Axel Haverich, head of the Division of Thoracic and Cardiovascular Surgery, Hannover Medical School, Hannover, Germany, and clinical director of the Hans Bors Centre for Heart and Stem Cell Research, Hannover, Germany, talks to Barry Shurlock, MA, PhD.

“My Overall Aim Is to Rebuild an Entire Human Heart From ‘Ourselves.’ I’ve Got About 10 Years Before I Retire, and I Think We Will Do It by Then”

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“On other pages...”

Spotlight: Jose Zamorano Gomez, MD, FESC

Jose Zamorano Gomez, professor of medicine, University Complutense of Madrid, Madrid, Spain, director of the Cardiovascular Institute, University Clinic San Carlos, Madrid, president of the European Association of Echocardiography, and secretary of the European Society of Cardiology, says, “I am going to commit part of my life to merging the cardiovascular risk factor with imaging to better assess the real risks for our patients.”

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‘No, no, it’s a mistake,’ I said. ‘He wants to talk to you,’ she insisted. I couldn’t believe it, but it was true. I was the first surgeon ever to win it!” He still is the only surgeon on a list peppered with mathematicians, philosophers, theoretical physicists, and the like.

Professor Haverich won the prize for his work on heart–lung and isolated lung transplantations. A year later, he left Kiel to return to the top job at Hannover, where he was appointed head of his former alma mater, the Division of Thoracic and Cardiovascular Surgery of the Hannover Medical School. There, armed with prize money of 3 million Marks (∼€1.5 million), he set up the Leibniz Research Laboratories for Biotechnology and Artificial Organs (LEBAO), which currently has a professional and technical staff of 38.

As a transplant surgeon, Professor Haverich realised there would probably never be enough hearts available for all patients with end-stage disease, and the only solution was to make artificial ones. He describes how he and the LEBAO team developed the idea of tissue-engineered heart valves: “The concept started with the entire heart. We realised that muscle [myocardium] would be difficult to reconstruct because of the many small blood vessels, so we thought why not start with heart valves? I was aware of some work on deposition of endothelial cells on artificial surfaces for below-knee grafts. And decellularisation had been around since 1991. So, with a little idea from here and an idea from there, we managed to do what no one else had done.”

“Since September 2008, Implantation of the Valves Within Germany Has Been Made Possible by an Exceptional Regulation”

Professor Haverich's decision to leapfrog European Union regulations and implant the first 19 tissue-engineered heart valves in Moldova enabled him to gain 7 years in his research project, but it has not gone without criticism. It may have even cost him the German Future Prize for 2008, awarded each year by the president of Germany to support outstanding research. He and his colleagues, Dr Cebotari and Dr Michael Harder, were shortlisted for the award. The German press accused them of using the Moldavian children like “rabbits,” and they did not win the prize. Professor Haverich rebuts the accusation by pointing out that the operation probably saved the children’s lives, and the children are, in any event, all “doing well.” He adds, “I was upset and disappointed by the result, not only for myself but for my colleagues. There were ethical issues. European regulations always complicate things. It would have taken a lot of time to get through the regulatory processes—in fact, there was no regulatory body that could consider the concept. Serghei Cebotari was the driving force to start the work in Moldova.”

Tissue-engineered valves are marketed by a company closely associated with the University of Hannover that specialises in products and new technologies for cardiovascular and cardiothoracic surgery. These valves are expected to have considerable advantages over existing mechanical valves, which require lifelong anticoagulation, and animal valves, which are of limited durability. Since September 2008, within Germany, implantation of the valves has been made possible by an exceptional regulation, and Professor Haverich has to date (March 11, 2009) carried out 5 operations on children in Hannover. He expects to carry on, at the rate of ≈1 a week, in children and adults. Within a few months, he expects similar operations to be performed elsewhere in Europe, probably first in Zurich, Switzerland, and Paris, France.
“An Italian Cardiologist Told Me Recently That She Had Carried Out Echocardiography on a Recipient and Couldn’t Detect the Artificial Valve!”

Paradoxically, Professor Haverich’s vision of moving away from cadaver-associated material has been limited by the LEBAO team’s discovery that valves from pigs and calves cannot be satisfactorily decellularised and only homografts are effective. However, working with valves taken from patients who have received a heart transplantation, Professor Haverich has estimated that, within Germany alone, the current rate of 400 heart transplantations a year should yield 500 valves.

He comments, “All recipients of tissue-engineered valves have done well so far. Children over 8 to 10 years of age can accommodate a tissue-engineered adult valve. We were not sure whether we would see what we had seen in sheep—that is, no long-term degeneration, but to date there clearly is no degeneration [in the children]. An Italian cardiologist told me recently that she had carried out echocardiography on a recipient and couldn’t detect the artificial valve! There is also work being carried out with tissue-engineered valves at various centres in the United States, with a different ‘recipe,’ but they have reported degeneration. They use material cryopreserved in liquid nitrogen, whereas we always use fresh homografts. There is some controversy between the 2 groups, but we are talking and getting closer and closer.”

