

on the agenda, but even if that solves the scattering loss in whole blood samples, "we don't know yet about going across skin and fat," Arnold adds.

Despite Arnold's sobering portrayal of the task at hand, some competitors in the race seem to think success is only a matter of time. Purdy and Rosenthal look at their own efforts with optimism, though they refuse to reveal details of their technology, citing proprietary concerns. "We now are working on our second generation of portable [prototype] units and we are hoping and praying that we have gotten the bugs out," Rosenthal says.

A team of researchers from Sandia National Laboratories in Albuquerque and the University of New Mexico is also optimistic. At a meeting of the American Diabetes Association in June, the group reported progress toward their own version of a Dream Beam, also based on the combo of near-infrared spectroscopy and chemometrics. "We simultaneously look at a large number of intensities [wavelengths] and build an empirical model that relates all of these intensities to the concentration of glucose in known samples," notes chemist David Haaland of Sandia. The researchers claim to have gathered infrared signals from human test subjects, used the model to develop a calibration table, and determined glucose levels from human subjects that matched results using standard blood-letting methods. "We have shown it is feasible [to get accurate glucose measurements noninvasively]," says Haaland, though he quickly adds: "But we have yet to show that it can be practical." Right now, the equipment is too bulky, complicated, and expensive for home use and its general reliability awaits many additional tests. If the technology does fly, it will probably end up in hospitals long before the homes of diabetics, Haaland predicts.

High fences. John Peterson of the biomedical engineering and instrumentation program at the National Institutes of Health isn't impressed by any of these claims, however. Too many things can go wrong too easily, he says, and all of the possible pitfalls would have to be thoroughly understood before the FDA would approve the technology. Noell of Miles points out another troublesome nuance: The methods are so complicated and dependent on data processing that trying to distinguish between actual signals from glucose and signals that might merely correlate with glucose levels may be impossible. Moreover, any instrument that relies indirectly on signals that seem to correlate well—though perhaps not under all circumstances—with glucose levels, will need extensive, costly testing to determine if the correlations hold under all clinically important conditions.

In view of the technological fences that have yet to be jumped, many companies are hedging their bets. Several groups are trying

to improve conventional glucose monitoring systems now on the market by reducing the amount of blood that has to be drawn. And others, such as George Wilson, a chemist at the University of Kansas, are taking a different course entirely. Wilson is pursuing implantable, hair-thin electrodes that would measure blood glucose constantly and set off an alarm whenever concentrations reach an alarming level. Peterson is not optimistic about this approach either, however, citing biocompatibility and short device lifetimes as significant problems yet to be overcome.

With as much as \$500 million in prize money awaiting the first company to cross the finishing line, few of the contenders in the race for noninvasive monitoring have balked at the technological fences. And everybody agrees that a Dream Beam is possible in principal. It may be a long, long time, however, before concerned grandmothers and the millions of diabetics who are anxiously awaiting freedom from their blood letting ritual might know for sure that a Dream Beam is more than just that.

—Ivan Amato

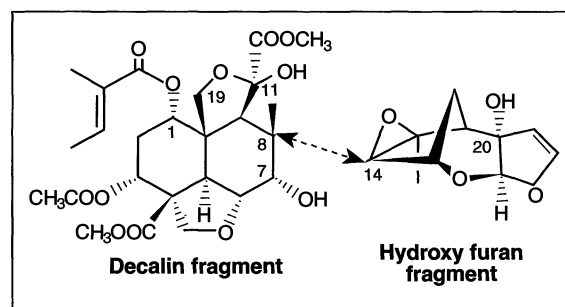
CHEMICAL SYNTHESIS

Neem Chemical: The Pieces Fall in Place

It's an environmentalist's dream: a natural insecticide found in the seeds of the neem—one of the commonest trees in India and Burma—that zaps pest species, yet leaves pollinating insects and mammals unharmed. But, while a National Research Council panel waxed lyrical earlier this year about the neem's potential as a "tree for solving global problems" (*Science*, 17 January, p. 275), the big agrochemical companies have been slow to jump on the neem bandwagon. The reason? It's extremely costly to extract the insecticide molecule, azadirachtin, from neem seeds, and no one's been able to take out a broad patent covering the molecule because its structure was published way back in the 1970s.

What's needed, say business-minded pest-control experts, is a cheap way of making azadirachtin-like compounds that can be patented. Now the doorway to such a new generation of azadirachtin-based insecticides may have been forced open by a group of chemists led by Steven Ley at London's Imperial College. They have succeeded in synthesizing the two chemical structures that together make up the azadirachtin molecule. Ley and his colleagues made the "easy" part of the molecule—the hydroxy furan fragment—last year. Their latest achievement is the synthesis of the larger decalin portion, which they describe in the November issue of the Royal Society of Chemistry's *Perkin Transactions 1*. That feat puts them only one bond—the one that joins the two fragments together—away from synthesizing azadirachtin from scratch. And, more important, it means that chemists can start tinkering with Ley's reaction pathways to produce synthetic derivatives of each part of the molecule. It may even be possible to make compounds that are more effective than the natural chemical, says David Morgan, a chemist from Keele University, who was the first to isolate azadirachtin from the neem.

Ley—who moved to Cambridge Univer-



Bit by bit. Both fragments have now been synthesized.

sity last month—is now setting off down that road. He's collaborating with entomologist Monique Simmonds, from the Royal Botanic Gardens at Kew, in London, who's already shown that the two azadirachtin components have different insecticidal effects. The decalin portion disrupts insect growth and development, while the hydroxy furan deters insect pests from feeding—although it's not quite as potent an antifeedant as the intact molecule. The next step is to try to make simpler analogs that have similar effects.

If Ley's previous work on natural azadirachtin is anything to go by, it may indeed be possible to improve on nature. One big drawback of azadirachtin is that sunlight and even acid rain quickly break the molecule down after it's sprayed onto a crop. Ley's group has, however, improved azadirachtin's resistance to acids by alkylating a single hydroxyl group. And they've also reduced the sunlight problem by hydrogenating all the molecule's double bonds, which are attacked by ultraviolet light.

Now that chemists are able to play with the synthesis of azadirachtin's two component parts, they'll be looking for other improvements. "[W]e need to get it to act faster," says Kew's Simmonds. Insects dosed with azadirachtin don't cause much damage, thanks to its antifeedant qualities—but they don't die quickly. "Chemical companies like to see insects with their legs up in the air," says Simmonds.

—Peter Aldhous