Disease Models & Mechanisms 2, 433-435 (2009) doi:10.1242/dmm.004176
Published by The Company of Biologists 2009

Taking translational research to heart: an interview with Sir Magdi Yacoub

Sir Magdi Yacoub is a founding editor of DMM, whose work as a cardiac surgeon and researcher has devised new operations for congenital and acquired heart disease, and has advanced heart and heart-lung transplantation techniques. He and his collaborators have studied the sophisticated functions of living heart valves and are using stem cells to produce a tissue-engineered valve that can reproduce their functions. Here, he discusses with fellow DMM founding editor Nadia Rosenthal, how his career evolved and why he hopes research will put heart surgeons like himself out of business.

Sir Magdi Yacoub is quite arguably the world's leading heart and lung transplant surgeon. He has been a part of numerous firsts in cardiothoracic surgery: the UK's first heart transplant and first live lobe lung transplant, as well as the first ever domino operation, in which a patient with failing lungs receives a new heart and lungs, and a second patient receives the first patient's fully functioning heart.

Sir Yacoub has performed more transplants than any other surgeon in the world. However, his contributions to healthcare don't end in the clinic. He developed transplantation technique guidelines for the United States' National Heart Lung and Blood Institute, and led the Harefield Hospital to become the UK's leading transplant center. Additionally, his research on cardiac disease and cardiac therapies holds great promise for the future. For instance, Sir Yacoub and colleagues produced the first human heart valve from stem cells.

In this Model for Life article, Sir Magdi spoke with fellow DMM founding editor and leading researcher Dr Nadia Rosenthal, Head of the European Molecular Biology Laboratory (EMBL) in Italy. He reflects on his journey into cardiology and organ transplant research and surgery, discusses new projects to help address disparities in human healthcare, and prognosticates on the contribution of model organism work to translational research and medicine.

Sir Magdi Yacoub is Professor of Cardiothoracic Surgery at Imperial College London
(e-mail: m.yacoub@imperial.ac.uk)

As a doctor, you chose to work on the heart; how did you start?

My dad was a surgeon and I was fascinated with the profession of being a doctor and looking after people. Then something happened when I was 4 to 5 years old; my dad's sister died of heart disease while she was only in her twenties. She was his younger beloved sister and he went into a state of depression. He kept saying that this should have been prevented. It was all due to a narrow heart valve, and some people around the world in those days were starting to open these valves. This specialty of heart surgery was starting to save lives and so I declared to him 'I am going to be a heart surgeon!' He said, 'Oh, don't be ridiculous!' but at that very young age it inspired me to follow that line and to see what was being done to help heart patients. I targeted certain individuals around the world who happened to be in Sweden, Denmark and Britain. One person who inspired me most was [cardiac surgery pioneer] Mr Brock, who later became Lord Brock of Wimbledon. As a youngster I really wanted to work for him, and to learn from him, and eventually I became his Senior Registrar. The rest is history since this started me on my path.

What really absorbs my attention now is the massive divide in the world between those who have and those who have not, and the great differences in life expectancy in different parts of the world

That's a poignant story, because narrow valve syndrome actually relates to your current research. Now that you have become one of the great heart surgeons of the world, how do you feel that this experience has influenced your life as a researcher? What aspects of your experience in the operating room dealing with patients come back to influence you when working with your research assistants and fellows?

I spent the early part of my career trying to learn more about the heart and how to deal with structural problems. I became really fascinated with the function of the heart, just watching it. I came to understand that it's a lot more than a contracting organ and it is the result of a very sophisticated system of tissues, cells and molecules coordinated to perfection. I wanted to know more about

this organ. I spent a lot of my time and career – hours, days, years – focused on the heart because I wanted to know more about its workings.

Then it dawned on me that it's one thing to save people who are in trouble, 'pulling them out of the river', if you like, and it's another to try and stop them falling into the river in the first place. I heard about many preventive measures but they were relatively primitive because they didn't address the fundamental mechanisms underlying the disease process. Initially, I wanted to know the fundamental mechanisms of the normally functioning heart. When I started my academic research career, which was after I had significant experience as a heart surgeon, I dedicated a lot of my time, effort and funding to build a Department of Surgery at Imperial College that was dedicated to molecular and cellular biology rather than surgery. Some people would say, 'Well, that sounds really odd because you are researching things that will prevent the need for cardiac surgery, which is your specialty' and I respond, 'That would be the happiest day of my life, to stop this cruel type of surgery!' I am not going to give up surgery because it still saves people. But it would be so much better to understand how to treat the disease without actually cutting people and that's why I am fascinated with this science.

