

INSULIN:

does it
do a

heart

good?



SUPPORTED BY A \$30 million GRANT,
UB endocrinologist PARESH DANDONA
AIMS TO find out.

On February 2, 2004, a paper appeared in the journal *Circulation* that had the potential to change the way acute heart attacks are treated. The authors were neither clinical cardiologists nor heart researchers. They were endocrinologists from UB, and the paper reported the startling news that insulin—which had been used solely to treat and control type 1 and type 2 diabetes and which conventional wisdom considered destructive to the arteries and the heart—actually was cardioprotective.



STORY BY LOIS BAKER | PHOTOS BY DOUGLAS LEVERE
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arlier in 2000,

the same authors reported insulin's ability to suppress inflammatory mediators in cell cultures, and in 2001 they showed the hormone's potent anti-inflammatory properties in a group of obese subjects.

In the 2004 paper, they described a pilot study in which they demonstrated that infusing insulin along with the standard mix of anticoagulants and vessel relaxants into heart attack patients in the emergency department could reduce the amount of arterial inflammation contributing to a heart attack, as well as limit the amount of heart tissue destroyed during myocardial infarction.

What was to be made of these surprising new characteristics of "plain old insulin?"

As it turns out, answers to this big question may soon be on the horizon. A \$30 million clinical trial of insulin's cardioprotective potential is set to begin this fall, headed by Paresh Dandona, MD, PhD, UB Distinguished Professor of medicine and pharmacology, the unorthodox mind behind this new use of insulin. Coprincipal investigator on the study is Richard W. Nesto, MD, associate professor of medicine at Harvard Medical School and chair of cardiovascular medicine at Lahey Clinic Medical Center, a teaching hospital of Tufts University School of Medicine.

A Storied Molecule

The insulin molecule's storied history spans 150 years, highlighted by four Nobel Prizes. In 1869, Paul

Langerhans, a medical student in Berlin, discovered the clumps of tissue in the pancreas that secreted the yet-to-be identified hormone. The glands eventually were named the islets of Langerhans in his honor.

Two Polish-German scientists later removed the pancreas from one of their research animals and noticed that flies swarmed to its urine. This observation revealed the role of the pancreas in using and regulating glucose in body tissues. Twelve years later, another scientist established the link between the islets of Langerhans and the disease of diabetes.

Work stalled for the next few decades, then picked up again, this time at the University of Toronto. In 1921, Fredrick Banting, along with his medical student assistant Charles Best, and J. J. R. Macleod, professor of physiology and Banting's supervisor, developed a method to extract insulin from animals, a product they called

"isletin." A 14-year-old boy dying from diabetes in Toronto General Hospital received the first injection of isletin in 1922, but its impurities caused a serious allergic reaction. James Collip, a biochemist who had joined the group, spent the next 12 days purifying the extract, and to the group's enormous relief, the second injection reduced the boy's glucose overload and eliminated his excessive urination and thirst.

With their elixir in hand, the researchers descended like angels of mercy into the hospital's diabetes wards full of dying children and grieving parents, administering insulin to patients one by one. The first children treated awakened from their comas before the physicians reached the last bed, according to accounts of this momentous chapter in medical history.

Had these dedicated medical men held on to the patent for this new miracle drug, they would have become wealthy beyond imagining. Instead, they sold the patent to the University of Toronto for one dollar.

