Savoring Chemistry in the Land of the Cod

From 22 to 27 April, members of the American Chemical Society met in Boston for their 199th national meeting. As always, they served up a rich bouillabaisse of research results ranging from agriculture to medicine to chemistry. A taste:

A Safer Way to Make Plastics

A newly discovered class of catalysts could point the way toward environmentally safer ways of making many plastics, according to inorganic chemist Bruce Novak of the University of California at Berkeley. Instead of carrying out polymerization reactions in huge tanks of benzene and other carcinogenic solvents—which are hard to dispose of properly and which are among the major contaminants at superfund cleanup sites—companies could use the new catalysts to make their plastics in a much more benign solvent: water.

"You still get a toxic sludge once you've finished the evaporation [of the wastewater]," says Novak, "but it's much smaller in volume and easier to handle."

Making polymers in water flies in the face of conventional wisdom in this field, he says, namely, "that catalysts for polymers are air- and moisture-sensitive, so all reactions have to be conducted in organic solvents." That dogma is true for the current generation of catalysts, most of which are highly reactive compounds containing titanium, tungsten, molybdenum, and other transition metals lying toward the left-hand, or "early" side, of the periodic table. But starting in the late 1980s, while Novak was still a student of Robert Grubbs at the California Institute of Technology, he began exploring catalysts containing "late" transition metals lying further to the right in the periodic table.

Nobody had paid these catalysts much attention before because they're not as reactive as the conventional ones. But that very lack of reactivity makes them tolerant of less than ideal conditions. And much to his astonishment, says Novak, he eventually found a ruthenium-based compound that not only tolerates water, "it actually goes faster when you add water."

The particular reaction catalyzed by the ruthenium compound produced a plastic known as polyoxanorbornene, which is too pliable and flimsy to be of much commercial interest on its own. Within the last year, however, after finishing his degree and setting up his own laboratory at Berkeley, Novak, along with his students, found a way to combine polyoxanorbornene with silica. The result, he says, is "beautiful, clear, transparent stuff," half the weight of conventional glass and several times as tough. "It's difficult to break—even with a hammer," he says. Moreover, the glass is relatively easy to mold, and can be formed at only 50°C, compared to 1500°C for normal glass. Potential applications include eyeglass lenses and aircraft windows.

Meanwhile, Novak and his students have discovered a nickel-containing catalyst that works in acid aqueous solution to produce polyisocyanide, a component of high-impact plastics. "That's two examples [in this class of catalysts]," he says. "And we think there will be more."

Shrink-Wrapped Transplants for Parkinson's

Polymer chemistry may one day take the controversy out of a recently developed surgical treatment for patients with Parkinson's disease, a degeneration of certain neurons that secrete the neurotransmitter dopamine.

The results of such surgery are undeniably dramatic: Patients whose movements have been impaired for decades by the disorder have been returned to near normal functioning by dopamine-secreting tissues transplanted directly into their brains. And yet, the method has been politically and ethically sensitive in the extreme: to minimize the chance of rejection by the patient's own immune system, the transplanted tissue is taken from aborted human fetuses.

Soon, however, a new technique for encasing clusters of living cells in a porous polymer envelope could allow surgeons to treat parkinsonism with dopamine-secreting animal cells or even cultured cells. "The pores in the polymer are large enough to let the dopamine molecules out and the nutrients in," says Patrick Aebischer of Brown University's Artificial Organ Laboratory, who described the process at the ACS meeting. "But the pores are too small to let cells or molecules from the immune system in or out."

Creating the envelope is tricky, says Aebischer, since the polymer—an acrylic thermoplastic—must be precipitated from an organic solvent that is fatal to cells. But he and his colleagues have found that if the cells are suspended in a culture medium, the water in the medium protects them while the polymer forms at the interface.

The result is a capsule 500 micrometers across containing some 100,000 cells. (Aebischer and his colleagues are currently using an immortalized line of cells originally derived from rat adrenal glands, which also secrete dopamine.) The capsules are inserted into the brain by placing them at the tip of a thin, porous plastic tube that runs from the scalp to the basal ganglia.

