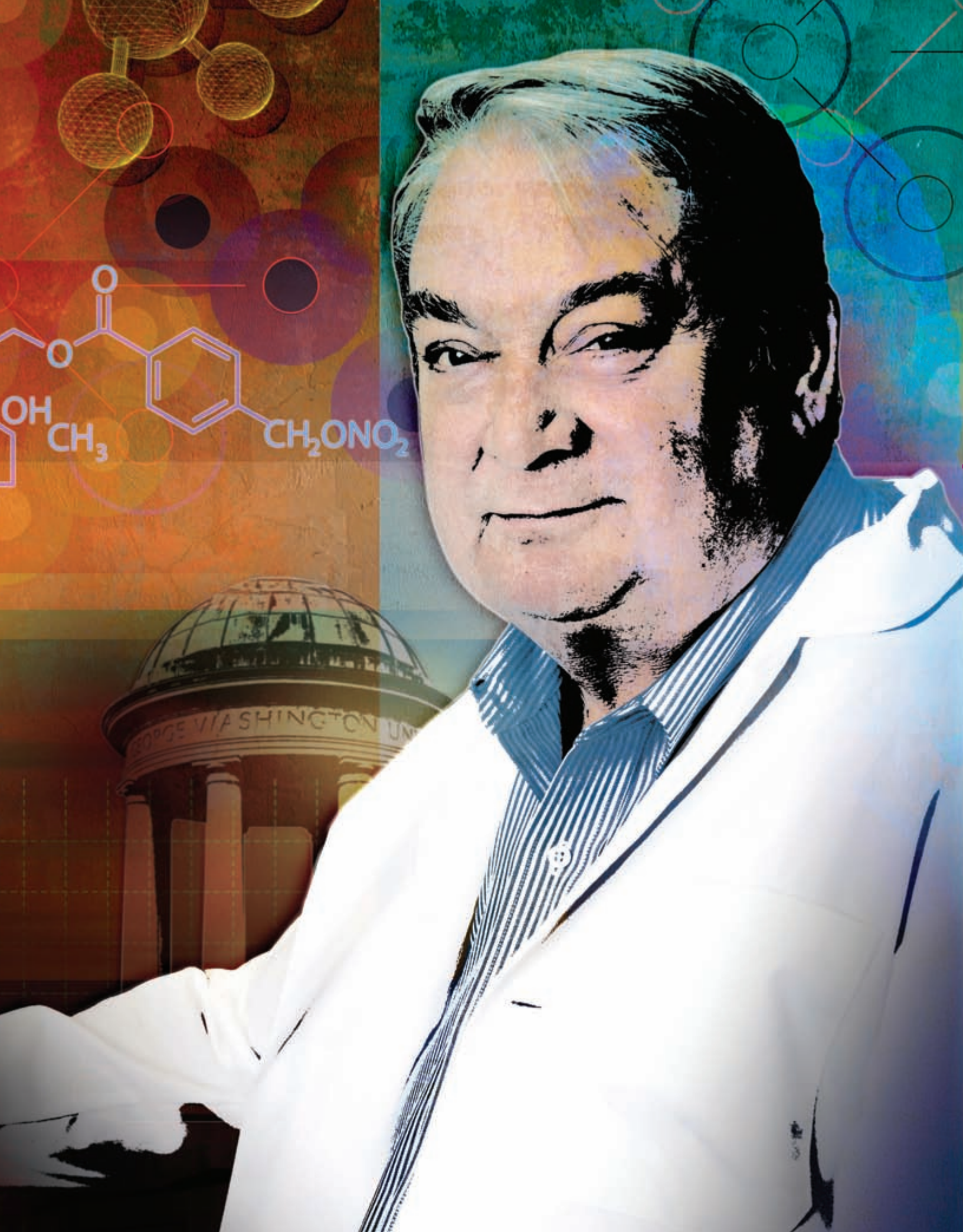
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Nobel Ambition

For new GW faculty member Ferid Murad, winning the biggest prize in science has meant dedicating himself to fostering future laureates. And if he wins a second medal along the way, all the better.

BY DANNY FREEDMAN

The spell of restless nights had fallen, like clockwork, upon Ferid Murad during the early days of October 1998.

It had been this way each October for a couple of years, ever since the murmurs began that his name was on the lips of his peers at such an auspicious point on the calendar.

