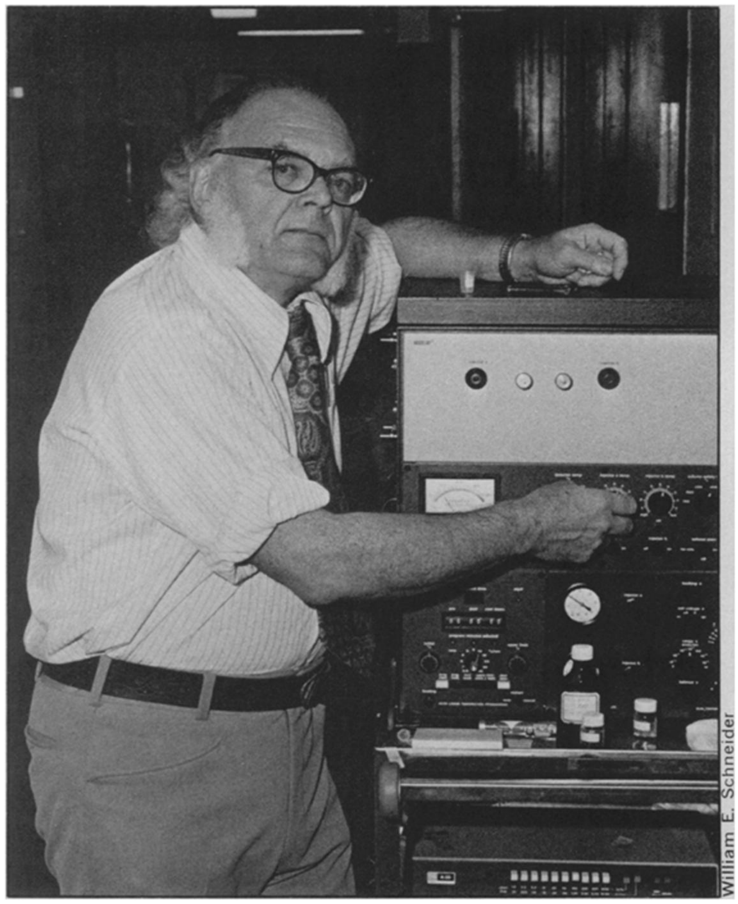
Bloodless & Breathless

Artifical blood and breathable liquids are nearly ready for human testing. Discovered by chance, they are strange but potentially useful.

by Janet H. Weinberg



Leland Clark: Serendipitous discovery leads to medical potential.

Once upon a time, a chemist named Leland Clark took off his white coat and prepared to leave his laboratory for the day. As he was shutting the door, two facts, floating peacefully through his brain, collided and formed a new idea. He stopped. He went back into the lab and filled a beaker with silicone oil, then bubbled air through it for a few minutes. Then he took a rat from a cage, tied a weight to its tail and dropped it into the beaker.

He was not surprised to see it staring back at him through the glass. They watched each other for almost half an hour before the rat stopped breathing (yes, breathing) and died. Subsequent rats and mice lasted longer in the oil—some upwards of six hours.

Clark has been living in this true fairy tale ever since, along with several other respected researchers. Eight years and thousands of animals later, they are nearing completion of artificial blood and breathable liquids—strange but potentially lifesaving medical tools.

Clark worked at the Medical College of Alabama back in 1966 when he put together two fundamental chemical facts to make his discovery. He knew silicone oil can dissolve and hold about 20 percent oxygen. And he knew that, coincidentally, air holds about 20 percent oxygen. It occured to Clark that if an animals' organs and tissues are sustained by the 20 percent in the air, they could be sustained by that amount in fluids. And he was right.

In order to understand breathable liquids, one must keep in mind that the lungs are functional organs not necessarily violated by the presence of liquid. In the lungs are millions of tiny capillaries. These convey red blood cells which exchange oxygen for carbon dioxide. If a fluid medium can bring enough oxygen to the red blood cells and carry away enough carbon dioxide, then normal exchange can take place and the animals' needs can be met. This appears to happen with Clark's breathable silicone oils and perfluorochemical compounds, another class of compounds capable of absorbing great amounts (up to 60 percent) of oxygen.

But even if the lungs aren't necessarily violated by the presence of fluids, why do most animals drown in fluids while Clark's test animals breathe? Clark, now director of the neurophysiology division at the Children's Hospital Research Foundation in Cincinnati, points out that drowning occurs for three different reasons. First, if an animal breathes fresh water into his lungs, the water enters his blood cells causing them to burst and he dies. Fresh water is hypotonic—it has less salt than the blood—and the osmotic pressure in the red cells admits too much water for the cell walls to contain. Second, if the animal breathes salt water (which has more salt content than the blood, or hypertonic) the larynx goes into spasms and the animal suffocates. Third, if an animal breathes an isotonic solution (the same salt content as the blood) at normal atmospheric pressures, the water can dissolve only about 3 percent oxygen, not enough to meet the animals' needs, and his brain dies from lack of oxygen. If that same isotonic solution is forced with a hyperbaric chamber to dissolve 20 percent oxygen, the animal can breathe it and survive.

Research toward breathable liquids has progressed from pressurized saline to the use of perfluorochemical liquids, such as perfluorodecalin. The structure of this compound is similar to naptha.

It has two 6-membered rings side by side, but fluorine atoms replace each of napthas' hydrogens. Although perfluorodecalin is about twice as heavy as water, test animals seem to breathe it in and out about as well as air, Clark says. They use their diaphrams, but in a different way, pulling the fluid in slowly over long periods. Most test animals can remain submerged for several hours and survive, but their lungs are frequently damaged.

