The Sticky Business of Noncaloric Sugars

Gilbert Levin has had sweet dreams for a long time. Levin is the president and founder of Biospherics Inc., a Beltsville, Md.-based environmental and health technology company. For nearly two decades, he has sought a noncaloric sweetener boasting both the bulk of table sugar and the ability to withstand cooking heat--in short, the ultimate food additive. Now he thinks he's found it, in a sugar called tagatose. He and the other Biospherics scientists who have studied the tagatose molecule hope

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Now he thinks he's found it, in a sugar called tagatose. He and the other Biospherics scientists who have studied the tagatose molecule hope to prove the substance's usefulness as a noncaloric sweetener and find a cheap way to produce it in large quantities. This spring, three of the company's scientists received a patent for what they say is a low-cost method of synthesizing the sugar.

But the 67-year-old Levin knows he's still a long way from tasting victory. Indeed, the road he's traveled in pursuit of his dream offers some valuable lessons to any scientist-entrepreneur determined to follow an offbeat idea. The trip has included constant, but often losing, battles to persuade colleagues his ideas are sound, an unending search for sufficient capital to bring his ideas to fruition, heart-stopping climbs and plunges on the stock market, and detours that led to surprising destinations. It also illustrates something Levin calls a truism: Pursuing an individual dream means spending time, emotion, and effort on building and sustaining a support structure for the work one really wants to do.

"It's hard to introduce something new," he says, "particularly when you're an outsider. It's a long process to develop your idea, then change people's minds so they'll accept it. But there's great satisfaction if you do."

Levin began his scientific career in 1948 after earning a master's degree in sanitary engineering from Johns Hopkins University in Baltimore. As a public health officer charged with maintaining safe water supplies, first in the Maryland and later the California state health departments, Levin became an expert at detecting microorganisms and published more than a dozen articles on the subject. He used that knowledge to design life-detection experiments for NASA and develop biological methods for waste-water treatment.

A background in waste-water management might seem unlikely preparation for a scientist who proposes to hit it big in the sugar-substitute business. But, Levin insists, many of science's best ideas come about in just that way. As a prime example, he cites Nobel Prize-winning chemist Albert Szent-Gyorgyi.

"Years ago, I heard [him] give a talk called `Fifty Years of Scientific Poaching,' " Levin recalls. "He described jumping into a field where he didn't have adequate background and investigating things that guys in the field wouldn't look at. He got his most fruitful ideas by bypassing the prejudice that can come with too much field-specific knowledge.

"I like to think I've done that, though much more modestly. That's the beauty of science, isn't it? The rules apply everywhere, and what's true in one realm may prove to have extremely interesting consequences in others."

Chemical compounds can exist in forms that are mirror images of each other. Like gloves, they can be either left-handed or right-handed.

Sugars are such "handed" molecules. Human digestive enzymes have evolved to act upon right-handed sugar molecules, while often allowing left-handed forms to pass directly through.

Both l-tagatose, the left-handed form, and d-tagatose, the right-handed form, are approximately as sweet as table sugar. Gilbert Levin's researchers at Biospherics Inc. originally investigated l-tagatose, but later they hit upon d-tagatose as a potentially better candidate. D-tagatose is metabolized by the body and thus puts no extra load on the kidneys. And, lab officials say, it doesn't appear to create fat, as most sugars do, possibly because of the rate at which it metabolizes.

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That kind of field-jumping characterizes Levin's career. For example, his journey from testing water quality in California's Santa Monica Bay in the early 1950s to his present search for the perfect sugar substitute took him, at one point, to Mars. As a public health officer, Levin developed a method for quickly determining bacterial presence in water by lacing a nutrient with a radioactive isotope of carbon. Any microbes present would create an easily detectable radioactive gas when they metabolized the nutrient.

"It was my first neat idea that really developed into something," Levin says, "and it launched me onto a whole bunch of hare-brained ideas, real scientific poaching." One such idea was the notion of applying his microbial detection method to test for life on Mars. In the late 1950s, Levin began work on several life-detection experiments that eventually flew on NASA's 1971 Mariner 9 Mars Orbiter and the 1975 Viking mission to Mars and that earned him a NASA Public Service Medal for his contributions to the agency.