For the biochemist, who at the time was a professor and department head at the University of Texas Health Science Center at Houston, sleep simply wasn't in the cards.

So Dr. Murad was awake when the phone rang at 4 a.m.

"I'm sorry to disturb you," the caller said.

It was Nils Ringertz, from the Nobel Assembly, with news that most people wouldn't mind being disturbed for. "Congratulations," he said. "You got the Nobel Prize.

"Please don't tell anybody for the next 30 minutes," he said, "until we make the press release here in Stockholm."

"And I thought to myself," Dr. Murad recalls, "Who am I going to call at 4 o'clock in the morning?"

Not that he had time, anyway. Dr. Murad scrambled into the shower and into a suit. Within an hour media began to gather outside his door, touching off a deluge of interviews and flower deliveries and emails and phone calls.

"That first day was pretty wild," he says.

It's a whirlwind that has been blowing now for more than a decade.

Within just the first year his audiences included President Bill Clinton, Supreme Court Chief Justice William Rehnquist, and Palestinian leader Yasser Arafat. He was feted at medical conferences, he served as grand marshal of a July Fourth parade in his hometown of Whiting, Ind., and in Macedonia he met for the first time a small army of relatives.

"It's been amazing," he told the *Houston Chronicle* of that first year of Nobel status. "You don't have a lot of time to savor it."

In the years since, the invitations to lecture, to meet, to consult, to dedicate buildings continued. He's been to dozens of countries, some so many times he has lost count, traveling what he estimates to be in the ballpark of 1.5 million miles. (That would put him on par with the recently retired space shuttle Discovery, which traveled to space and back 39 times.)

It's a long journey that once again has landed Dr. Murad in Washington, D.C., this time to stay.

This spring he joined the faculty of GW's School of Medicine and Health Sciences with the rare designation of university professor—GW's highest

ILLUSTRATION BY ROY SCOTT

WILLIAM ATKINS

academic rank. At the announcement in January, GW Provost Steven Lerman said Dr. Murad's presence on campus "is an honor that elevates both the stature of his department and the prestige of the entire university."

Within the Department of Biochemistry and Molecular Biology, Dr. Murad is establishing a new lab that will have in its crosshairs at least three big scientific questions, the kinds of questions which, successfully answered, may even be Nobel-worthy ... again.

Never mind that no one has ever garnered two Nobels in the area of medicine. As Dr. Murad says: "Wouldn't it be nice to be first?"

At the heart of all this activity is one doozy of a molecule.

Nitric oxide was, for decades, considered merely an environmental hooligan—an unstable no-goodnik of a chemical. Born of vehicle exhaust, smoke stacks, and burning cigarettes, this toxic gas was known to have a hand in smog, acid rain, and possibly the depletion of the ozone layer.

"[T]his gas," noted a 1992 article in the journal *Science*, "had a bad reputation."

But by the 1980s it had become clear to scientists that nitric oxide was far more than a mere troublemaker. If it has an ugly side—and it does—nitric oxide also is strikingly important to the inner workings of the human body. And beyond that, it is a molecule that heals.

In naming it "Molecule of the Year" in 1992, *Science* dubbed the changing face of nitric oxide no less than a "Cinderella story," offering "a classic example of nature's continuing power to surprise."

It was in the labs of Dr. Murad and the two other pharmacologists with whom he shared the 1998 Nobel Prize in Physiology or Medicine—Robert Furchgott and Louis Ignarro—that a more complete picture of nitric oxide was assembled.

Over the course of more than a decade, their work revealed nitric oxide as a gas generated by the body to help transmit signals between cells in the cardiovascular system—in this case, flipping the switch that allows smooth muscle cells (muscles that work involuntarily) to relax and dilate the blood vessels, which increases blood flow and relieves blood pressure.

The fact that nitric oxide does its work by leaving its cell of origin to penetrate and regulate other cells represented "an entirely new principle for signaling in biological systems," according to the Nobel Assembly. Today it remains the only gas known to act as a messenger in the body.

At the front end of this effort, in the mid-1970s, Dr. Murad solved the century-old riddle of how the drug nitroglycerin and others that also contain nitrogen work as treatments for angina pectoris—chest pains often caused by clogged arteries that are beginning to choke off blood supply to the heart.

The answer, Dr. Murad eventually found, was that these drugs are converted in the body to nitric oxide. All that nitric oxide, in turn, stimulates an enzyme and initiates a chain reaction to relax smooth muscle cells.

