

A TRIAL FOR THE AGES

Nir Barzilai wants to launch the first rigorous test of a drug that could put the brakes on aging

By Stephen S. Hall

On a blazingly hot morning this past June, a half-dozen scientists convened in a hotel conference room in suburban Maryland for the dress rehearsal of what they saw as a landmark event in the history of aging research. In a few hours, the group would meet with officials at the U.S. Food and Drug Administration (FDA), a few kilometers away, to pitch an unprecedented clinical trial—nothing less than the first test of a drug to specifically target the process of human aging.

"We think this is a groundbreaking, perhaps paradigm-shifting trial," said Steven Austad, chairman of biology at the University of Alabama, Birmingham, and scientific director of the American Federation for Aging Research (AFAR). After Austad's brief introductory remarks, a scientist named Nir Barzilai tuned up his PowerPoint and launched into a practice run of the main presentation.

Barzilai is a former Israeli army medical officer and head of a well-known study of centenarians based at the Albert Einstein College of Medicine in the Bronx, New York. To anyone who has seen the ebullient scientist in his natural laboratory habitat, often in a short-sleeved shirt and always cracking jokes, he looked uncharacteristically kempt in a blue blazer and dress khakis. But his practice run kept hitting a historical speed

Barzilai hopes to persuade FDA to bless the proposed anti-aging trial, which is unconventional in its goals and design.

bump. He had barely begun to explain the rationale for the trial when he mentioned, in passing, "lots of unproven, untested treatments under the category of anti-aging." His colleagues pounced.

"Nir," interrupted S. Jay Olshansky, a biodemographer of aging from the University of Illinois, Chicago. The phrase "anti-aging ... has an association that is negative."

"I wouldn't dignify them by calling them 'treatments,'" added Michael Pollak, director of cancer prevention at McGill University in Montreal, Canada. "They're products."

Barzilai, a 59-year-old with a boyish mop of gray hair, wore a contrite grin. "We know

incidence increases dramatically with age: cardiovascular disease, cancer, and cognitive decline, along with mortality. When it comes to these diseases, Barzilai is fond of saying, "aging is a bigger risk factor than all of the other factors combined."

But the phrase "anti-aging" kept creeping into the rehearsal, and critics kept jumping in. "Okay," Barzilai said with a laugh when it came up again. "Third time, the death penalty."

The group's paranoia about the term "anti-aging" captured both the audacity of the proposed trial and the cultural challenge of venturing into medical territory historically

associated with charlatans and quacks. The metformin initiative, which Barzilai is generally credited with spearheading, is unusual by almost any standard of drug development. The people pushing for the trial are all academics, none from industry (although Barzilai is co-founder of a biotech company, CohBar Inc., that is working to develop drugs targeting age-related diseases). The

trial would be sponsored by the nonprofit AFAR, not a pharmaceutical company. No one stood to make money if the drug worked, the scientists all claimed; indeed, metformin is not only generic, costing just a few cents a dose, but belongs to a class of drugs that has been part of the human apothecary for 500 years. Patient safety was unlikely to be an issue; millions of diabetics have taken metformin since the 1960s, and its generally mild side effects are well-known.

Finally, the metformin group insisted they didn't need a cent of federal money to proceed (although they do intend to ask for

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Jay Olshansky, University of Illinois, Chicago

the FDA is concerned about this," he conceded, and deleted the offensive phrase.

Then he proceeded to lay out the details of an ambitious clinical trial. The group—academics all—wanted to conduct a double-blind study of roughly 3000 elderly people; half would get a placebo and half would get an old (indeed, ancient) drug for type 2 diabetes called metformin, which has been shown to modify aging in some animal studies. Because there is still no accepted biomarker for aging, the drug's success would be judged by an unusual standard—whether it could delay the development of several diseases whose

some). Nor did they need formal approval from FDA to proceed. But they very much wanted the agency's blessing. By recognizing the merit of such a trial, Barzilai believes, FDA would make aging itself a legitimate target for drug development.