Clark is looking into the possibility of using breathable liquids to help cystic fibrosis patients. "Cystic fibrosis is a very ugly disease," he says. "The person essentially has too much mucus in the lungs and usually suffocates in his own mucus as a teenager. If we could use these liquids to wash out their lungs, we may be able to get them past the worst years, from 12 to 15."

Another application would be the prevention of the bends after deep sea diving. Clark has decompressed a mouse breathing the fluid from the laboratory equivalent of a depth of 500 feet in one second. The animal survived. "This is because the liquid is not compressible, and bubbles did not form in the animal's blood," Clark says. If deep sea divers carried tanks of oxygen-rich fluorochemicals instead of compressed gases, theoretically they too could pop up to the surface without getting the bends. But the lung-damage problem must be licked first, he says.

Potentially more important than work toward breathable liquids is research on artificial blood which grew out of Clark's never-never-land discovery.

It occurred to Clark and other researchers that if fluorochemical compounds could carry oxygen and carbon dioxide to and from the red blood cells, perhaps they could function as "synthetic red blood cells" within the body. Blood extenders, such as saline solutions and blood and sugar mixtures, have been available for some time, but they don't carry oxygen and therefore must be combined with red blood cells. A safe, synthetic blood substitute would have enormous practical value for the medical profession. This would be especially true if, like fluorochemicals, it were long-lasting, required no refrigeration, had no protein factors and therefore didn't require blood typing and were cheaper and easier to obtain than whole human blood.

Clark tested a liquid fluorochemical on an isolated rat heart and maintained its activity briefly. But not until another group developed fluorochemical emulsions could the organs be maintained for long periods of time. Henry A. Sloviter and Toshiharu Kamimoto of the University of Pennsylvania medical school at Philadelphia in 1967 put together a mixture of a fluorochemical (which acts as an artificial red blood cell) and albumin dispersed in water (which functions as a synthetic blood plasma) and successfully maintained the electrical activity in an isolated rat brain.


William E. Schneider

Breathing in a fluorochemical bath.

The brain requires proportionately more oxygen than the other organs, and, says Sloviter, "Knowing that the material is capable of meeting the oxygen requirements of the brain, one could expect that it would adequately deliver oxygen to all of the other organs."

In recent work, Sloviter and his colleagues maintained an isolated kidney for 24 to 48 hours in "reasonably decent condition." Maintaining a kidney before transplantation with artificial blood could be an important technical advance, Sloviter says, because blood cells pumped for long periods of time rupture and have to be continually replaced to ensure adequate oxygenation of the tissues. Sloviter is hopeful that fluorochemicals can be used in this way, but thinks some proposed applications may be too dangerous. "Clark has shown that wide-scale retention of the fluorochemicals in the liver and spleen are a problem," and some fluorine compounds are carcinogenic, he says. Also, some animals die soon after being given fluorochemicals; the reasons are not well understood. "These fluids aren't too dangerous to use for an isolated kidney, but we haven't yet reached what we consider a satisfactory level" for the use of large quantities in the human body, Sloviter says.

Clark, on the other hand, is more confident about the intravenous use of fluorochemicals. He has replaced up to 80 percent of the whole blood in mice, rats and dogs and kept many of them alive afterwards for years with "no signs of ill effects." (Some do die during or after the transfusions.) Clark reported last summer the use of perfluorodecalin, which he found, is not retained in the tissues for long periods like most other fluids tested. This eliminates one of the more serious problems. Carcinogenesis is still a worry, he says, although none of his test animals have developed tumors.

Artificial blood could fill many medical needs, Clark says. After his current test series of transfusions on dogs and monkeys, he would like to start working toward use for terminal cancer patients. In some cancers, Clark says, red blood cells are destroyed or are not replaced after they deteriorate. "Because of this, [the patients] become much sicker. The phone rings here each day with someone who could benefit from this kind of treatment," Clark says.

Another near-future application would be used as a primer for heart-lung machines, which require several pints of blood before an operation. "The machine could be filled with artificial blood and the patient's own blood would be removed and saved. After the open heart surgery, the artificial blood could be thrown out and the patient's blood replaced." Also, Clark says, 90 percent of the world's people don't have access to blood banks, and artificial blood would allow emergency care of patients in areas where none now exists.

Harvard University nutritionist Robert Geyer is taking another approach to artificial blood research. Unlike Clark's partial replacement (transfusion), he and his students are attempting complete blood replacement. Geyer washes out a rat completely, transfuses it with a fluorochemical emulsion, then provides it with oxygen-rich air until it slowly excretes the artificial blood and regenerates its own. This system not only allows for study of blood synthesis, but allows for chemotherapy with drugs which are normally destroyed by antibodies and blood factors. "Many chemicals are destroyed by the blood—ATP [an energy-storing molecule] for example, is destroyed almost instantly. ATP can be successfully circulated in a bloodless animal," Geyer says. Artificial blood might also have "a useful place in immunotherapy of tumors."

Clark says artificial blood research is progressing much faster than work on breathable liquids because it has "more implications for medicine." Before the blood can be used in medicine, applications and tests must be completed and approved by several Government agencies. Clark believes strongly in his fairy tale discovery and is anxious to see it used to allay human suffering. "For all I know it might not work," he says, "but we won't know until we try it, will we?" □