfully debilitating condition that develops in deep-sea divers who surface too quickly. The model showed that those bubbles contain not only nitrogen, but also oxygen.

The question then was posed: Is there a way to repli-

cate that process so that the bubbles could carry desperately needed oxygen in the blood of trauma victims?

The researchers turned to DDFPe, which is liquid at room temperature but when injected or infused into the human body, it literally boils. Just as a pot of water bubbles furiously on your kitchen stove at the right temperature, in the body the very fine particles of DDFPe when warmed to body temperature boil into a bounty of tiny bubbles.

These microbubbles initially are filled with fluorocarbon gas—no help to anyone. But because they are so small, they can be carried in the bloodstream into the microscopically small capillaries in the lungs and thus can pick up oxygen, “like a sponge, if you will,” Lundgren says. Similarly, the oxygen-laden bubbles can pass through the capillaries in the brain, the limbs, the organs—everywhere the blood serves up its life-giving nourishment—and release their oxygen to the cells.

Initial work on the substance resulted in two patents, which were issued in 1999 and 2000. The current study aims to measure how soon the treatment must occur after bleeding begins, and how much blood loss can be compensated for by the introduction of DDFPe. Laboratory animals—pigs and rats—are anesthetized; quantities of blood are removed; DDFPe is introduced in carefully controlled regimens; and the animals’ survival rates are charted.

IF THE RESEARCH SUCCEEDS, Lundgren says, the compound would undergo further refinement in preparation for human testing as required by the Food and Drug Administration before it could be approved for market. UB is currently in negotiations with a pharmaceutical company interested in developing the product for sale.

“Our findings should help to lay a solid foundation for pursuing FDA approval for human use of this blood substitute,” Lundgren says. “In the best of circumstances, it would be carried in every ambulance.”

The UB research is far from the only activity to



Difficulties with currently available hemoglobin-based blood products:

The manufacturing process for hemoglobin-based blood products is costly.

Some hemoglobin-based blood products are distilled from outdated donor blood, which means the supply is uncertain and the possibility of infection is ever-present.

Hemoglobin-based substitutes are bulkier than the compact DDFPe, presenting problems of storage.

Some hemoglobin-based products have the effect of raising blood pressure dangerously high.

Finally, some people have moral or religious objections to receiving medical products based on human blood.

develop a blood substitute for use in trauma situations. In fact, another research team is working on a fluorocarbon-based substitute that remains liquid in the bloodstream and dissolves oxygen before transporting it. Lundgren confidently says DDFPe, because of its microbubbles, is 500 times more effective in its oxygen-carrying capacity than this other fluorocarbon blood substitute. Also, he says, the competing fluorocarbon

substitute tends to remain in the body for a long time, with uncertain effects; DDFPe, by contrast, “may last for three or four hours, and then it can be repeated if necessary.” The other substitute also requires that the patient be given pure oxygen to breathe, which can be cumbersome or impossible for emergency workers to use in some situations, and may harm the lungs.

There are also at least four hemoglobin-based blood substitutes in late stages of clinical development, including one, PolyHeme, that has progressed to the stage of human testing.

It would seem logical that a hemoglobin compound would be the best bet in times of trauma. After all, it’s the sudden shortage of hemoglobin that puts the body into

an oxygen crisis in the first place. However, as described in the sidebar on page 14, Lundgren and other critics see logistical and other problems with the hemoglobin-based blood products.

When first studying DDFPe, Lundgren says, researchers administered pure oxygen with a respirator—something medical technicians could sometimes do in the field, but which would be unwieldy in, say, a combat situation. However, he notes, one of the most promising aspects of the substance is that it seems to work when the patient is breathing regular air, which is 21 percent oxygen.

If the promise of the research by Lundgren’s team holds true, those tiny bubbles could be making big news on the frontiers of emergency medicine. **BP**

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