By the time the scientists were done, the rehearsal—which was being filmed for a television documentary—had the feel of a pep rally. They spoke with unguarded optimism. “What we're talking about here,” Olshansky said, “is a fundamental sea change in how we look at aging and disease.” To Austad, it is “the key, potentially, to saving the health care system.”

As the group piled into a van for the drive to FDA headquarters, there was more talk about setting precedents and opening doors. So it was a little disconcerting when Austad led the delegation up to the main entrance of FDA—and couldn't get the door open.

Barzilai, who is quick to see the humor (black or otherwise) in any situation, leaned over to a colleague and muttered, “I hope it's not symbolic.”

AMIABLY AGGRESSIVE, Barzilai credits his military service with shaping his scientific temperament and administrative mettle. “The most helpful years in my life were in the Israeli army,” he says. Born in Haifa in 1955,

he joined the military as a medical instructor and in 1976 served as a medical officer in the special forces raid on Entebbe, Uganda, that freed 102 hostages from a hijacked Air France airliner. (“I did nothing,” he claims. “I happened to be there.”) By his early 20s, he had been decorated for his military service and had become chief medic of the Israeli army. “I had an office, a secretary, a car, and I would do inspections with a helicopter,” he recalls. “It's a whole lifetime, okay? With a lot of lessons. But the major thing is that you realize that you can do a lot! If it doesn't frighten you, you can do a lot.”

After obtaining his M.D. in internal medicine from the Technion-Israel Institute of Technology in 1985, Barzilai focused on endocrinology and metabolism during several research stints in the United States. He had every intention of returning to Israel, but a fellowship at Yale University in 1987–88 upended his plans. At Yale, he studied the mechanism of several oral drugs that lowered blood sugar in diabetics. One was metformin. During his time in New Haven, Barzilai ended up meeting his wife-to-be on a blind date. Metformin, he laughs, “is the reason I'm in the United States!”

In 1993, he landed a position at Einstein and discovered, in nearby neighborhoods, a cohort of unusually long-lived Ashkenazi