Later that year, the pharmaceutical giant Eli Lilly developed a method to produce large quantities of purer insulin, and soon the product was available for sale to physicians. At this point, insulin still was derived from animals, primarily pigs, which produce an insulin molecule most similar to

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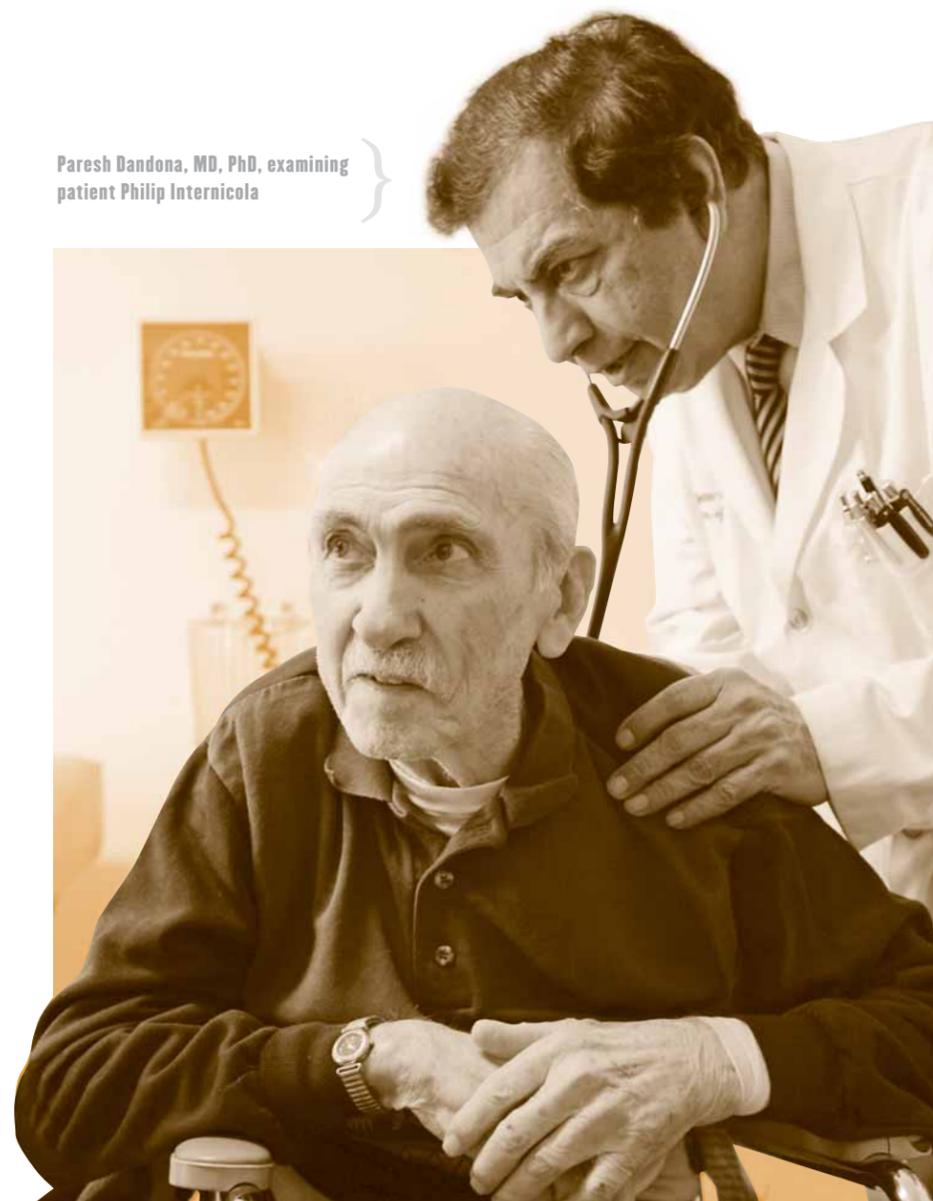
that of humans. Genentech developed the first genetically engineered human insulin, which Eli Lilly began marketing in 1982. There are now more than 20 types of insulin available on the market. As of January 2006, all insulin distributed in the United States must, by law, be human or analogs of the human molecule.

Stellar Outcomes

Dandona likely would have gotten along famously with Banting, Best and Macleod. He thrives on developing new medical hypotheses and following his hunches. "My best facility is innovation and novelty; that's what I live on," he says, from behind his desk stacked with medical papers and journals in a cramped office in Buffalo's Millard Fillmore Hospital. "If that were taken away from me for routine work, I'd be dead."