But Levin learned early in his NASA work that not even successful science always wins over the skeptics. "One day, [NASA] called me downtown and said, `We've got a problem.' They said the experiment was going fine, but that when it went to Mars they couldn't have a sanitary engineer with just a master's degree talking about it. They wanted me to accept another scientist as principal investigator. But I said, `The hell I will.' "

Levin solved the problem the hard way: He enrolled in a doctoral program in environmental engineering and chemistry at Johns Hopkins, earning a Ph.D. there in 1963. He completed the degree in three years while working full-time as a public health officer and continuing his work with NASA.

The additional coursework also helped him refine his Mars experiments by including more kinds of molecules to which living organisms might respond. "I learned for the first time how handedness works in organic compounds," he says (see accompanying story). "When I found out about living systems metabolizing a right-handed sugar molecule but not the left-handed form, it occurred to me that life on another planet might have evolved to do the opposite, and that we'd better send both to Mars." "The handedness is one of those seminal ideas that don't apply in just one place," Levin says. That realization gave him the chance to engage in another bit of scientific poaching.

"I thought a lot about those left-handed sugar molecules," he says. "Since the body doesn't use them, could they turn out to be a sweetener with zero calories?" Thus was born Levin's dream of turning an unusually shaped sugar molecule into the ultimate in noncaloric sweeteners.

That idea isn't new, say other scientists. "In fact," says Cornell University professor emeritus Robert Shallenberger, "it comes up like sunspots, because naturally occurring sugars have the qualities you'd most like in a sweetener. They act as preservatives, give bulk and texture."

If the idea is so common, why haven't other scientists rushed to follow up on such an obvious idea? Some have, but they have been stymied by the fact that forms of sugar that the human body will not readily metabolize to fat and energy exist only in tiny quantities in nature.

"Academic methods to synthesize the sugars do exist," says Bernd Meyer of the University of Georgia's Complex Carbohydrate Research Center in Athens. "But the difficulty of optimizing such a process commercially makes it extremely unlikely that anyone will spend the time and resources to succeed." Anyone but Levin, that is. Expending time and energy doesn't seem to bother him. But finding sufficient resources is another matter. Levin's solution, in 1967, was to establish a company that could provide a solid, if relatively small, financial base for the sugar work. Once again, the opportunity arose as he was headed in another direction.

What Levin was seeking was an academic position. But one day, in the course of traveling to interviews, Levin stopped by an unoccupied Maryland laboratory once owned by a company for which he'd worked.

"The `For Rent' sign was there," he says. "On a lark, I called the landlord and asked if he'd rent it to me. I didn't have any lines out for moneymaking work. But over the weekend I made the decision to do it, anyway."

Levin says he founded Biospherics "with a service aspect, so what I did on that end could support research. We would have died without it. But the service part is very demanding until you get a critical mass of people and funded work. You work all day on what's already funded, and all night on writing new proposals."

For two decades the plan worked smoothly. Biospherics, which became a public company in 1972, grew from a one-man operation to a business with more than 400 employees. Its service departments have turned small but steady annual profits and provided at least basic support for his research. An information division edits scientific documents and disseminates health and environment information through projects like the National Cancer Institute's hot line telephone number, based at Biospherics. The chemical analysis division does environmental testing, including pollution monitoring and testing for various toxic substances.

During the past decade, the firm's research and development lab intensified its sugar investigations, supported by profits from the service departments. In the mid-1980s, Levin hired organic chemist Lee Zehner as director of biotech programs to further focus the research.

But a few years ago, the environmental testing lab's business began to fall off, causing the company to lose money three years in a row. As a result, Levin was forced to become more of a manager than a researcher.

"Stemming that tide has taken a lot of my time recently," Levin says. "Now we've stabilized the turnover [caused by the company's business problems] there and combined their sales and marketing effort. We think we see it turning around."