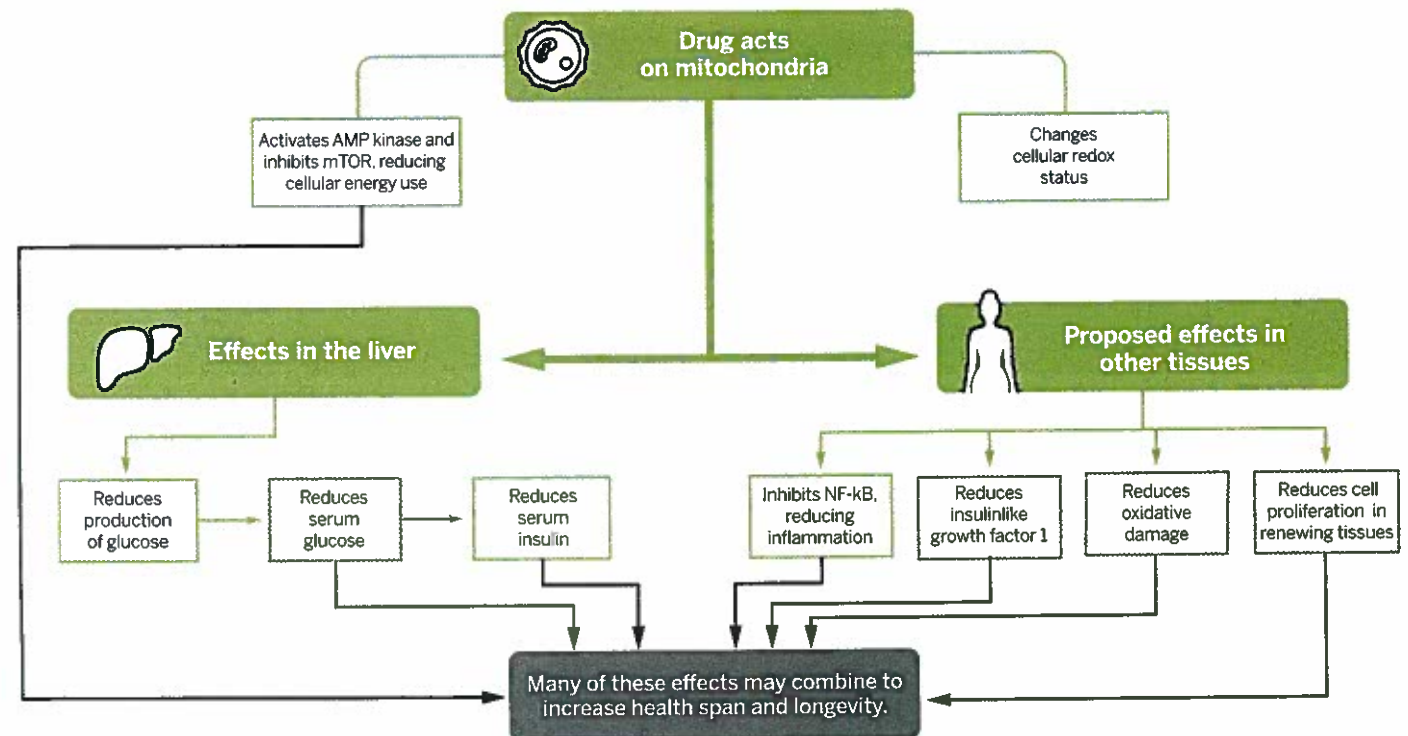
Jews. Barzilai and his Einstein colleagues tracked down and studied more than 600 of the “oldest old,” ranging in age from 95 to 112 years. Since then, the researchers have collected data on the genetics, epigenetics, blood chemistry, and lifestyles of both centenarians and their children.

The Einstein team has identified, for example, variants in two genes associated with increased levels of high density lipoproteins (which have a protective effect on cardiovascular health in this population). They have found that centenarians more often carry a genetic variant that down-regulates insulinlike growth factor 1 (IGF-1), part of a hormonal pathway that not only regulates growth, but also has been implicated in aging. They have also found that the families of centenarians produce unusually high levels of a peptide created in mitochondria, the cell's power plants, and then released into the body; called “humanin,” it is one of several related mitochondrial proteins that may protect against aging. (Barzilai and collaborator Pinchas Cohen of the University of California, Los Angeles, have puckishly dubbed them “Schleps,” for “small humaninlike peptides,” or SHLPs.)

The study of the Bronx centenarians built on a surge of basic aging research in model organisms like yeast, fruit flies, and

Double dividends

Metformin acts on the mitochondria, the cellular power plants. The result is two sets of effects, one in the liver that explains the drug's benefits in diabetes and the other, less well understood, that could slow aging.



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nematodes. By manipulating individual genes and measuring effects on life span, researchers could test the role of specific molecular pathways in aging. In perhaps the most dramatic mammalian example, Andrzej Bartke, a biologist at the Southern Illinois University School of Medicine in Springfield, showed that mice with mutated growth pathways, which disabled both growth hormone and IGF-1, were much smaller—but lived much longer.

Within the last decade or so, researchers have settled upon what Felipe Sierra, director of the division of aging biology at the National Institute on Aging (NIA), calls “the major pillars of aging.” These pathways and mechanisms, roughly half a dozen in all, affect metabolism, growth, response to stress, stem cell vigor, inflammation, and proteostasis—the cell’s quality control system for proteins. And their identification has opened the door to a previously outlandish notion. It “allows us to think that, okay, if we understand how this happens, we can maybe manipulate it,” Sierra says.

MORE THAN A DECADE AGO, Barzilai and others began lobbying FDA to consider drugs that might do just that. But those discussions bogged down, he says, after the sides couldn’t agree on the kinds of biomarkers associated with aging that could be quantified and tracked during a clinical trial.