“I Got the Idea of Tissue Engineering Muscle With Jejunum as I Was Driving Back From a Skiing Trip at Easter in 2001”

Professor Haverich and his team are also working on tissue-engineered myocardium, using segments of jejunum, which will be decellularised and then reseeded with endothelial cells and cardiomyocytes, probably from induced pluripotent stem cells. The team has also developed a biodegradable coronary stent. He says, “My overall aim is to rebuild an entire human heart from ‘ourselves,’ and we are getting near it. I had my 56th birthday recently, so I’ve got about 10 years before I retire, and I think we will do it by then. I got the idea of tissue engineering muscle with jejunum as I was driving back from a skiing trip at Easter in 2001. My youngest daughter and a friend were sitting in the back of the car—and when I got the idea I said, ‘Write this down!’ The beauty with jejunum is that after decellularisation you still have the matrix of blood vessels in place.”

In May 2008, LEBAO became part of the Hans Borst Centre for Heart and Stem Cell Research, a brand-new purpose-built facility where 110 researchers (due to increase to 150) work on a range of projects concerned with diseases of the heart, blood, and liver. The centre is run by Professor Haverich as clinical director and biologist Professor Ulrich Martin as director of research. Funded to the tune of €13 million by the Braukmann-Wittenberg Foundation, a local charity, the Hans Borst Centre for Heart and Stem Cell Research is part of an ambitious cross-institution, cross-discipline “cluster of excellence” in the city, housed under the title “Regenerative Biology to Reconstructive Therapy.” In 2006, Regenerative Biology to Reconstructive Therapy was granted €40 million by German state and federal governments to fund it for the next 5 years.

“At the Age of 21, I Found Myself Helping Him [Hans G. Borst] With an Operation. I Never Looked Back; He Had Me on the Hook”

Every time Professor Haverich thinks of the Hans Borst Centre for Heart and Stem Cell Research, he cannot help but think of the man who gave his name to the building, Professor Hans G. Borst, a “hugely important mentor” and his predecessor as head of the Division of Thoracic and Cardiovascular Surgery at the Hanover Medical School. He recalls, “I remember in my second year as a medical treatment assistant when I was helping him with a patient. I don’t know what I was doing, but he was very kind and friendly to me. He was always asking me questions and encouraging me to ask questions as well. He was a great mentor and a great person.”

Professor Haverich (middle), with Stephanie Galeiwa (nurse, left), and Dr Gregor Warnecke (right) during a coronary bypass procedure. Photograph courtesy of Professor Haverich.

Dr Breymann (right) and Professor Haverich with a young patient on the intensive care unit the day after implantation of a tissue-engineered heart valve. Photograph courtesy of Professor Haverich.
student being so impressed by one of the lectures by Professor Borst that I went up to him at the end and asked if I could watch him in the theatre. He agreed, and at the age of 21 I found myself helping him with an operation. I never looked back; he had me on the hook!” Professor Borst started his career in Munich, Germany, but for many years he worked in the United States at Harvard University, Cambridge, Mass, and Stanford University, Stanford, Calif, before returning to Germany, first to Marburg, and then in 1968 to head up thoracic surgery at the Hannover Medical School. The Hans G. Borst Award for Thoracic Aortic Surgery of the European Association for Cardiothoracic Surgery, which he helped to found, commemorates an area of surgery to which he made major contributions. He is still active, promoting the development of cardiothoracic surgery in Eastern Europe. When leaving office in 1996, he reminded Professor Haverich “to take care of the cardiac surgery programme in Moldova,” adding, “They are very good people.”

“I Carried on Playing [Semiprofessional Handball] for 10 Years, Until I was 28” Professor Haverich is a “country boy” who grew up in the small village of Barntrup 80 miles from Hannover. His best subjects in school were “mathematics, sport, and religion” (a careers adviser’s nightmare!), but he thinks he decided to read medicine because of the influence of a family doctor. The old man played piano and the young boy played cello, and together with others they performed classical music at school and in the local church.

When it came time to choose a medical school, Haverich was playing handball in a semiprofessional capacity for a local team called Lemgo (“They are still in the top league”), and he was obliged to train several times a week. “So I needed to go to a medical school where I could go home to train during the week. I had a car—the team paid for it—and I went back 4 times a week. I carried on playing for 10 years, until I was 28, and went to the United States to learn how to do heart and heart lung transplantation. Almost more important was that I also learnt there how to do experimental research, with large and small animals. That was very important for me.”