"For more than a hundred years it was used as a vasodilator [to increase blood flow]," Dr. Murad says. "But nobody knew precisely how it was working."

(Alfred Nobel—as in the Nobel Prizes—was so wary of nitroglycerin as a treatment for his heart disease that in 1890 he refused when a doctor recommended it. The inventor of dynamite

was no stranger to the volatile ingredient that also gives dynamite its punch. "Isn't it the irony of fate that I have been prescribed [nitroglycerin], to be taken internally!" he wrote to a colleague.)

Dr. Murad's findings in 1977 on the beneficial role of nitric oxide, and his suggestion that the body may even produce the gas itself, created a scientific stir and several years of disbelief. "Even my closest friends and colleagues were skeptical," he remembers.

Nonetheless, he pressed on. Meanwhile, efforts by Drs. Furchgott and Ignarro to identify an unknown signal molecule produced by the body led to the realization that it was actually nitric oxide, validating Dr. Murad's speculation.

The findings "triggered an explosion in the nitric oxide field, opening the floodgates of discovery," celebrated scientist Joseph Goldstein noted when presenting Drs. Murad and Furchgott the 1996 Albert Lasker Basic Medical Research Award, often considered America's version of the Nobel Prize.

Or as Dr. Murad puts it: The field from that point has just "gone bananas."

Researchers have generated more than 130,000 scholarly articles on the subject, he says, and nitric oxide now has at least one scientific journal solely dedicated to understanding its work.

The reach of nitric oxide, scientists now know, extends far beyond the cardiovascular system. In the nervous system, it helps control disparate functions, from memory to vision, and it's a weapon in the immune system's arsenal against bacteria, parasites, and tumors. Its role in the body also has helped inform doctors' understanding of a range of diseases and conditions, from diabetes and arthritis to septic shock and cancer.

In the area of drug development, premature newborns who are not getting enough oxygen, known as "blue babies," can be given nitric oxide gas to aid the movement of blood; and enhancing nitric oxide's effect on blood flow in the penis is the magic behind the blockbuster Viagra.

"There are very, very few biological processes that won't be regulated by nitric oxide," Dr. Murad says. "So it's got a lot of potential."

he butterflies didn't stand a chance.

Dr. Murad recalls going as a preteen to catch butterflies with friends in his hometown along Lake Michigan, south of Chicago. The plan was to mount the insects in a homemade display, but he knew that excessively handling them could ruin their prismatic wings.

He figured the answer—and here is where a budding scientist of some renown might stand out in a crowd of youngsters—was to poison them with cyanide gas. "So I went to the local pharmacist and I said: 'Could I have some potassium cyanide and hydrochloric acid to kill butterflies?' And he gave it to me."

"That's when I became interested in chemicals," he says with a laugh.

He would follow that curiosity, as well as interests in medicine and teaching, all the way to a PhD in pharmacology, a medical degree, and a career spent mentoring students in academic centers.

Of course, it takes much more than smarts (and access to toxic chemicals) to propel a child to success. The rest—discipline, hard work, determination—Dr. Murad would learn early on inside the bubble of his family's small restaurant.

His parents both were runaways: his father from a family of Albanian shepherds living in Macedonia, his mother from a large, hard-luck family in Illinois. They married in 1935 and raised three boys in a small apartment behind the family business.

"When we were able to stand on a stool to reach the sink we washed dishes," Dr. Murad wrote in an autobiographical essay for the Nobel website, "and later when we could see over the counter, we waited tables and managed the cash register."

He made sport of memorizing a roomful of orders and tallying bills in his head. The regulars, he says, ranged from bankers and businessmen to laborers and his teachers from school. "Many of them became very close friends and, really, advisers," he says.

Between school and the restaurant, he found time to letter in track and cross-country, among other sports, as well as sing in the chorus and play the lead in operettas.

His parents "always would stress the importance of education," Dr. Murad recalls. "If you wanted to do something and not work so hard as us, they would say, then go to school. And we did."

He was the first in his extended family to go to college. Both of his younger brothers would follow his lead into graduate programs, one

(Right) Dr. Murad's Nobel diploma.

becoming a dentist and the other an anthropologist.

Dr. Murad attended DePauw University, in Indiana, and left there with a fiancée, Carol Ann Leopold. She was studying English and Spanish at DePauw, though the pair met a thousand miles away in Fort Lauderdale, Fla., over spring break.