Barzilai now believes the answer is to design a drug trial that, rather than targeting aging per se, tries instead to delay the onset of “comorbidities”: the chronic diseases whose incidence rises sharply as people get older. “Basically, I think the FDA will be more willing to accept something called ‘comorbidities’ than it is to accept something called ‘aging,’” Barzilai says. “Even in our mind, in my mind, aging is not a disease,” he adds. “It’s, you know, humanity! You’re born, you die, you age in between ... I’m kind of saying, ‘I don’t care what they want to call it, if I can delay it.’”

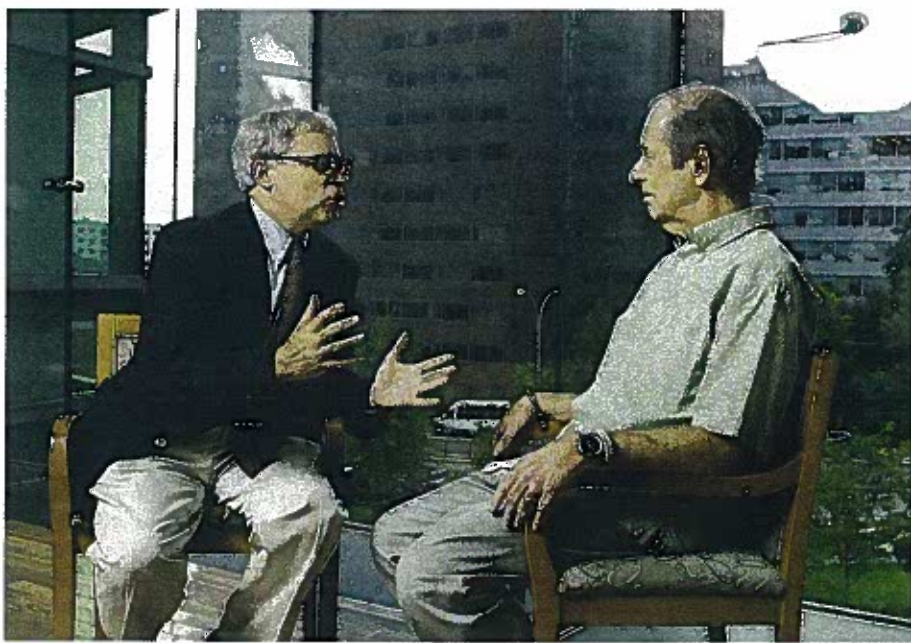
The comorbidity strategy is key to a concept known as the “longevity dividend,” first proposed by a group of public policy and health care experts in 2006. The idea is that slowing down the process of aging, even modestly, would have enormous benefits for quality of life and the economics of health care. “We’re not arguing—and we’ve never argued—that we’re trying to achieve life extension,” says Olshansky, who has pushed the concept while criticizing some of the more outlandish claims in the aging field, such as British gerontologist Aubrey de Grey’s prediction that human life spans of 1000 years are possible. “We’ll probably live a little longer if we succeed, but that’s not the goal,” Olshansky says. “The goal is

the extension of the period of healthy life.”

Even a modest delay in aging could increase average life expectancy by 2.2 years, compress the period of morbidity at the end of life, and save perhaps \$7.1 trillion in health care costs over a period of 50 years, Olshansky and colleagues estimated in a 2013 paper in the journal *Health Affairs*. To achieve those benefits, “we’ve got to act quickly,” he argues. “The numbers of people that are frail and disabled [are] rising fairly rapidly, and we’re seeing an increase in unhealthy life span.”