In the next 5 to 10 years, what do you envision as the forward advances in modeling cardiac function using animals, tissues or cells? Where do you see the big breakthroughs coming through at this point, for the field or for your own research?

I think that developing models, whether they are molecular, cellular or transgenic, gives us an incredible handle on clinical problems. When we start looking at diseases like hypertrophic cardiomyopathy, it's tempting to take a simplistic view and consider it as a monogenic disease – with one gene that produces a defective protein that causes a problem – but there's a lot more to it than that. It is true that there is a mutation in the gene encoding a sarcomeric protein in hypertrophic cardiomyopathy, but it affects many other systems in the heart. This results in what we call an extended phenotype because it goes beyond hypertrophy, and it's an oversimplification to say that the cardiomyopathy in this syndrome is due solely to hypertrophy. There are affected patients who present without hypertrophy, for example. In addition, hypertrophy itself is not as simple as the name implies. It is accompanied by an increase in specific types of fibrous tissues that affect the cardiac system, conduction, the mitral valve and possibly other parts of the heart. This may underlie the arrhythmias we see in this disease.

If we turn to developmental biology and consider where each part of the heart originates, we see that the cells responsible for different affected parts of the heart have a common lineage, which provides an indication of how the phenotype has occurred. This promotes a unifying hypothesis for hypertrophic cardiomyopathies based on lineage, and is very exciting. But generating a hypothesis is one thing, validating it is another. That's where joining forces with somebody with expertise in animal models like yourself, Nadia, would be so exciting, because we can then start to validate the components of our hypothesis. By using animal models with conditional expression of certain molecules and mutations at different stages of development, we can test whether this is the case. These studies could have massive implications for understanding the disease and for treating the people who have incomplete phenotypes. Without engaging the appropriate model organisms, we will continue to speculate and offer non-specific treatment. It's less than optimal.

There is also power in mixing information from models and clinical data. With my Florentine colleagues Franco Cecchi and Iacopo Olivotto, we have successfully begun exploring the evolving theory that gene expression dynamics are altered in hypertrophic cardiomyopathy. In Florence, we have a very helpful team who carefully phenotyped and followed-up a large number of patients. Physiologists such as Corado Pogessi have looked at the muscle filaments and found functional abnormalities caused by specific mutations that affect the sarcomeric proteins. This process of looking at the human patient population, recording the effects of the disease, and then bringing material to the lab to look at molecules is a very effective approach. We have a powerful combination of people who can address the problem identified in the population with physiology or surgical treatment. Surgery still has its role in that we relieve obstructions and improve patients' conditions but arguably even more importantly, surgery generates human tissue for examination. That is the advantage of translational research: we then come to someone like you, Nadia, to ask for help to create the necessary model organisms.

Great, I am ready! Now let's talk about some of the less conventional ways you have married clinical experience with research. The left ventricular assist device (LAVD) was originally used to support a weak heart until a donor heart could be identified. In the last decade your work has transformed LVAD use from a bridge-to-transplant into a bridge-to-recovery procedure using a combination of surgery and pharmacology. Many patients no longer need transplants. This breakthrough treatment came from your unconventional way of looking at the problem. How would you advise young people to step outside of mainstream approaches to become a little more adventurous?

Having worked with the heart for so long, I was intrigued by its biology and sophisticated functions, and this convinced me that, to emulate some of these functions, I needed to think outside the box. I was initially attracted to transplantation and transplantation immunology. However, so many heart failure patients need a transplant but are not going to get one owing to the massive shortage of donor organs. So, I investigated the use of assist devices, which take over much of the heart's pumping function. Although they are not a real substitute for a human heart, these devices could have a niche in patient treatment since they can keep a patient alive for a period of time and improve his or her quality of life. More importantly, they interact with biological systems of the heart and about 5% of patients on LVADs recover well enough to have the device removed. So I thought, it is really essential to try and raise that figure from 5% to something more consistent. By applying mechanical and pharmacologic therapy in two stages, my colleagues and I could get about 70% of the hearts with non-ischaemic cardiomyopathy to recover to the extent that the device could be taken out. This was an achievement that Emma Birks and the rest of my group reported in *The New England Journal of Medicine* [Birks, E. J. et al. (2006). *N. Engl. J. Med.* 355, 1873-1884].

