Why did you decide to do your basic medical training in France?
First, there were personal reasons. I wanted to go to another country in Europe, and I was interested in learning another language. I liked French at school. Then there were professional reasons. At the time, in the late 1970s, medical studies in France were better than in Germany, in the sense that they were much more practical. After the first 2 years you worked half the day in a hospital, and you broadened your clinical experience by changing departments every 3 to 6 months. This sort of practical medical education was very difficult to obtain at the time in Germany.

Why, after 8 years’ study in France, did you move back to Germany for your specialist training?
When I obtained my doctorate, I wanted to train in cardiology. At this time, specialist training was quite different in the various countries of Europe, with the accompanying problems of reciprocal recognition of professional medical qualifications. Since I wanted to have the option of working in Germany as well, I primarily began my specialist training in my home country.

I think that if I made the decision now, however, it might be different, because of the Bologna Reforms. These educational reforms were agreed by the countries of the European Union in 1999, in an attempt to achieve uniformity of educational qualifications in many subjects, including medicine. And if I were to do it all over again, I would probably try to spend a year or two in the United Kingdom, or the United States, to improve my English.

When you returned to Germany you worked in Munich, and then after a few years you moved to Berlin. What took you to these cities?
Munich was a personal choice — much of my family lived therabouts. I went to Berlin in 1992. German reunification in October of 1990 for the first time opened the possibility of working in former East Berlin at the famous Charité Hospital of the Humboldt University, with its 7 Nobel Prize-winners in medicine. And, of course, I couldn’t pass up the opportunity to move to the Charité when I received an offer from Gert Baumann, MD. He had been appointed to the chair of cardiology at the Charité.

It was only 2 years after the reunification of Germany, following the fall of the Berlin Wall in 1989, and it was a very exciting period in German history. Our Department of Cardiology and Angiology was the first of the departments of the Charité to be exposed to the ways of the West. I was a resident in internal medicine and was responsible for setting up the intensive care unit. I also established the research laboratory.

Were there political difficulties to resolve at this time?
Yes, it was difficult, but also thrilling at times. The process of growing together among the staff from East and West demanded mutual understanding and good will from both sides. But, in the end, the political experiment and the new start did in fact succeed quite well. But this new beginning was not so successful in all departments.

Gender-specific cardiology is one of your interests. What are the main issues?
It has been only during the last few years that we have learned about the appreciable differences in cardiovascular diseases between men and women, with respect to clinical presentation, diagnostics, and treatment. Most studies do not take account of this fact. To give only one example: In the pharmacological treatment of heart disease in women we have little evidence-based data. In most major clinical trials, women are under-represented for all forms of treatment of cardiovascular disease, and make up only 20% to 30% of study cohorts.

We cannot therefore be certain whether women benefit from a wide range of modern cardiovascular pharmacotherapies. For example, one retrospective study of digitalis for heart failure found that mortality was higher in the treatment group. The main reason for this is probably overdosage. For a given drug, we tend to use the dose validated in the major studies,
and accordingly give the same doses to men and women. The European and US guidelines make no distinction by sex, yet pharmacokinetic studies of β-blockers and angiotensin-converting enzyme inhibitors show plasma levels 50% to 70% higher in women.

**What is being done in Europe to improve this situation?**
The European Society of Cardiology (ESC) is active and has launched the Women At Heart Initiative. Together with 50 or 60 other cardiologists, I attended an ESC policy conference in June 2005. Heart disease in women was also the main theme of the ESC congress held last September in Stockholm, Sweden. It must be required that the design of future studies will include a sufficient number of women to assure conclusive power.

Although already published studies will never be repeated for women, we hope for the future that sufficiently large cohorts of women will be recruited. This effort is gaining ground, and the first World Congress of Gender-Specific Medicine was held here in Berlin in February of 2006. The congress covered cardiovascular medicine and also many other specialties.

**What new approaches have you been working on?**
Endothelial dysfunction is well-known as a fundamental initial step in atherogenesis. We have been investigating endothelial nitric oxide synthase (eNOS), which is responsible for generating nitric oxide in the blood vessel wall. We characterise genetic variants of this enzyme and have identified several functionally relevant isoforms. Additionally, we have found that a component of green and black tea (epigallocatechin-3-gallate) directly activates the eNOS system. It is a promising idea, and an extract of the compound is available, although clinical trials have not yet been carried out. We have also been studying the ubiquitin-proteasome system and have found that extremely low, nontoxic, nanomolar doses of proteasome inhibitors dramatically stimulate eNOS production. It is an approach that might also be promising for drug-eluting stents, since proteasome inhibitors exert protective endothelial effects in addition to demonstrating anti-inflammatory and antiproliferative properties.

**What are your ambitions now in midcareer?**
I am quite happy here in Berlin at the Charité. It’s an excellent place to work and I can do the research I want to do here. My husband Karl is also a professor of medicine, and we work closely together.