Still, Biospherics provides Levin with less than what he'd like for his sugar experiments. And his search for well-heeled financial partners hasn't turned up much. A $10 million deal to share research costs and results with an Italian sugar company, the latest of several such efforts, fell through in the late 1980s. Nevertheless, the lab's four full-time research and development scientists have doggedly continued the sugar research, and last March were rewarded with a patent for a low-cost method of synthesizing the right-handed form of the sugar.

Standard laboratory methods for synthesizing rare sugars from other, more common sugar molecules can cost as much as thousands of dollars per gram. But their new method, Levin and Zehner say, should be competitively priced with high-intensity sweeteners such as aspartame, which must be used in conjunction with bulking agents.

News of this past spring's patent on a substance many analysts call the ultimate food additive sent the price of Biospherics stock soaring, from $4.50 a share to $29 a share less than two weeks later. Within a few weeks, however, the price had dropped back to around $4 as the reality of the long and expensive process of gaining Food and Drug Administration approval hit home with investors, according to stock analysts. That recalled a similarly wild price fluctuation in 1981, after the company patented a more costly process to produce a left-handed version of the sugar, the analysts note.

Through it all, Levin says he has tried to focus his and the company's energies on the long haul, without being too distracted by the overnight successes and disappointments. "Though those meteoric rises feel good, capitalizing on them is another thing," he says.

The news of Levin's progress has had less of an impact on scientists in the field, most of whom doubt that an economic method of synthesis can be developed. "I just can't see it," says Cornell's Shallenberger. Adds Henry Lardy of the University of Wisconsin's Institute for Enzyme Research at Madison, "The processes are so time- and chemical-consuming."

Still, the two scientists say they are willing to be proved wrong. "If they've actually found one," says Lardy, "I'd suggest they make hay while the sun shines. Tagatose is a naturally occurring sugar. That's got to go over like a bang in today's market, where natural is the thing to be. It'd be at least a six-month money-making wonder, like oat bran."

Zehner says he's taken that advice to heart. Zehner left "a Fortune 50 company" to join Levin's sugar work. He hit upon d-tagatose as a good candidate for a sugar substitute several years ago.

"It's important to go at this full-speed, no matter what," Zehner says. "This is a sexy area. A lot of people are working on it. I don't think anybody has anything competitive with tagatose, but we don't want to get [beaten by an] end run."

In running with their idea, the next hurdle Levin and Zehner must clear is gaining the approval of FDA. That will mean hiring an outside laboratory to test the details of how d-tagatose metabolizes and to check the sugar's safety for each of its proposed uses, such as in baked goods or candy. They hope to find a financial partner willing to put $15 million into that effort over the next three to five years.

But other scientists say the process of gaining approval could take much longer and cost much more. The University of Georgia's Meyer points to Johnson & Johnson's lengthy, ongoing struggle for approval of its new sugar substitute, sucralose. "The toxicology studies alone have taken three years," he says. "And besides that, you're trying to verify to the last decimal point where the metabolytes go, and, with a food product, testing it also on people who don't have a normal metabolism." Meyer adds, however, that sucralose, a molecule that contains chlorine, automatically raises more regulatory doubts than would a simple sugar such as tagatose.

It won't be easy, Levin says, but it also won't be the first time he's tried to overturn the status quo. In the late 1960s, he developed a biological method for removing phosphates from waste water. Despite extensive, successful tests of the process, it wouldn't sell. Levin blames conventional wisdom--in this case, the standard text on waste water incorrectly stated that such a method wouldn't work. "All the people in the know parroted that," he says. "For 10 years, the EPA [Environmental Protection Agency] told cities it wouldn't work, even though it was working in several cities."

Now, Biospherics is negotiating to give Tetra Technologies Inc. of Houston the rights to the phosphate-removal process, called PhoStrip. Tetra is a market leader in nitrate-removal technologies and, according to Paul O'Boyle, vice president of marketing, the company spent a lot of time looking for an efficient means of phosphate removal before discovering Levin's method.

"We looked at bigger names," O'Boyle says, "but this is the best to be found--most economical, easy to retrofit to existing plants. It works."

Levin expects the same thing to happen with tagatose. "It took a long time for people to be ready for PhoStrip, too," he says. "I'm convinced we are going to hit a home run on the sugar. And I've been right before."

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