From Global to Microscopic Views of Cardiovascular Disease

The 71st Scientific Sessions of the American Heart Association in Dallas, Tex, November 8 through 11, 1998, began with a plea from president Valentin Fuster, MD, PhD, to take a global view of cardiovascular disease on the eve of a new millennium. But some of the most startling science was concentrated at the level of genes.

In his presidential address, Fuster warned that although recent data indicate that acute treatment and secondary prevention have decreased death due to cardiovascular disease and stroke in the United States, the statistics hide the real problem. “In reality, however, the severe impact of these cardiovascular diseases on mortality has been postponed for a few years,” he said.

Cardiovascular disease is not only the leading cause of death in the United States and in most developed nations, it is also the most costly in terms of money and disability. “At present, nearly 10 million people are affected,” Fuster said. “These diseases bear the highest cost: about $274 billion each year in medical expenses and lost productivity.”

According to Fuster, by the early part of the next century, cardiovascular diseases will be the leading cause of death and disability in the world. Combating this “evolving epidemic” means meeting 3 challenges, Fuster said.

“First, how will we be able to support and energize cardiovascular and stroke research?” In part, the US Congress has begun that process by proposing double funding for the National Institutes of Health over the next 5 years, he said. In fiscal year 1999, Congress has already allocated $2 billion more to biomedical research, for a total of $15.6 billion.

Organizations such as the AHA facilitate such research by targeting their money to specific diseases and problems, Fuster said. “One of the American Heart Association’s goals is to identify and provide initial support to the most promising young investigators as they embark upon productive science careers,” he said. Integrating funding for basic and clinical science is key to avoiding divisiveness among researchers and meeting the needs of a society facing a devastating disease. Training new investigators is a key part of the plan to maintain research priorities, whether the education be paid out of government or private dollars.

As the second challenge, Fuster asked a question: “Is it realistic to expect that this epidemic of cardiovascular disease and stroke can be modified through just professional and public education, or perhaps is there a need for more aggressive implementation strategies?” The AHA’s delegate assembly has set as its goal the reduction of coronary heart disease, stroke, and risk factors by 25% over the next 10 years. To achieve that goal, they hope to aim intensive prevention programs at people with the highest risk and to encourage earlier acute treatment of heart disease and stroke events.

Populations with atherosclerosis, either in the coronary arteries or outside them, make up the group at highest risk of stroke or myocardial infarction, Fuster said. Although educating patients and their physicians is part of the plan, “I believe most important is a supportive health system geared to aggressively implement such strategies,” said Fuster.

He described as barriers to implementing effective preventive measures the lack of incentive or reimbursement and a lack of time to allow physicians to deliver their preventive message and to provide effective treatment. Another barrier is the lack of knowledge or motivation about the need to prevent heart disease risk among patients, as well as a lack of sound policies or guidelines that could direct a risk-reduction program or get patients to the hospital in a timely fashion.

The third challenge Fuster issued was for organizations such as the AHA to streamline their operations and to think cooperatively and internationally about the problem. “What will it mean for the United States or for the American Heart Association when we win the battle against the tobacco industry if we do not cooperate with the less-developed countries and therefore permit the tobacco industry to find new and easy markets?”

“What will it mean for leading pharmaceutical companies to produce on great scale vaccines against cancer or even potent weapons against cardiovascular diseases if economically accessible vaccines for respiratory diseases, lethal diarrheal illness, tuberculosis, and malaria cannot be delivered as well?” he asked.

Global to Genetic

But while Fuster was issuing this global ethical challenge, Frances Collins, MD, PhD, was waiting to issue a similar one with regard to the legal, ethical, and social issues involved in the Human Genome Project. Collins, head of the National Human Genome Research Institute, delivered the Lewis A. Conner Memorial Lecture.

“It is incumbent on all of us to deal with the legal, ethical, and social implications” of the Human Genome Project because virtually all disease has a genetic component, said Collins. He anticipates that problems will arise sooner than anticipated because the sequence is expected to be completed within the next 5 years, shaving 2 years off the previous estimated finishing date. The year 2003 is only 50 years after...
the publication in Nature of the seminal 1-page article by James Watson and Francis Crick describing the structure of DNA.

Collins said it is important that the sequence information be available in a public database to which researchers and eventually clinicians can refer. “Hunting down disease genes is a lot of fun,” Collins said. “But what can you do with a gene to benefit people?”

One benefit is in diagnosis, he said. For example, the code for BRCA1, one of the genes linked to breast and ovarian cancers, can be put on a silicone chip and used to detect the presence or absence of that gene in a blood sample.

In some diseases, such a diagnosis allows treatment to occur before the patient is injured, he said. For example, hemochromatosis, an overload of iron, occurs in 1 in 300 people, he said. Without treatment, patients can suffer cirrhosis, heart failure, diabetes, and arthritis. The disease is often undiagnosed because its symptoms so closely mimic other diseases. However, if it is recognized, patients are bled to reduce the iron excess. Collins said the federal government is now considering funding a pilot genetic screening program to identify people with hemochromatosis who might otherwise go undiagnosed until they were very ill. If the pilot proves to be of benefit, then a nationwide screening program could be contemplated.