**Do you have time for things other than medicine?**
It’s very important for me to do something physical — to improve my endothelial function! In the summer I run home from the Charité every day — it’s about 7 km. And in the winter I go to the fitness studio. I am also very interested in modern art, and Berlin is a good place for that. I go to as many exhibitions as I can. I like the British artist Francis Bacon and many modern German painters. I would also like to paint. I have all the materials and find it very relaxing, but don’t have the time. I also read a great deal of literature in German, as well as in French, to keep up my second language.

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**Cardiology in Bosnia and Herzegovina**

Emir Fazlibegovic, MD, FESC, (right), Mustafa Hadžiomerovic, MD, FESC, Adis Muslibegovic, MD, Zijad Šetka, MD, and Ranko Šmulja, MD, discuss the problems associated with the development of cardiology in Bosnia and Herzegovina.

The greatest problem facing European cardiology today is the unequal level of economic progress that affects the development of cardiological practice. This gap is so large that on the one hand there are countries with highly developed technology for cardiological diagnostics and interventions (such as Sweden, England, France, and Germany), and on the other hand there are countries with the highest levels of coronary heart disease (CHD) mortality in the world that are without cardiology specialists and have only basic cardiological equipment and diagnostic laboratories. Examples of such countries are Bosnia and Herzegovina, Albania, Macedonia, and Romania. These differences are more pronounced with the spread of the European Union to the east, and the acceptance of new countries with low levels of development into this sociopolitical organisation.

Special problems exist in some of the Balkan countries, which became independent with the breakdown of the former Yugoslavia. During the 1992–1995 war these countries were robbed, destroyed, and burnt to the ground by the aggression from Serbia and Montenegro. During that time, more than 200 000
people from Bosnia and Herzegovina emigrated, and the resources, economy, and healthcare services for those left behind were completely devastated. Ten years after signing the Dayton peace agreement between Bosnia and Herzegovina, Croatia, and Serbia and Montenegro, Bosnia and Herzegovina still has not managed to find a way out of this crisis and has been unable to develop a stable economic and sociopolitical recovery.

The reasons for this situation are the many unsolved economical problems and separatist tensions. The Society of Cardiologists of Republic Srpska was formed under the patronage of the Cardiology Society of Serbia and Montenegro to form a separate organisation from the Association of Cardiologists of Bosnia and Herzegovina. Separatist tensions also occurred with the formation of the Croatian Society of Medicine in the federation of Bosnia and Herzegovina.1

The former Yugoslavia had a highly developed cardiological treatment service with one centre for cardiac surgery in each capital city of the republics and provinces. These were in Ljubljana, Zagreb, Sremska Kamenica, Beograd, and Skoplje. Only Bosnia and Herzegovina, Kosovo, and Montenegro did not have their own centre.2

After the war, when Bosnia and Herzegovina was accepted as a country in its own right with the help of United States, cardiac surgery centres were formed in Tuzla and, later, in Sarajevo. The initial moves to start invasive cardiological diagnostics and cardiac surgery in Sarajevo had first occurred in 1992.1

Since 1961, the cardiologists of Bosnia and Herzegovina were a separate section within the Cardiologists’ Society of Yugoslavia. After the war, the Association of Cardiologists of Bosnia and Herzegovina (ACBH) was formed, which now has 115 members and 13 working groups, and has become a part of the European Society of Cardiologists and the World Health Federation.

Since 1995, the ACBH has organised 17 official meetings with cardiological topics and 3 congresses with international presentations. The Echocardiography School in Mostar has now been in existence for 3 years, and under the patronage of the ACBH provides continuous echocardiography education for young cardiologists. The society is also responsible for forming the National Peacemaker Centre in Sarajevo, and a centre for education where seminars on cardiology are held. There have also been 2 seminars about electrophysiology of the heart and the use of pacemakers.1

The society is also publishing a book which will be the official reference for teaching cardiology to students and young doctors in the medical faculties and teaching hospitals. Before the 1992–1995 war, the ACBH introduced a programme for postgraduate education in cardiology that lasted 2 years. There is now an ongoing process to improve postgraduate education in cardiology according to the recommendations of the European Society of Cardiologists, with cardiology training for those qualified in internal medicine that lasts for 4 years.

Mostar will be host of the fourth congress of cardiologists and angiologists of Bosnia and Herzegovina called the Congress of Integration, which will take place from 17–19 May 2007. For more information on this meeting, e-mail info@cardio-ukbih.org.

Drs Emir Fazlibegovic and Mustafa Hadziomerovic are cardiologists of the Division of Cardiology at Clinical Hospital, Mostar, and Drs Adis Muslibegovic, Zijad Setka, Ranko Smulja and Safet Mujic are cardiologists at the Division of Cardiology, Regional Medical Centre, Mostar, Bosnia and Herzegovina.