But the questions immediately arose: why only 70%? Should we use LVADs for all heart patients? Shouldn't we be studying the mechanisms responsible for recovery? These questions motivated us to go to the human system and look at human tissue using a variety of methods. My colleagues Paul Barton and Enrique Lara-Pezzi at Harefield, and Jennifer Hall in Minneapolis, were very helpful in these studies. In the meantime, some of our young surgeons at Harefield and Brompton devoted 3 years to work on animal models. Gopal Soppa worked with Cesare Terracciano to perform ectopic heart transplants in rats and mice, and to decipher the effects of various procedures. For instance, they investigated the effect of cardiac unloading and mechanical factors versus pharmacological agents, particularly clenbutyrol, which we already used with patients. Comparing the effects of combination therapy with each therapy alone has provided insights into what is happening in a variety of carefully defined situations. Analyzing only human tissue was not enough and the animal models, in the case of transplantation, yielded extremely important and valuable information. Unconventional combinations of approaches are often the best way to crack the problem, particularly when applied with persistence and resolve.

What's exciting right now?

Apart from working with developmental biologists to decipher basic, fundamental mechanisms, what really absorbs my attention now is the massive divide in the world between those who have and those who have not, and the great differences in life expectancy in different parts of the world. Where we happen to be lucky enough to be living in developed countries, life expectancy is around 80 years for men and even more for women. However, there are parts of the world where human life expectancy is 27 years. This just cannot be right. There are countries with populations of 75 million that have no heart surgery and, even worse, they have very talented people who have no chance of developing their talent. It's a massive waste for their country but also for humanity in general. That's what is behind a lot of my current work. I am contributing to develop services to meet people's medical needs directly, but much more importantly, I am involved with building research institutes to allow young people to know and address the problem, particularly in my own subject of heart disease and heart surgery. Some argue that research in these countries is not a priority, but if health is not a priority then I don't know what can be.

What about your work in Africa?

I am actively working in Mozambique in support of Dr Mocumbi, a very talented native Mozambican who has finished her PhD on neglected endemic disease and endomyocardial fibrosis. She is a shining example of what researchers can do for the future of their own countries. We are working in Ethiopia to establish a new pediatric heart hospital. It is just now open to the public, and it will also treat adults. It is attached to a large research institute that is supported by the vision of one of the local benefactors. We are also working in Aswan, which is an inspirational place in Egypt. The Nubians have lived there since the Stone Age and have made major contributions to human culture since ancient Egyptian times. Now they find themselves without adequate medical facilities. Developing services there could be a very useful venture from a research standpoint as well. It is a relatively isolated population and thus could yield incredible information about the genetics of disease susceptibility over the time course of thousands of years. In addition to Africa, we also work in the Caribbean; a group of talented individuals in Jamaica are establishing a pediatric heart surgery hospital and they too are thinking about establishing an associated research centre.

In the course of establishing so many centers, you must have developed a pretty good feel for the necessary components of a successful translational research institute that can use both animal and human data to model disease. This is something you have done very successfully here at Harefield also. Are there any particular features that you could think of that would help others to reach this successful level of interchange between clinicians and researchers?

I think that involving clinicians in basic science and asking them to spend time in the lab has been a difficult but gratifying experience. Trying to get some of my younger clinical colleagues into the lab initially made them nervous and unhappy. They didn't feel that they belonged, but after a very short period of time they became part of the team. They inspired their lab mates, and the basic scientists inspired them in return. It's an exhilarating experience watching the interaction between the two groups. The clinicians continued to have some ties with the hospital, and would come back to visit the basic scientists to recount tales from the clinic and human suffering that could be solved by basic science.

Then, when I was really doing a lot of clinical work day and night, I had my office in the science section so I couldn't go to the operating room (OR) without walking through the labs. People from the labs were stopping me to find out what's happening in the OR, and I was asking them what was happening in the lab. Some of them wanted to come to the OR to see what was going on. That very close interaction is crucial. It's not good enough to point to a bridge – people need to be physically integrated. I think we have amalgamated the two activities together. When we built the Heart Science Centre here, the planners kept asking, 'Do you really have to do that inside the hospital?' I think the answer is obvious.

Professor Nadia Rosenthal, the interviewer for this piece, is a founding editor of DMM, the Founding Director of the Australian Regenerative Medicine Institute and the Head of the European Molecular Biology Laboratory (EMBL) Monterotondo Outstation in Italy. She also holds a Chair in Cardiovascular Science and is Scientific Director of the National Heart and Lung Institute at Imperial Collage in London. She is a leading researcher identifying the mechanisms for skeletal muscle and cardiovascular regeneration, and uses her expertise in murine genetics to pioneer relevant mouse models of human disease.

DMM greatly appreciates Sir Magdi Yacoub for sharing his story, and thanks Nadia Rosenthal for her time and for coordinating this interview. The interview text has been edited and condensed by Nicole Garbarini and Kristin H. Kain, DMM Associate Reviews Editors, with approval from the interviewer and interviewee.