MEDICAL DEVICES

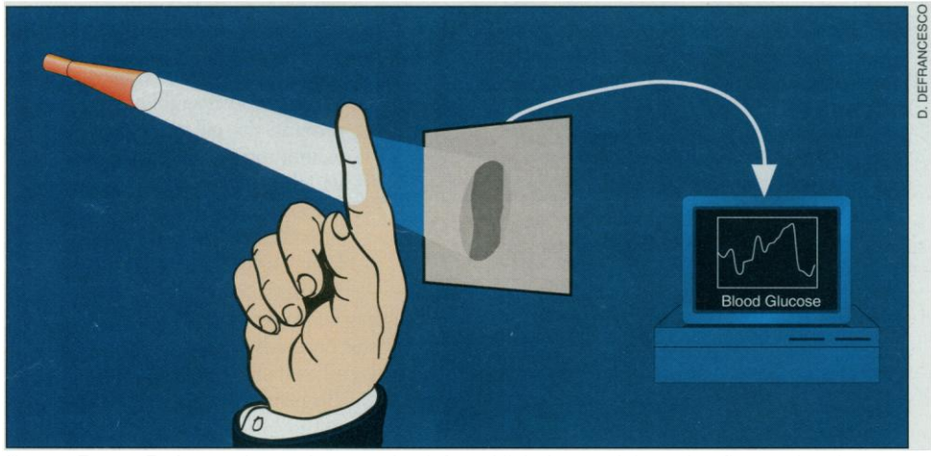
Race Quickens for Non-Stick Blood Monitoring Technology

It was a passionate letter from the grandmother of a diabetic girl that set Robert D. Rosenthal, president of Futrex Inc., on to the task of inventing what the diabetic community has dubbed a "Dream Beam." What the desperate grandma wanted was a way to liberate her granddaughter from the distressing daily ritual of drawing blood for the glucose measurements that govern the child's diet, physical activity, and insulin injections. For Rosenthal—whose company already had developed a light-based, no-pain device for measuring body fat—that meant a challenge: develop a device that uses light to monitor glucose levels in blood without breaking the skin, something akin to the thumb-sized diagnostic gizmo that Star Trek doctors wave over the sick and injured of the 23rd century.

Rosenthal took the woman's entreaty to heart. Creating a noninvasive (no cutting or puncturing of tissue), portable, affordable, and easy-to-use glucose monitor has become a high priority for Rosenthal and his Gaithersburg, Maryland, company. Compassion for the millions of diabetics who have to make themselves bleed every day isn't the only incentive: The glucose monitoring market is estimated to be in the $500 million range, and the first company to produce a needleless (or lanceless) system will make a financial killing. "It's a hot race and we're one of the horses," Rosenthal says.

Dozens of other companies—from small biotech firms such as Biocontrol Technology Inc. of Indiana, Pennsylvania, to giants such as Miles Inc.—are also in the race, but it's not yet clear that any of them will actually cross the finish line. The obstacles are daunting: Researchers must find a way to shine light though a pinch of skin, detect the faint signals emitted when glucose absorbs specific wavelengths, extract those signals from the morass of background noise generated by other blood constituents and surrounding tissue, and calculate glucose concentrations from those weak signatures with pinpoint precision.

"I'm not even convinced it is possible," admits Mark Arnold, an analytical chemist at the University of Iowa who has corporate backing to be one of the contenders. Arnold, who described his research efforts at the August meeting of the American Chemical Society (ACS) in Washington, D.C., has made enough progress to stay in the race, however. Rosenthal and David Purdy, president of Biocontrol, are more sanguine, claiming to have produced prototype devices that are almost there. But that kind of talk hasn't completely persuaded Richard Kahn, who tracks global technology developments in his role as chief scientific and medical officer for the American Diabetes Association. Says Kahn: "Everybody wants to be first and everybody is talking as though he is."



Dream Beam. By harvesting and processing infrared light beamed through a finger, chemists aim to develop a means for measuring blood glucose painlessly.

Probing the invisible. As a basis for an entirely noninvasive method, Arnold, Rosenthal, and Purdy are pegging their hopes on near-infrared spectroscopy, coupled with a battery of sophisticated mathematical and statistical techniques, collectively known as chemometrics. These computerized methods serve to filter out the cacophony of signals from nonglucose sources and extract glucose's faint spectral signature. In the menagerie of spectroscopic methods, near-infrared spectroscopy, which centers on invisible wavelengths of light just beyond visible red wavelengths, is particularly suited for both safely penetrating human tissue and yielding chemically revealing information. Still, it's a spectral tightrope act. The wavelengths most strongly absorbed by glucose, and so most revealing about the chemical's presence and abundance—it normally accounts for only about 1/1000 of the mass of blood—are also absorbed by other, far more plentiful body components including water and fat. Indeed, Futrex's fat monitor, which the letter-writing grandmother heard about from a TV program, relies on that spectral happenstance.

The trick for glucose monitoring is to focus on those specific wavelengths that, although weakly absorbed by glucose, are even more weakly captured by surrounding tissue. Then "the key to success is to be able to pull out very small glucose signals [using chemometrics] from large amounts of [spectral] noise," generated from skin, bones, water, muscle, fat, and other bodily components, says Arnold.

Temperature, certain drugs, and other confounding factors make interpreting signals even more treacherous, warn Arnold and J. Oakey Noell of Miles, a leading maker of conventional blood glucose monitoring systems. The company is tracking Dream Beam efforts carefully, Noell says. Moreover, those in the glucose monitoring race know that reliability and accuracy will be paramount, Kahn adds. Erroneous measurements could result in inappropriate or missed insulin treatments, which over time could result in blindness, loss of extremities, even death.

One step at a time. Arnold, who collaborates with Gary Small of Ohio University in Athens, says his tack is to learn systematically how to measure glucose in ever more complex matrices, on up to living flesh. He started with a simple solution of glucose in water, then added protein to simulate cell-free blood plasma, then tried real blood plasma from cows, and now is up to testing whole blood brimming with red blood cells. Even with plasma from different cows, whose blood protein levels varied as they would in the diabetic population, Arnold and colleagues were able to develop chemometric routines to extract a glucose signal from the noise and accurately determine glucose concentrations. At first, temperature variations during the measurements threatened even that success, but Arnold says the problem has been solved, again with chemometrics.

More flesh-like matrices may not yield as readily, though. When Arnold and his colleagues tried whole blood samples, the infrared light strongly scattered off the red blood cells, dimming an already faint glucose signature. "Right now, the scattering is killing us," Arnold said at the ACS meeting. Using more intense light sources to pump up the signal is

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 bloodletting 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.

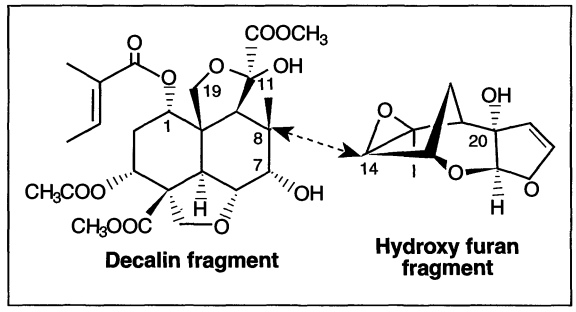
With as much as $500 million in prize money awaiting the first company to cross the finishing line, few of the contenders in the race for noninvasive monitoring have balked at the technological fences. And everybody agrees that a Dream Beam is possible in principal. It may be a long, long time, however, 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.



Bit by bit. Both fragments have now been synthesized.

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 University 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