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MRI and Iron-Overload Cardiomyopathy in Thalassaemia

New developments in MRI may change the management of the cardiac complications of thalassaemia in Europe. Professor of cardiology Dudley Pennell, MD, FRCP, talked to Olwen Glynn Owen, MSc.

New MRI techniques developed in Europe are revolutionising the management of heart complications resulting from transfusion-related iron-overload, most notably in thalassaemia. This condition is prevalent in countries bordering the Mediterranean, the Middle East, Southeast Asia, and India. In southern Europe, the carrier prevalence varies from 1% to 19%.1 Currently, over 70% of patients with β-thalassaemia major die from heart failure caused by an iron-overload cardiomyopathy. This is a restrictive cardiomyopathy that manifests as

Illustration of a distorted erythrocyte in β-thalassaemia. Seventy per cent of patients with this disease die from heart failure.
systolic or diastolic dysfunction secondary to increased deposition of iron in the heart. The exact mechanism of iron-induced heart failure is uncertain, but the toxicity of iron in biological systems is probably due to its ability to catalyse the generation of oxygen-free radicals. A major problem in management has been the inability of clinicians to measure iron levels in the heart directly, or to monitor the response to chelation treatment. Until recently, clinicians relied on serum ferritin and liver iron concentrations, but it is now recognised that these bear little if any relationship to cardiac iron levels.

During the past few years, pioneering studies using an MRI technique developed at the Royal Brompton Hospital, London, have been carried out in European centres treating thalassaemia in Italy, Greece, and London. The technique gives a direct measure of the cardiac iron load, so it has important implications for optimising the management and increasing the survival of patients with iron-overload cardiomyopathy.

Dr Dudley Pennell, MD, FRCP, professor of cardiology at the National Heart and Lung Institute, Imperial College, London, and director of the Cardiovascular Magnetic Resonance Unit of the Royal Brompton Hospital, London, described the benefits of the new approach. “The technique uses validated software and has been tested in sites around the world. The whole procedure is completed in 1 to 2 minutes, and liver-iron concentration can be assessed during the same scan,” he explained. “Variation of results among sites has been less than 5%, suggesting it provides reproducible values for each centre.”

MRI helps in this situation because of the paramagnetic nature of iron. Protons are scanned in tissue, and these are energised by electromagnetic pulses; when they relax and return to equilibrium, they release energy that can be measured over time. The normal magnetic field within tissues is disrupted by iron stores, resulting in a shortening of relaxation times. Relaxation times are measured as longitudinal and transverse parameters. The T2* parameter, measured in milliseconds, detects a lack of tissue magnetic homogeneity and therefore signals an abnormal increase in tissue iron deposition.

Studies in heart failure show 9 out of 10 patients have a T2* score below 10 ms. Dr Pennell suggested, “For risk assessment, a score below 10 ms indicates high risk of cardiomyopa-thy, between 10-20 ms denotes intermediate risk, while above 20 ms, risk is low. A threshold of 10 ms is useful for alerting us to a need to change chelation therapy or increase it.” When T2* is below 20 ms, myocardial dysfunction is suspected, although symptoms may not yet be apparent.

Two studies discussed during the recent 10th International Conference on Thalassaemia and Haemoglobinopathies, held in Dubai, United Arab Emirates, and published in online editions of the US haematology journal, Blood, reflect the usefulness of MRI in detecting iron-overload cardiomyopathy.2,3 One shows how MRI assessment of myocardial iron and cardiac function are affected by different iron chelation therapies in the short term. The other shows the longer-term impact of the same therapies on morbidity and mortality outcomes.

The 2 studies tally well, said Dr Pennell. “Using this MRI technique, we now have a direct measure of iron in the organ responsible for three quarters of deaths. We can then use that measurement to understand which chelator works best.” He continued, “The rate of clearance with oral therapy (deferiprone) was found to be 2.5 times higher, probably because the molecule is smaller and uncharged, allowing it better intracellular access to cardiac myocytes and easier exit. Deferoxamine (the injectable therapy) undergoes a conformational change within cells when it binds to iron that can leave it trapped inside.”

In the second study, again involving the MRI assessment of cardiac iron overload, led by Dr Caterina Borgna-Pignatti, MD, of the University of Ferrara, Italy, cardiac events and heart failure deaths among patients with ß-thalassaemia major treated with the two drugs over an 8-year period were compared. The results showed no cardiac events or deaths on deferiprone, but standard deferoxamine therapy was associated with 52 cardiac events, including 15 deaths.

Dr Pennell concluded, “We can now look at iron-loading in cardiac tissue, measure current iron levels, adjust therapy accordingly, and monitor the response — simple general internal medicine principles. Put all that together,” he said, “And you have an extremely powerful way of managing thalassaemia to minimise risk of cardiac complications and increase survival.”

Olwen Glynn Owen is a freelance medical writer.

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