Dandona earned a medical degree from All India Institute of Medical Sciences, and in 1975 he completed a PhD at Oxford University, where he was a Rhodes Scholar. Since 1970, he has authored or coauthored 430 papers covering a wide range of metabolic, endocrine and vascular conditions. Recruited to UB in 1991 as chief of endocrinology after practicing medicine in Britain for more than 20 years, he remains an Anglophile to the core.

Paresh Dandona, MD, PhD, examining patient Philip Internicola



His passion for the new coexists with dogged determination to elicit the best from the tried and true. Soon after his arrival at UB he founded the Diabetes-Endocrine Center of Western New York. Housed on the tenth floor of Millard Fillmore Hospital, the center serves nearly 3,000 patients at any one time.

The northern U.S. in general, and much of the northeast in particular, including Western New York, has a high incidence of diabetes, due in part to diet—obesity is a major risk factor—long winters that discourage outdoor activity, and a generally sedentary lifestyle.

The Diabetes-Endocrine Center of Western New York has one of the best patient outcomes on record. Dandona compares his outcomes with that of the renowned Steno Diabetes Center in Copenhagen, Denmark, the oldest and one of the most famous hospitals in the world dedicated entirely to diabetes.

Type 2 diabetics are at very high risk of heart disease, stroke and especially circulatory problems, which often result in such pernicious complications as foot ulcers, which, if not treated adequately, lead to gangrene and amputation. A recent Steno study using an intensified program of treatment in a cluster of patients to control diabetes and other vascular problems produced a 50 percent reduction in rates of complications and mortality, but also reported some amputations.

“We’ve done better than that right here in Buffalo,” Dandona states. “We haven’t seen a single foot ulcer, gangrene or amputation for the last 10 years. Plus, our cholesterol numbers are the finest and our blood pressure numbers are outstanding. On each count we are better than Steno. So I can really say that we are better than the finest in controlling diabetes.”

How has his clinic achieved this record, when convincing patients to take medications as prescribed is a continuing and vexing problem? Moreover, the majority of his patients take insulin, which requires self-injecting the drug several times a day, a significant obstacle to compliance.

“Sheer aggression and commitment,” replies Dandona,

“Many physicians actually have given up the battle,” he adds. “They say, ‘These patients will not change. They’re noncompliant.’

“Noncompliance is a term I left behind 25 years ago!”

In his clinic, Dandona explains, the prevailing philosophy is that it is unacceptable to conclude that a patient is noncompliant if, as a team, they have not put the full weight of their conviction and commitment behind their efforts to motivate the patient.

“Nobody here uses the term ‘non-compliant,’” he says. “We just tell our patients, ‘We’ve got to get it done, and I have ways of getting it done, but we must work together, because without

treatment you are endangering your eyesight and your kidneys and your heart and your brain.

“‘You’ve come to the right place,’” he continues with his hypothetical doctor-to-patient encounter, “‘and now there is no way your diabetes won’t be controlled. We will control it. You’ve come to me for good advice. I’ve given you good advice, and you will take it.’ That kind of thing has an impact.”

Keen Observations, Smart Hunches

In the mid-1990s, Dandona and his colleagues began to notice characteristics of insulin that went beyond the hormone’s ability to regulate blood glucose. Insulin appeared to relax blood vessels and to cause the release of nitric oxide in cultures containing endothelial cells that line the vessels. Intrigued by these new data, Dandona began to investigate further, and provocative results began to emerge.

The group published a study in the July 2000 issue of the *Journal of Clinical Endocrinology and Metabolism* showing that insulin reduced the expression of a molecule that promotes inflammation and the clogging of arteries. Meanwhile, they had already begun a study in patients. Results revealed that insulin suppressed components that generate cell-damaging free radicals, which induce inflammation and damage blood vessel lining. In essence, they had proved for the first time—all former

evidence to the contrary—that insulin suppressed inflammation rather than increasing it. They submitted the paper for publication and waited.