Collins also sees the birth of a new test (pharmacogenetics) that determines who will or will not respond to a particular treatment on the basis of the genes carried by the patients. Genes might also point the way to the best therapy. By identifying the genes associated with long-QT syndrome, researchers have found that 2 involve defects of the potassium channel and 1 involves a defect of the sodium channel. If a patient were genotyped before treatment, it would be easier for the physician to determine how that patient should be treated. Genetic discoveries allow “for true individualized medicine,” according to Collins.

Of course, there are genetic diseases that can be diagnosed today for which there is no effective treatment, he said. The answer in many cases would be gene therapy. “We wish to have that happen as soon as possible,” said Collins. However, the scientific issues involved are extremely complex, and the promise of such treatment “carried too high expectations,” he said.

Perhaps the greatest threat of gene testing is to jobs and health insurance, according to Collins. Last year, the US Congress had bipartisan support for a bill to block the use of genetic information to deny people health insurance or jobs. However, the legislation got lost in the furor over the presidential sex scandal. Collins hopes it will be rapidly passed this year. “We must all band together to make sure this legislation gets passed this year. ‘We must all band together to make sure this legislation gets passed this year.

Coronary Arteries and Genes

At the 70th Scientific Sessions of the AHA in Orlando, Fla, in November 1997, researchers presented the first use of genes to promote angiogenesis and prevent restenosis. However, those first efforts were directed at arteries on the periphery, most often in the feet and legs. At the 1998 meeting, the emphasis had shifted upward to the heart and the coronary arteries.

Jeffrey Isner, MD, created the most stir when he brought one of his patients, a Texan, to the meeting with him. “He is 1 of 16 patients we have treated at St. Elizabeth’s Medical Center in Boston,” Isner said during a press conference on his treatment. “Last year, we hoped to administer naked DNA without a virus vector simply using a small needle and syringe and injecting it in much the way people administer vaccines,” he said. In that instance, he injected the gene for vascular endothelial growth factor (VEGF) into the legs of people with inadequate blood flow to the extremities. “We have basically taken the same approach and transposed it to the hearts of patients who did not have enough blood flow to the heart muscle,” said Isner. He estimated that as many as 250,000 people per year would be candidates for a procedure like this because the flow of blood to the coronary arteries becomes blocked despite the best medical and surgical techniques, including bypass and angioplasty. “They still have angina that does not allow them to live a normal life,” he said. “There is currently no other treatment option available.

“There were 16 patients in this group in whom we elected to try direct intramuscular gene transfer designed to affect new blood vessel growth in the hearts,” Isner said. “Injection into the heart was the sole intervention these patients received at the time.” Because it was the only treatment, Isner felt it would be easier to attribute changes in the patients’ health status to the gene transfer than it would be if another modality of treatment were attempted.

“We gained access to the heart muscle using a technique called minithoracotomy or MIDCAB incision,” he said. All 16 of the patients had had at least 1 and no more than 3 previous heart attacks. Eleven had undergone angioplasty, and 15 had had coronary artery bypasses. In fact, the average number of bypasses per patient was 2, said Isner. “They had received the best that contemporary cardiology and cardiovascular surgery had to offer. Despite this, they were having an exceptional amount of angina.”

The MIDCAB procedure took ≈1 hour, he said. Most patients were extubated before they left the operating room. There was no evidence of acute myocardial infarction around the time of surgery. All patients were discharged from the hospital within 3 to 4 days after the operation.

Using an ELISA, researchers documented the expression of the VEGF gene in the series of patients. But what was most surprising was patient response, Isner said. All 16 patients were in New York Heart Association (NYHA) functional class IV when they were enrolled in the study. In other words, they developed angina with only minimal exertion. At the most recent follow-up, none of the patients remained in class IV, and none were in class III. Sixty percent were in class II, and 40% were in class I. Of 11 patients followed up for ≥90 days, 6 were entirely free of angina. Nitroglycerin use in the group had plummeted. Coronary angiography demonstrated improved blood flow to the heart, and nuclear perfusion scans showed a statistically significant increase in the number of segments of the left ventricle that were perfused after the gene therapy.

The dosage was no more than 120 μg, said Isner. By comparison, those treated for impaired blood flow in the legs and feet received as much as 4 mg of VEGF. The dose is being...
escalated, and the last 10 patients to be enrolled in the study will receive 500 μg, which is still less than that given for treatment of the legs. “The fact that this has had such an effect with a low dose and no significant complications makes us encouraged about the role this therapy may play in reducing the need for bypass operation or angioplasty,” said Isner.

In the future, the gene might be injected with a catheter, eliminating the need for surgery altogether. “Then it might be possible to employ this strategy at an early phase of the disease,” Isner said.