But the FDA drug approval process abides by the “one disease, one drug” model. Would the agency be open to a trial that had multiple illnesses as an endpoint? As an initial step, earlier this year Sierra organized seminars at FDA in which NIA researchers

mal experiments to test compounds that might alter or slow down the aging process. NIA-supported researchers have tested 16 compounds in mice. Five have shown a positive effect, Sierra says: aspirin, acarbose (a widely prescribed diabetes drug), 17- α -estradiol (the nonfeminizing form of estrogen), nordihydroguaiaretic acid (an herbal compound derived from the creosote plant), and the immunosuppressive drug rapamycin (used in organ transplant recipients). (Among the compounds that had no impact are fish oil, green tea extract, curcumin, and the much-ballyhooed red wine ingredient resveratrol.) Rapamycin was the most impressive. “It has advanced to the point in which we not only know it extends life span,” Sierra says, “but more importantly, it extends health span.”



Barzilai probed aging factors from by studying centenarians and their children, including Jerome Wiesenber, 83.

described recent findings in the biology of aging. In May, Robert Temple, deputy director of FDA’s Center for Drug Evaluation and Research, spoke at an NIA retreat.

Encouraged by the tenor of these discussions, Barzilai and a core group of collaborators—Einstein’s Jill Crandall; Austad; Olshansky; Stephen Kritchevsky at Wake Forest School of Medicine (where the multicenter trial would probably be based); and James Kirkland, a diabetes researcher at the Mayo Clinic, among others—pushed ahead with plans for the trial.

The next question was: What would be the best drug to test?

THERE WAS NO SHORTAGE of possibilities. Buoyed by the advances in basic research, NIA in 2003 inaugurated a program of ani-

Metformin, the drug the group ultimately decided to take to FDA, was not among the compounds that starred in the animal trials. But it has both a promising history and a long, reassuring track record.

“It all starts in the Middle Ages,” says McGill’s Pollak. “There were herbalists in Europe—and, independently, herbalists in China—who found plant extracts that were useful when people came in complaining of urinating too much.” The extracts derived from a perennial herb (*Galega officinalis*) known variously as goat’s rue, French lilac, Spanish sainfoin and false indigo. “It worked for some people,” Pollak says. “In retrospect, [we know] the people for whom it was working were diabetic.”

It wasn’t until the late 1800s that chemists isolated the active ingredient in French

lilac—a compound known as guanidine. But guanidine itself proved too toxic to humans, so chemists began to synthesize less toxic analogs known as biguanides, including metformin. In the 1950s, a French physician and pharmacologist named Jean Sterne began to test biguanides in patients with type 2 diabetes at a hospital in Paris. “The best one in terms of efficacy was metformin,” Pollak says.

Sterne coined the name glucophage (“glucose eater”) when he published his results in 1957, the same year the drug was approved for use in France. Approved in the United Kingdom in 1958 and in Canada in 1972, metformin went on to become the biggest selling diabetes drug in the world. However, U.S. regulators didn’t approve it until 1994. (FDA requested additional studies, Barzilai drily notes, “to see if metformin works in the same way as in the United Kingdom, because we are so different here.”) By now, companies churn out an estimated 37,000 metric tons of the compound annually, most of it in India.

Hints that metformin might also prevent diseases associated with aging began to emerge over the past several decades. In a 1998 report by the United Kingdom Prospective Diabetes Study Group, metformin use not only reduced the risk of all diabetes-related complications (including death) by 32%, but also significantly lowered the risk of cardiovascular disease, including heart attack and stroke. A randomized, placebo-controlled trial called the Diabetes Prevention Program showed similar effects, cutting the onset of type 2 diabetes by 31% in a middle-aged population at high risk of developing the disease.

Epidemiological studies have also suggested that metformin reduces cancer risk and mortality and preserves cognitive function. And in a big-data study that, although observational, got the attention of many aging researchers, British researchers reported late last year that in a retrospective analysis of 78,000 adult type 2 diabetics in their 60s, those who took metformin on average lived longer than healthy age-matched controls.