Because the results were so unexpected and unorthodox, the following months were filled with anxiety for Dandona and colleagues. “I was worried that the study would never see the light of day,” he recalls. “Why? Because the whole world at that time thought that although insulin is a good thing to treat diabetes, it is in fact a terrible molecule because it causes atherosclerosis. And so, when you say insulin is anti-inflammatory, and the whole world believes that it causes atherosclerosis and the whole world also knows that atherosclerosis is an inflammatory process, how the hell are the reviewers of this paper going to accept it intellectually? It was totally counter to everything that had been said about insulin at this point.”

This time Dandona was wrong. Not only was the paper accepted and published in the July 2001 issue of the *Journal of Clinical Endocrinology and Metabolism*, it won the Pharmacia/Pfizer Prize from the Endocrine Society in 2002 as one of the four best papers in clinical endocrinology that year.

Dandona’s group was now ready to take the next giant step: to organize a pilot study aimed at proving that insulin’s anti-inflammatory capacity could dampen the inflammation generated during an acute heart

attack. Dandona wrote the protocol and received approval from the Institutional Review Board to proceed. But there was a catch: Endocrinologists don’t treat heart-attacks, so he would need the cooperation of cardiologists.

Despite assurances that they would help recruit patients, the cardiologists in Western New York remained uninterested. Dandona received no referrals over two years and was growing despondent. Finally, David Janicke, MD ’88, PhD, a UB clinical associate professor of emergency medicine with clinical trial experience in acute coronary syndromes who practiced at Millard Fillmore Hospital, signed on to the study. It was carried out in 32 patients, with support from Ajay Chaudhuri, MD, UB assistant professor of clinical medicine, and members of Janicke’s team.

The trial was a stunning success. Not only did it show that insulin could indeed lessen the inflammation that contributes to a heart attack, but it also protects heart tissue from destruction during an attack.

“Showing that insulin was cardioprotective, which we discovered for the first time, was a tremendous bonus,” says Dandona. “The markers of myocardial damage that we measured were reduced significantly. That was very,

INSULIN APPEARED TO RELAX BLOOD VESSELS AND TO CAUSE THE RELEASE OF NITRIC OXIDE IN CULTURES CONTAINING ENDOTHELIAL CELLS THAT LINE THE VESSELS. INTRIGUED BY THESE NEW DATA, DANDONA BEGAN TO INVESTIGATE FURTHER, AND PROVOCATIVE RESULTS BEGAN TO EMERGE.



very exciting. Not only may we have found another different use for insulin, we may have discovered a very effective way of reducing damage during an acute heart attack. The drugs that have been coming out recently have shown only marginal improvements in that regard, so something like this could make a lot of difference.”

Following publication of those results in *Circulation* in 2004, the endocrinologists set out to prove this new property of insulin in a large clinical trial and applied for a grant from the National Institutes of Health (NIH). Evaluators were intrigued, but they pointed out that such a study should be conducted in multiple medical centers. Dandona wondered how he could pull that off, when cardiologists would have to be major players and past experience had shown they weren't receptive.

Then, opportunity knocked. After the *Circulation* paper appeared, invitations to speak poured in. One invitation came from the pharmaceutical firm Sanofi-Aventis, which recently had entered the diabetes field.

“Being a Johnny-come-lately, they were looking to do something spectacular, academically speaking, that would show that they were really serious about diabetes treatment,” explains Dandona. “Fortunately for us, our proposal appealed to them more than anything else.”

The ensuing \$30 million study is set to begin late this fall in 90 centers in the U.S. and Latin America. The Diabetes-Endocrine Center of Western New York will be one of the vanguard centers, and its research facility in the UB Center of Excellence will serve as the core laboratory.