Aebischer and his colleagues have already published studies of this technique in rats, and are now beginning experiments on monkeys with artificially induced parkinsonism. The preliminary results are quite encouraging, he says: the monkeys showed nearly complete recovery after the operation, and they still show no sign of rejection or regression after 3 months. In principle, he adds, the same approach could be used to treat Alzheimer's disease and other degenerative conditions in the brain. Indeed, he says, there is no reason one couldn't use cells that have been elaborately tailored to specific purposes by genetic engineering.

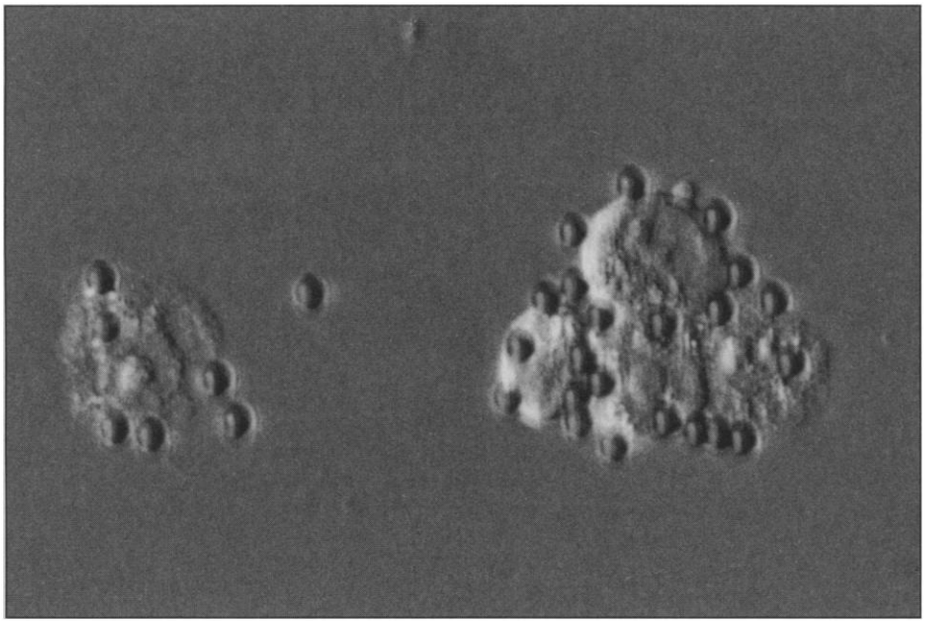
Aebischer also noted that he and others have recently founded a private company to support development of the technique.

Purging Cancer from the Bone Marrow

A new technique for magnetically stripping cancer cells out of bone marrow, now under development by engineers at Dartmouth College, could significantly improve the survival rate for patients with several common malignancies, including breast cancer and small cell lung cancer—the latter being currently incurable.

The technique would not be suitable for patients in the advanced stages of the disease, cautions Dartmouth physician Edward Ball, one of the team who described their method at the ACS meeting. "We're going here for 'occult' disease, where it's not yet visible in the marrow. If you *can* see it already, you're probably asking for too much." Nonetheless, he says, that still leaves a large population that could benefit, including patients who have been newly diagnosed with metastasic breast or lung cancer.

The separation device was designed to be



The last roundup. *In the Dartmouth experiments, each bone marrow cancer cell ends up sticking to about 25 magnetic beads on the average. The beads are 4.5 micrometers across.*

used in conjunction with massive doses of radiation or chemotherapy, Ball explains. Ordinarily, such dosages are limited by the fact that both these treatments can kill the stem cells found in the bone marrow, which are the source of the all the body's blood cells. However, an increasingly popular approach is to extract a portion of the patient's marrow before the treatment and then reinstate it afterward. This allows the physician to use higher doses, destroying cancers that would otherwise be incurable. But there is one large caveat: the marrow itself must be free of cancer cells that could otherwise grow and revive the disease.