None of these studies proves that metformin will delay the onset of age-associated

diseases, and scientists haven’t identified an exact mechanism by which the drug might work. But it appears to act on some of the same molecular pathways identified by basic aging research. Besides its effects on blood glucose, metformin affects multiple pathways involved in growth, inflammation, and metabolism (see graphic, p. 1276).

Pollak has demonstrated what he and others see as the key effect, which may trigger the other benefits of the drug: It inhibits oxygen consumption in mitochondria, in effect turning down the cell’s metabolic thermostat. “When a furnace is burning,” he says, “it’s heating up and it’s cracking and it begins to degrade. When you keep your house at a lower temperature, your furnace is going to last longer.”

As it turns out, Barzilai is very familiar with metformin—not only as a doctor who has prescribed it and as a researcher who has studied it, but as a patient who has taken it for 5 years. (He says he is considered prediabetic.) He can testify to its safety and tell you exactly how to avoid its most common side effect, gastrointestinal upset. “There’s nothing we don’t know about metformin,” Barzilai says—especially its record for safety, which he calls “critical” to the proposed trial.

His colleagues agreed, sometimes reluctantly. “Rapamycin would have been my first choice, because the animal results have been so spectacular,” Austad says. “But Nir said, ‘We can’t afford in this first trial to kill anybody.’ And I thought, ‘Strategically, he’s right.’”

Barzilai concedes that he and the AFAR-sponsored group are as interested in setting a precedent as in scoring an impressive initial success. Satisfying FDA concerns about a trial that breaks tradition and measures multiple disease endpoints in an aging population, they say, will open the door for pharma to enter the field.

“Metformin is for us a tool—a very exciting tool,” Barzilai said prior to the FDA meeting. “It’ll work, I think. But I don’t want to waste the hour talking about metformin. You know, we chose metformin in order not to talk about it anymore.”

When he and the rest of the AFAR delegation finally made it into FDA’s meeting

room, Barzilai scanned the large contingent seated around the table. “Too many young people here!” he joked. “We should leave now!” But the turnout was encouraging—14 FDA staff members, including Temple and several division chiefs. The meeting ran nearly 30 minutes past the scheduled hour, and by the time Barzilai and the others emerged, they wore surprised smiles. Austad flashed two thumbs up. “I don’t think it could have gone much better,” he said.

Barzilai, whose enthusiasm occasionally exceeds his command of English, sent out an email the next day to everyone who had helped prepare for the FDA meeting, thanking them and describing the meeting as “hysterical.” Historical, Barzilai later explained, because “I think that in their heart, they buy it. Or many of them, or the important people, are buying what we are saying.” Olshansky left the meeting convinced that FDA had given a green light, contingent on several adjustments to the protocol, which the group is now making.

Other participants, like Sierra, struck a more cautious note. When asked whether FDA representatives expressed skepticism about the proposed trial, he said, “Conceptually? No. But in the details, yes.”

SANDY WALSH, an FDA spokeswoman, says the agency does not comment on drugs under development or under investigation. But in a followup communication to the AFAR group, Barzilai says, FDA indicated that although it is not yet convinced that the proposed trial design can establish that metformin has an anti-aging effect, the agency recognizes the potential value in a drug that could improve quality of life and survival—whether the indication sought is aging or multiple morbidities—and is not opposed to the idea of a trial.

Now, trial advocates need someone willing to foot the cost—“\$50 million, plus or minus \$20 million,” according to Barzilai—of tracking some 3000 people between the ages of 65 and 79 for a minimum of 5 years. Olshansky says the metformin group has already targeted “high net-worth individuals” to bankroll the trial. Federal funding would be welcome, Barzilai says, but private money would probably allow the trial to start sooner. “For me,” he says, “the best thing that can happen is that people are writing about it, the television will show it, somebody will call me one day and say: ‘You know, I’m rich like I don’t know what, and I don’t mind helping. Is \$50 million enough?’ And then we’ll get going.” ■

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Metformin has its roots in centuries-old herbal remedies including goat’s rue, which helped people with symptoms now recognized as diabetes.