Haverich’s time at Stanford University was funded by a 3-year grant from the German Research Foundation. He trained with the legendary Norman Shumway, MD, and on his return, he was immediately appointed a senior resident in Hannover.

“I Want to See More Abstracts at Meetings That Are on Research Rather Than Just [Everyday] Surgery” As his career advanced and Professor Borst moved towards retirement, Professor Haverich realised that if he were to succeed him, he had to leave Hannover. The German university system has a feature—not quite a law, but a strong understanding—that candidates applying for senior positions at any university must have worked elsewhere for at least 3 years before making the application. The goal is to widen the experience of applicants, and it has the incidental effect of spreading around the expertise at centres of excellence. Hence, in 1993, Professor Haverich headed off to lead the Division of Cardiovascular Surgery at the Christian Albrechts University in Kiel, about 120 miles north of Hannover. This put him in a strong position 3 years later to contest for his mentor’s old job, which he obtained and still holds. Despite many commitments—editorial boards, government committees, and appointments to professional societies (he recently completed a stint as president of the German Society for Thoracic, Cardiac, and Vascular Surgery)—he spends half of his time as a working surgeon.

Professor Haverich is now at a stage in his career where he can clearly see the major goals he wants to achieve. In addition to constructing a tissue-engineered artificial heart, he wants to encourage more cardiothoracic surgeons to undertake the research in a way that will take the specialty forward. He says, “I want to get research, especially basic research, into the minds of cardiac surgeons. I want to see more abstracts at meetings that are on research, rather than just [everyday] surgery. And I want to be influential in getting the next generation of young people interested in cardiothoracic surgery. I’m glad that interest in Germany at the moment is very high.”

References

Barry Shurlock is a freelance medical journalist.
Spotlight: Jose Zamorano Gomez, MD, FESC

In the Future “Imaging Data Will Be Incorporated in the Risk Classification for Patients”

Jose Zamorano Gomez, professor of medicine, University Complutense of Madrid, Madrid, Spain, director of the Cardiovascular Institute, University Clinic San Carlos, Madrid, president of the European Association of Echocardiography, and secretary of the European Society of Cardiology, talks to Marilou Davis, BScMedTech, RN, MScBIT.

As a young boy growing up in the cosmopolitan city of Madrid, Spain, Jose Zamorano Gomez wanted to be a doctor and a football player. Despite having few medical relatives, he says, “I was sure that I wanted to be a doctor. I always knew that it was going to be an important part of my life.” Now he is professor of medicine at the University Complutense of Madrid, Madrid, Spain, director of the Cardiovascular Institute, University Clinic San Carlos, Madrid, president of the European Association of Echocardiography, and secretary of the European Society of Cardiology (ESC). He embarked on medical studies in 1981 at the University Complutense of Madrid, where he was particularly influenced by Professor Pablo Gil Loyzaga, who taught cellular biology, and Professor Juan Tamargo, an expert in pharmacology. He recalls, “The 2 professors taught me how to perform a study and conduct it with proper ethics, why you set up a study, what you aim for in doing a study, and how to determine its clinical relevance.” Zamorano’s enthusiasm for basic science, specifically research involving rats, resulted in his first article when he was a third-year medical student.

After qualification, Zamorano worked as an intern in the Department of Cardiology, where Professor Pedro Zarco, Professor Luis Sánchez Harguindeguy, and Professor Carlos Macaya, proved influential. Professor Zamorano recalls, “They made me see what cardiology really means. It is important to acknowledge that they ‘opened doors’ for many young clinicians like me. Their influence on me was not only as a doctor, but also on the teaching aspect of my life—they passed on the enthusiasm to be a teacher in the future, and that it is not only important to diagnose and treat, but also to teach others.”

Specialist Echocardiography Training in Germany Led to Career Opportunities in Madrid

After a period of training in both transthoracic and transesophageal echocardiography under the expert guidance of Professor Raimund Erbel, MD, director of the Department of Cardiology, University Clinic Essen, Essen, Germany, and a pioneer of these techniques, Zamorano returned to Madrid to work in the echocardiography laboratory in the University Clinic San Carlos, Madrid. Although he was the youngest in the group and some of the individuals who had trained him were already working there, Professor Macaya offered Zamorano the opportunity to be the director of the laboratory in 1999. Professor Zamorano considers that this was an example of established professionals “promoting young people to open doors to the future and take on personal responsibilities. He says, “Together, we [the team] decided to make the echo unit one of the best labs in Europe. We started doing clinical work and became the research centre for big companies using prototypes. Also, we were one of the first echo units in Europe to use 3D Echo.”