Enter Dartmouth's magnetic separator, which is being developed by graduate student Frank Powers under the direction of engineering professors Carole Heath and Alvin Converse. The basic idea is to flood the extracted marrow with upwards of a million tiny magnetic beads, each coated with a monoclonal antibody that binds to cell surface antigens typical of tumor cells but not of normal cells. When the marrow is passed through a series of powerful magnets, the beads are pulled out and the cancer cells come with them.

Dartmouth is only one of several U.S. medical centers working on this technology, says Ball. Indeed, at least two centers have already been successful in using magnetic separation to treat childhood neuroblastoma. However, the Dartmouth group appears to be the first to achieve a high separation efficiency for breast cancer and small cell lung cancer. With a number of refinements, such as the use of three different monoclonal antibodies to minimize the number of unrecognized cancer cells, their apparatus is now able to remove at least 99.997% of the tumor cells while retaining 61% of the normal cells.

Obviously, says Ball, the ideal would be to get *all* the cancerous cells out, since any one of them could potentially give rise to a new tumor. And indeed, the Dartmouth team plans to continue working toward that goal, while increasing the recovery rate of normal cells to 80%. But even now, says Ball, the separator leaves only about 100 cancerous cells in the marrow, and it is not clear how clinically significant that is. It may well be that only a small percentage of those cells are capable of proliferating. "We just don't know," he says. In any case, that possibility will be tested soon, since Dartmouth expects to start clinical trials this summer.

Bittersweet Findings

"People have talked about sweet taste receptors for years, but nobody's ever found them," says a man who should know: product development director Grant DuBois of the NutraSweet Company. "We haven't either. But we're very close."

In fact, says DuBois, his company's latest results suggest that a long-standing hypothesis in this field—that the tongue has many different types of sweetness receptors—is dead wrong. "Our work is very hard to understand unless there is only *one* receptor," he says. And, paradoxically, the same receptor also seems to be responsible for the perception of bitterness.

The sense of taste has been something of a black box over the years, explains DuBois, who was the lead speaker in a symposium on the search for new artificial sweeteners. This is largely because no one has ever been able to culture the taste bud cells where the receptor molecules are presumably located. Nonetheless, the argument for multiple sweetness receptors has always seemed strong, because compounds having no structural resemblance to one another can trigger much the same sweet taste. Sucrose, for example, is the prototypical sugar molecule, whereas aspartame, the basis of NutraSweet, is a peptide. Most researchers found it unlikely that a single receptor could respond to such different chemical structures.

Recently, however, NutraSweet chemists have been working with a particularly potent sweetener originally discovered at the Université Claude Benard in Lyon, France. This compound has the property of being photolabile: when exposed to light, the molecule will convert weak hydrogen bonds linking it to the receptor into much stronger covalent bonds. The researchers' idea was to place the compound on the tongue of a rhesus monkey and flash a light to tie up whatever receptors were involved in tasting it. Then, while monitoring the nerves connected to the tongue, they tested the monkey's response to a variety of sweeteners. The result: little response to any of them.

The strong implication is that there is, in fact, only one sweetness receptor, says DuBois; otherwise, there would have been many unbound receptors left over to taste the other sweet compounds. "The most likely explanation is that the receptor is allosteric," he says. "That is, different compounds latch onto different parts of the receptor molecule, and induce the same conformational change."

Intriguingly enough, he adds, the photolabile sweetener also blocked response to at least one bitter-tasting substance, suggesting that this same versatile receptor is responsible for that taste, too. And in fact, he says, "there has long been an association of sweet and bitter tastes. You often find compounds that are both sweet and bitter. Also, small chemical changes can make a given compound go from sweet to bitter."

Of course, DuBois admits, none of this is proved yet. But the very fact that a probe has been found for the sweetness receptor is a major step forward. NutraSweet is now working with a private laboratory in Philadelphia, the Monell Chemical Senses Center, to make a radioactive version of the compound. With that, he says, it should be a straightforward matter to label the receptor, fish it out, and clone it in *Escherichia coli* for detailed study. ■ **M. MITCHELL WALDROP**