Fluid flushed with promise

People who have offered to donate their body parts upon death can bring life to those in desperate need of a kidney, liver or other organ. But if the organs harvested from a cadaver cannot be preserved long enough or well enough to be successfully transported and transplanted to a recipient, all will be for naught.

Now it appears that such stories may have happier endings, because physiological chemist James F. Southard and his colleagues at the University of Wisconsin in Madison are making significant headway in improving organ preservation. Last week in Edmonton, Alberta, at the 24th annual meeting of the Society for Cryobiology, Southard reported that in dog studies, his group has extended the preservation times for a number of organs by using a preserving solution originally developed by Southard's coworker Folkert O. Belzer.

Researchers have shown that, unlike most conventional preserving fluids, an improved version of Belzer's solution can be used in more than one kind of organ and in more than one preserving process. If the group is as successful in human studies, Belzer's solution may well replace the existing fluids and make the preservation and distribution of donor organs much simpler and more efficient.

Scientists and surgeons have generally taken two routes in organ preservation: continuous hypothermic perfusion and simple cold storage. With continuous hypothermic perfusion, organs are kept at 5° to 10°C and are pumped with a cold preserving fluid that supplies nutrients and oxygen, removes waste products and keeps cells and membranes intact. With conventional perfusing fluids, says Southard, kidneys can be kept alive for three days. Now, using Belzer's solution, the Wisconsin researchers have extended that time to five days. All five of the dogs receiving the preserved kidneys have survived.

Belzer's solution was originally developed for continuous hypothermic perfusion, but Southard's group is the first to demonstrate that their perfusion fluid works as well in simple cold storage. In this method, organs are kept at 0° to 4°C after being flushed with certain fluids. With Belzer's solution – a fluid far more complex than those traditionally used – the researchers successfully preserved dog pancreases for 72 hours (clinically they are now preserved for only six to 10 hours). In addition, they showed that kidneys can be cold-stored for three days, more than 12 hours longer than current cold storage of human kidneys.

Perhaps most significantly, the group has succeeded in preserving dog livers for 24 to 36 hours. "Currently the liver is [cold] stored for about six to 10 hours in clinics," says Southard. "This makes the whole procedure extremely difficult . . . [often requiring the use of Lear jets to pick up organs]. . . . What you really need is about 30 hours of preservation." This would minimize the number of operations performed under emergency settings and increase the number of livers available to the people who need transplants, he says.

The researchers believe their solution works better than other fluids for a number of reasons. For one, it contains hydroxyethyl starch, which acts as a colloid in the blood vessels of organs. During perfusion, water may be pumped into cells; the purpose of a colloid is to draw the water out, so that the cells don't swell and burst. Other perfusing fluids have used albumin as a vascular colloid, but Southard says albumin can damage and leak out of the vessels. He suspects that, in cold storage, the starch also helps to flush out the organ better by keeping the vascular areas dilated.

Another improvement, according to Southard, is the use of anions with large molecular weight as a replacement for the chloride anions used in other fluids. Anions, or negatively charged ions, are usually added to make fluids neutral. The problem with chloride anions, says Southard, is that they are small enough to get inside the cells, and this can draw water into the cells. The anions in Belzer's solution are too large to permeate the cell membrane.

Southard's group plans to try Belzer's solution on other organs, including the heart, lung and small bowel. As for the kidneys, he says the researchers have applied to the Food and Drug Administration to use their starch-based fluid in human trials. If they can show that it works well in many organ types being either perfused or cold-stored, then they may have solved a problem plaguing the donor-organ network.

When the organs of a body are to be preserved, says Southard, the whole body ends up being flushed with preservation fluids. The problem is that a conventional fluid that preserves the liver, for example, may damage other organs such as the kidneys. Moreover, the preservation method and hence type of fluid used by different centers varies; small centers rarely have the resources to maintain a perfusion machine, and large centers sometimes have too many transplants to perform in too short a time to rely on the shorter-lasting cold-storage approach.

"One way to resolve this is to use one fluid [that works for both storage methods], letting surgeons decide what method they want," says Southard. "And we think [Belzer's] solution is close to a universal preservation fluid for all solid organs." – *S. Weisburd*

New bearers of nerve tidings?

Something repeated by one person and then another often becomes a garbled message. But in the nervous system, a crowd of chemical messengers accurately transmits signals from cell to cell. The neurotransmitters passed between nerve cells, along with the intracellular "second messengers" they frequently enlist, can work to keep open the lines of communication, instructing cells how to respond to a specific stimulus. Now scientists at Columbia University in New York City report a newly identified class of second messengers, which may play a double role in carrying signals both within and between cells. The finding eventually may further the understanding of certain neurological disorders.

Using the marine mollusk *Aplysia* – chosen because of its large, easily accessible neurons – the researchers found that one or more products formed during the breakdown of intracellular arachidonic acid apparently act as second messengers within cells, which are stimulated when neurotransmitters attach to receptors on their surface. The arachidonic-acid metabolites, called eicosanoids, may go beyond the usual second-messenger job of carrying out instructions brought by the neurotransmitter released from another cell, says Columbia's Daniele Piomelli.

"We think we have found a second messenger that allows the [message-receiving] cell to regulate the amount of neurotransmitter it itself releases," Piomelli told SCIENCE NEWS. The possibility of such a double-duty mechanism – first postulated by other scientists about 10 years ago – would require that the eicosanoids work outside, as well as inside, the nerve cell, says Piomelli, coauthor of a report on the study in the July 2 NATURE.

Eicosanoids are known to carry messages between cells other than nerve cells. In order to determine whether this also holds for nerve cells, the scientists studied the effect of various eicosanoids on the *Aplysia* neurons, whose electrical-impulse responses were measured after each application. In addition, they are working to identify which of the various metabolites is either directly responsible for signal transmission or is itself further changed into the mysterious second messenger, says Piomelli.

He says that in the past five years, scientists have found receptors for eicosanoids on the surface of mammalian brain cells, and that there is an increased release of the metabolites during epileptic seizures. Although such clinical implications are "worth investigating," he says that more basic research questions must first be answered. – *D.D. Edwards*