Harvard's Nesto will lead the clinical cardiology aspects of the trial. “Studies in the past that looked at the potential bene-

fits of insulin always were clouded by glucose levels that went up, because patients were given too much glucose,” Nesto says. “We will be giving insulin along with lower doses of glucose.”

“The treatment will be tailored to those patients who would benefit most—patients with glucose above 140 on admission and who have an anterior wall heart attack—the largest of heart attacks,” he continues. “It's the first large-scale trial that will be conducted using this strategy: treatment tailored by doctors for individual inpatients.”

During the two to three months post-heart attack, patients will undergo magnetic resonance imaging (MRI), which can detect subtle changes in cardiac structure and function.

More Hypotheses to Test

Dandona's passion for discovery meanwhile is propelling him and his research group down at least three additional new research avenues.

He has discovered that one in three of his male diabetic patients has low testosterone levels, known clinically as hypogonadism. This October, he began a clinical trial that examines the ability of a testosterone gel to raise hormone levels, as well as assess the drug's effect on obesity and atherosclerosis, both conditions associated with diabetes. The study includes a basic-science component, which will investigate the regulatory mechanism in the brain responsible for the underproduction of testosterone.

Epidemiologists determined 17 years ago that testosterone levels appeared to be low in diabetes. The fact that no one is following up on this problem clinically infuriates Dandona. “Those guys made that discovery and then just left it as a kind of epidemiological marker,” he fumes. “Why is it they did not describe this crisis of diabetes? Forty percent of diabetic males do not have sufficient male hormones in their system. Think about the clinical meaning of it!”

Another new interest involves identifying protective macro- and micronutrients. Dandona's endocrine group had previously demonstrated that fast-food meals high in glucose, fat and carbohydrates induce inflammation. They published a paper in the June 2007 issue of *Diabetes Care* showing that orange juice containing similar calories, however, does not induce inflammation. Orange juice appeared to be a healthy food for diabetics because of its high flavonoid content, despite its high caloric load of sugars.

Flavonoids are dietary components that can suppress destructive oxygen-free radicals generated by a high-calorie, high-fat meal. Now the search is on in his lab for other potentially naturally “protective” foods, one of which may be turmeric (the herb that makes curry yellow) and grape seed extract, and Dandona is planning pilot studies on both.

“This is very exciting for me,” he says, “because we are translating common daily activities, such as eating, into molecular biology. In the next five years, this information could give us a different sort of menu organization and prompt new eating habits—maybe even lead to a change in the labeling of foods.”

Perhaps most intriguing is his venture into the developing research area of pathogen-recognition receptors—how the body's immune system distinguishes bacteria from virus from fungus. One avenue appears to be via a group of molecules called toll-like receptors, the activation of which induces a cascade of inflammation far beyond what is needed to defeat the pathogen. Dandona's basic research group is ready to report that low-dose insulin can suppress these receptors and thus reduce excessive inflammation following infections.

“The whole pharmaceutical industry right now is trying to synthesize molecules that will suppress the toll-like receptor system,” Dandona says, “and here we have good old insulin suppressing it by 30 percent within the first two hours of infusion.”

With these and other projects under way, Dandona has his research and clinical agenda outlined for the next decade, perhaps even longer.

“It's a very exciting time, I can tell you that,” he says. “All of this may change standards of treatment.” **BP**

Manish Upadhyay, MD, an endocrinology Fellow in Dandona's laboratory, is a study collaborator



THE ENSUING \$30 MILLION STUDY IS SET TO BEGIN LATE THIS FALL IN 90 CENTERS IN THE U.S. AND LATIN AMERICA. THE DIABETES- ENDOCRINE CENTER OF WESTERN NEW YORK WILL BE ONE OF THE VANGUARD CENTERS, AND ITS RESEARCH FACILITY IN THE UB CENTER OF EXCELLENCE WILL SERVE AS THE CORE LABORATORY.