In 2004, the team decided to abandon the concept of “echo laboratory” and moved on to become a cardiac imaging centre with computed tomography and magnetic resonance imaging facilities. However, the centre remains clinically oriented, still trying to answer clinical questions. Since then, the unit has provided training in echocardiography for clinicians from Europe and South America. He says, “More than 100 people from outside Spain have been trained at the centre.”

More recently, Professor Zamorano was appointed director of the Cardiovascular Institute at the University Clinic San Carlos, Madrid. Professor Zamorano comments, “Being the director does not mean that you are the best. It is just that I have to devote my time helping others develop the Institute.”

“Three Years of Work Creating a Virtual Heart”

Professor Zamorano is passionate about research and has contributed to 220 articles in peer-reviewed journals. He is particularly proud of his contribution to a study on the use of 3D echocardiography in clinical settings. He says, “We started working with the first prototype of 3D echo many years ago. We created new formulas for calculations and made guidelines. From a research point of view, I would say it is my major contribution.” He foresees that imaging is going to become increasingly 3D. “We want to see the heart as it is in reality. Life is 3D and so is the heart. So cardiovascular imaging is going to be 3D, no doubt about that.”

Professor Zamorano cites his work in the production of the “Virtual Heart” as the most enjoyable of his research career. It is a collection of 7 DVDs showing the anatomy and physiology of the heart, its illnesses, and its treatments (http://www.elmundo.es/elmundosalud/especiales/2008/01/anatomia_corazon/localizacion_anatomica/index.html). He says, “It was 3 years of work creating a virtual heart. It is a ‘book of the 21st century.’”

In considering the future development of his research career, he says, “I am going to commit part of my life to
merging the cardiovascular risk factor with imaging to better assess the real risks for our patients. For example, almost 33% of the people who have serious cardiovascular events are classified as intermediate risk. This shows that we can improve on stratifying risks. I am sure that cardiovascular imaging will play a vital role. Imaging data will be incorporated in the risk classification for our patients.”

Professor Zamorano has become increasingly involved with the European Society of Cardiology (ESC) and the ESC is now a priority in his life. As president of the European Association of Echocardiography he says, “I will put a lot of time and effort to send a clear message to cardiologists that research is important, and that through the ESC we can grow together to help our patients.” He is also chair of the Grants Committee, and secretary of the ESC under the presidency of Roberto Ferrari, MD, PhD, FESC.

“It Is Important to Transmit Knowledge to Enable Others to Achieve More”

Of all the important roles Professor Zamorano has played in the hospital, university, and different organisations, his most enjoyable are being a clinician and a teacher in the hospital. He finds that every day he does something worthwhile no matter how small. He explains, “It is really an enjoyable experience because you combine being useful for sick patients while transmitting your knowledge to young doctors who might treat you in the future.”

He feels that one has to be generous in terms of teaching and says, “I have to open new pathways and work for the students and others, for the university, for research—trying to help young people and ‘open the doors’ for them so they go further than me. My mentors did the same thing for me.” His main philosophy is, “It is important to transmit knowledge to enable others to achieve more.”

Professor Zamorano’s advice to young physicians who want to follow in his footsteps is, “Never lose [faith in] your own judgment. If you have a clear idea or project aim, just go there even though some people will try to distract you. I have done many things where the aims are clear but the results have not been successful. However, it does not mean that they were not worthwhile. I have learned a lot from unsuccessful projects. It is also important to know what you are best at and to explore it.”

“I Remember My Mother Sitting in the First Row During the Opening Ceremony. I Consider That to Be the Happiest Event in My Entire Career”

Professor Zamorano has received many research awards, but he considers the first award he received from the Spanish Society of Cardiology in 1991 to be his favourite “because I was only a research fellow then.” He adds, “The Spanish Society of Cardiology now has grants amounting to almost €1 million, and I am proud to be a member of a scientific society that is so focused on promoting research.”

Another significant event in Professor Zamorano’s career took place 14 years ago. He says, “I organised the first international meeting here in Spain between the Mayo Clinic [Rochester, MN] and the University of San Carlos. More than 600 people attended, as well as Dr Jamil Tajik [MD] and many other faculty members of the Mayo Clinic. I was only 30 and it was the first time I had organised a meeting. I remember my mother sitting in the first row during the opening ceremony. I consider this as the happiest event in my entire career.”

Despite his professional achievements, Professor Zamorano says his family is his greatest achievement. He explains, “I am really proud of my wife and children. My wife is a gastroenterologist who understands my work in medicine, teaching, and organisations. And my children—2 sons, aged 16 and 14, and a little princess, aged 12—are hardworking and sensible. Although I am so busy, my family comes first.”

**References**


Marilou Davis is a freelance medical journalist.

The opinions expressed in *Circulation: European Perspectives in Cardiology* are not necessarily those of the editors or of the American Heart Association.