The treatment described by Ron Crystal, MD, director of the gene therapy core facility at New York Presbyterian–Weill Medical College of Cornell University in New York City, involves the use of adenoviral vector as a backbone and an E1-E3 deletion from a cytomegalovirus promoter with the E1-E3 adenoviral vector coding for the human cDNA of VEGF.

Crystal said he and his team have used viral vectors before, but they found they could not express the new gene persistently, although gene expression was robust in the beginning. “We started thinking about building things in the body where you only need to build things on a transient basis. Think of this as a concept of regenerative gene therapy. We all are taking diseased adult organs and returning them to youth,” he said.

The VEGF being used is the same that embryos use to make new blood vessels, said Crystal. But the mature body loses the ability to turn the VEGF gene on. “We are taking the gene, giving it back to the heart for a week or 2, and allowing it to express robustly,” said Crystal.

The adenovirus is a highly effective transporter, he said. “Take an adenovirus and put it on the surface of the cells; it gets to the nucleus and transfers the genetic cargo,” said Crystal. “We put the VEGF gene into a disabled adenovirus to transfer the gene and have it express and make VEGF protein to tell the heart to make new blood vessels.” He and colleagues Todd Rosengart, MD, and Wayne Isom, MD, first used the gene therapy in combination with CABG surgery in 15 patients and as a single treatment in another 6.

There were no adverse events related to the vectors, said Crystal. Also, the patients report that they feel better and can do more on treadmill tests. “Our conclusion is that because we are not seeing adverse events, it is rational to proceed to phase II studies, and we are embarking on that with many centers. Results from these studies are encouraging, but I would strongly warn everyone that all of this is phase I, and that’s why we carry out phase II and III, so that we can prove that in fact what we are doing does work.”

VEGF also figured prominently in a Finnish study that used liposomes to carry the protein fragment into the coronary arteries of 10 people who had undergone angioplasty. The liposome-gene combination was delivered by catheter to the patients, whose progress was compared with that of 5 controls. One of the patients treated with gene therapy developed restenosis in the 6 months that followed, said Seppo Yla-Herttuala, MD, PhD, principal investigator of the clinical gene therapy program at the University of Kuopio in Finland. “It is very encouraging,” said Yla-Herttuala. “There are no major side effects that we have seen, but the real clinical benefit needs to be studied in phases II and III.”

Nicholas N. Kipshidze, MD, of the Medical College of Wisconsin, combined gene therapy with an old treatment, the Vineberg bypass procedure. He said fibrin glue serves as a platform for sustained release of the VEGF gene. He tried the combination of fibrin glue and VEGF gene in 2 patients with critical limb ischemia with what he called good results. Moving to patients with coronary artery disease, Kipshidze delivered the VEGF gene to 5 patients through an intracoronary catheter. However, in the remaining 2 patients, he found it impossible to pass the catheter through the occlusion. “We used a needle to puncture the myocardium,” he said. All 5 had improvement in clinical status after 3 months, but angiography did not show growth of new blood vessels.

Kipshidze said that on the advice of a colleague, he tried combining the gene therapy with the Vineberg procedure, in which the mammary artery is freed and put directly into the myocardium. He hoped this would give a blood supply to the new arteries growing there. The procedure has been performed on 5 patients so far, along with injections containing VEGF in its fibrin platform, he said. He said 2 of those treated earliest demonstrated growth of new blood vessels on angiography.

Michael Mann, MD, and Victor Dzau, MD, are attempting to alter the course of biology by genetic manipulation of vein grafts used in leg artery bypass procedures. Mann estimated that as many as 50% of cardiac and leg bypass grafts will fail within the next year because of abnormal growth in the lining of the vessel. “Unlike native atherosclerosis, vein graft atherosclerosis has a clear beginning point,” he said. “We take an undiseased vessel and move it to a place where it develops atherosclerosis.”

“It is a unique situation because the vein graft is in the surgeon’s hand in the operating room. He has the best opportunity to perform efficient and effective manipulation,” said Mann, a surgeon and member of the faculty of medicine at Harvard Medical School. Dzau is chairman of medicine at Brigham and Women’s Hospital.

Before the veins are attached to achieve the bypass, the surgeon bathes the graft in liquid that contains an oligodeoxynucleotide, a short segment of DNA that blocks the action of genes needed to start the process of vein graft atherosclerosis, called neointimal hyperplasia. In the study, 17 patients received the gene therapy, and 16 patients served as control subjects. Mann said the results are good enough to encourage the researchers to begin to consider similar treatment of coronary arteries.

Fuster said the presentations represent several advances. “First, we are targeting the heart this year. Second, we are talking about safety this year along with the word ‘cautious.’ Third, I think we are undertaking the real thing, a rigorous approach to what all the preliminary data are trying to show. This is all very promising.”

“Of course, it doesn’t answer the question of impact,” said Fuster. It appears that gene therapy will work, but to what extent? Fuster has hope that gene therapy will be an important treatment advance. “Last year, we saw an opening door. This year, the door is open,” Fuster said.

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