"Within a month we were pinned and six months we were engaged," says Dr. Murad. The next summer they wed, just as he prepared to begin a combined MD/PhD program at Western Reserve University (now Case Western Reserve), in Ohio.

And just as he left college with a fiancée, Dr. Murad completed graduate school with a family—four girls. (A son would come along, too, before he finished medical residency.)

His experience at graduate school would also give him something of a Nobel pedigree. One of his mentors in the laboratory there, Earl W. Sutherland Jr., would later win a Nobel Prize in 1971. And Dr. Sutherland had come up through the lab of husband-and-wife duo Carl and Gerty Cori, who both won Nobel Prizes in 1947.

The years that followed found Dr. Murad swinging among the top rungs of the ladder for science and medicine, holding positions as a researcher, physician, or administrator at Massachusetts General Hospital, the National Institutes of Health, the University of Virginia, Stanford University, Abbott Laboratories, Northwestern University, and, most recently, the University of Texas Health Science Center at Houston.

Along the way, he carried with him an attribute picked up from his mentors in that graduate school lab: a willingness to take research into the murky unknown, even if it means failure.

"There's no way to do research without going down blind alleys," he says. And that will mean sometimes giving up and retreating.

"But if you give up," he says, "maybe you can come back a few years later when you've got the technology to readdress the question."

In the case of cancer "a few years" has meant a few decades for Dr. Murad's lab, but the time finally seems right.

"We gave up because we didn't have the tools, we couldn't answer the questions," Dr. Murad says of his efforts to mitigate cancerous tumors in the mid-1970s. Instead, he turned to nitric oxide and the work that would win him a Nobel Prize.

But by the early 2000s, with the development of new tools and techniques, the blind alley from the 1970s began to look navigable.

"We've come back sort of full circle now," he says. In recent work, Dr. Murad says, his lab has found that the growth of some cancer tumors—in particular glioblastoma, a very aggressive type of brain cancer—can be suppressed in the lab by manipulating the work of nitric oxide and another messenger molecule that had helped lead to the nitric oxide discovery, called cyclic guanosine monophosphate (or cyclic GMP).

When those tumors are put in the brains of mice and the messenger pathways are similarly altered, Dr. Murad says, the mice have lived up to four times as long—84 days, up from 21. Whether that will work in humans it's too soon to say. But it's one of the big questions he'll be taking up from his new lab at GW.

"If we could make any impact whatsoever, it'd be a big advance," he says of glioblastoma. "I don't think we're going to cure the disease but maybe we can add some months to the life expectancy."

Similar manipulations, his team has found, may be capable of influencing the growth and differentiation of human and mouse embryonic stem cells in the process of changing them into heart cells and possibly even brain cells.

"What do we have to do now to take those cells and begin to use them for transplantation to treat Parkinson's, or Alzheimer's, or myocardial infarction [heart attack], or people with liver failure?" he says.

The answer, for now? A heck of lot of work over the next two or three decades, as Dr. Murad sees it. However, that kind of medicine is certainly coming, he says. "It's only a matter of time."

Meantime, Dr. Murad also plans to work toward development of a drug that would block some of the crippling and even lethal bouts of diarrhea caused each year by cholera infection and one type of *E. coli* bacteria.

Cholera kills more than 100,000 people each year and affects perhaps 5 million overall. As for that particular type of *E. coli*, Dr. Murad is targeting one of two toxins it produces that together kill at least as many as cholera and strike millions more as a major cause of travelers' diarrhea and diarrheal disease.

That research relates back to the same messenger molecule, cyclic GMP, which is increased as the infections over-stimulate the intestines. Dr. Murad says his team has recently identified a chemical compound that would block that chain of events, relieving many from this Third-World scourge.

There is lab work yet to be done before it can move into clinical trials, though, and much money to be raised to get to that point—on the order of a million dollars, he estimates.

And though Dr. Murad worries whether funding sources will be interested in investing money in "new ideas and risk," he does not sound daunted. After all, he has met skepticism before and walked away with a Nobel Prize.

So he plans to continue swinging for the fences. "I think that's the only way to do research," he says.

As he does, Dr. Murad also will be focused on endowing students with the wealth given to him by his mentors—a sense of adventure in problem-solving and that Nobel pedigree. "One of my goals is to identify that next generation here at George Washington," he recently told faculty and staff. "So I want all your best students to come knocking on my door."