Interview

Professor Robert L Wilensky speaks to Laura Dormer, Launch Editor

Dr Wilensky is Professor of Medicine at the University of Pennsylvania (PA, USA) and an interventional cardiologist at the Hospital of the University of Pennsylvania. He obtained his MD from the University of Amsterdam where he graduated cum laude. He performed his internship/residency at Georgetown University/VA Medical Center in Washington DC and his fellowship in Cardiovascular Diseases at the Krannert Institute of Cardiology, Indiana University, where he was Chief Fellow. After 4 years on faculty at Indiana University he moved to the University of Pennsylvania, Philadelphia, where he divides his time in the cardiac catheterization laboratory and a large animal laboratory. He is author of over 150 papers and lectures internationally.

What led to your interest specifically in the field of interventional cardiology?

I took a road less traveled. When I was a fellow I was interested in becoming a bridge or translational medicine researcher looking at clinical problems in animals, and applying those results to clinical medicine. At that time I found one of the most intriguing aspects to be the study of atherosclerosis. Although I did not want to become a basic scientist in atherosclerosis, I did want to be able to treat the disease and understand its underlying pathophysiology. I thought that in order to be able to do that I would need experience in cardiac catheterization, which would allow me to be in contact with coronary atherosclerosis on a daily basis. I also felt that no-one would hire a cardiac catheterizer who did not also perform interventions. So I actually went into interventional cardiology in order to become a stronger catheterizing physician. Furthermore, I decided to learn other techniques for the treatment and evaluation of coronary artery disease, and found that I enjoyed the field immensely. I became increasingly interested in the whole field, which is why I have attempted to pursue it in an academic manner. I have also combined the research I do in the large animal laboratory with work in the human catheterization laboratory. If you talk to most interventional cardiologists, you will find that they had a deep love of the subject from very early on; they would hang around the catheterization laboratory and spend a lot of their free time there. However, I came to it a little bit later than others and realized what an enjoyable profession it is.

What has been the biggest advance in the field during your career to date?

There has really been a series of advances during my time in the field. I finished my fellowship in 1992, at which point angioplasty was an accepted treatment, but still a somewhat risky procedure. The results we were achieving were good, but not great; often it was necessary to come back in the middle of the night to repair what we had fixed the day before. In addition, patients occasionally did not do as well as we would have liked after the procedure. The big difference today is that procedures are faster and safer, the outcomes are more assured (the success rate is now between 95 and 99%), the infarction and death rates are very low, and patients generally only need to stay in hospital for 1 day. This has come about with improvements in several different areas: the training of physicians; pharmacologic treatment of potential thrombosis; and bare-metal stents (BMS) and drug-eluting stents (DES) have made major differences. If I had to choose one, I believe the development of BMS and DES have been the biggest advances that I have seen.

You are Director of Experimental Interventional Cardiology at the Hospital of The University of Pennsylvania; what does this role involve?

I am mostly involved in translational research in large animal models. I have run the laboratory since joining the University of Pennsylvania 13 years ago, and before that in my previous institution; so this has been my focus for approximately 20 years.

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“I...
We are involved in the cutting-edge development of catheters and approaches to coronary and myocardial disease.

- How is your time divided between research work and clinical work?
  I spend approximately half my time doing research and half doing clinical work. I have been very lucky to be at an institution that allows me to do that. Part of that is a result of the good collaborative relationship that we have within our group, and the fact that the division allows us to pursue academic goals.

- Do you collaborate with researchers both within & outside the university?
  I have the advantage of being part of the National Heart, Lung and Blood Institute (NHLBI) Dynamic Registry, and as a result I collaborate with people within that, and have done so for a number of years. This has been a very fruitful avenue of research and collaboration. Most of my other collaborations are done within the university; I am blessed with being in a university that has a large number of experts in their fields. One of the joys of being an academic physician is being surrounded by very intelligent people who are experts in areas one is interested in and wants to learn about. This is certainly one of those institutions.

- You recently published a study in *Nature Medicine* on complex coronary atherosclerotic plaque development [1]; briefly, what led you to this study?
  If you look at my research path, you will see that I started with the evaluation and treatment of restenosis, and was involved in the local delivery of medication in the arterial wall. At that time I was interested not only in medications, but also how to deliver them, when to deliver them, how much to deliver and what happens to medications when they go into the arterial wall. As a result of many investigators both within academia and industry it was clear that restenosis was no longer going to be a major problem. Early in my career I had the opportunity to perform some of the very early animal studies looking at the sirolimus-eluting stents, the results of which made me realize that the problem of restenosis had theoretically been solved, or was going to be solved (which is what has happened further down the line). I therefore realized that my research in restenosis was going to come to an end and I began to look for other areas of interest, one of which was diabetic atherosclerosis. This came about because I performed a lot of interventions on patients with diabetes, which is a major coronary risk factor. I decided that it would be very interesting to look at that in greater detail.

  A second clinical interest of mine was the evaluation of patients with acute coronary syndrome, and also their identification prior to an episode of instability. As a result of that we worked on a pig model, based on an original idea from another group, that had both diabetes and hypercholesterolemia. I spent considerable time evaluating the model and using it to evaluate newer medications, one of which was darapladib, which is an inhibitor of lipoprotein-associated phospholipase A₂. As a result we performed a study that looked at whether we could change the composition of atherosclerotic plaque in these diabetic, hypercholesterolemic pigs. The end result was that we could, and took them from having a higher risk plaque to a lower risk plaque. This body of data was presented in *Nature Medicine* in October 2008 [1].

- What further research have you performed in the area since?
  We have now taken that work further and looked at the reaction of the arterial wall to DES in this animal model – because it is a model of complex atherosclerosis and is more complex than the usual models used for these types of studies. In addition, we are also looking at ways to identify higher risk atherosclerotic plaques prior to a period of instability in these animals, utilizing invasive approaches for the evaluation of underlying pathophysiology and pathology. This work has really kept me busy over the last 5–10 years.

  I have also been involved in some mesenchymal stem cell work [2], which also came from the idea of local drug delivery.
What will be the next steps for this research?
We are currently working on a paper looking at the reaction of complex atherosclerosis to both BMS and DES. This is an attempt to determine the difference in pathophysiology and the role of inflammation, to the inflammatory response to DES.

We are also currently evaluating data on combination of intracoronary ultrasonography and near-infrared spectroscopy to evaluate the presence of lesions that have thin caps and large necrotic cores, in order to determine whether these tools can be used to predict the future behavior of plaques.

Has any of this work moved into human trials to date?
As a result of the study we carried out with darapladib, in addition to a study that was performed at Thoraxcentre in Rotterdam, a Phase III clinical trial has been initiated that is currently enrolling patients and is going to answer the question of whether this medication can affect the development of high-risk plaques and their clinical sequelae, namely sudden ischemic death and myocardial infarction.

Finally, what do you think will be the main areas of interest in the field over the next 5–10 years?
There are several major areas of interest to the interventional community. The first is structural heart disease, and the percutaneous repair of patent foramen ovale and atrial septal defects. It will be very interesting to see the development of transcatheter valve placement in the aortic valve position. Results with the percutaneous aortic valve, which is being performed by one of my colleagues here at the University of Pennsylvania, have been far better than I would have anticipated. My belief is that the majority of patients in the next 10 years will undergo a percutaneous approach for replacement of their aortic valve as opposed to undergoing surgery. The question then arises as to whether the mitral valve can be repaired in a similar fashion; I suspect this will prove more difficult than the aortic valve.

Second, there will be increased interest in niche intervention; current interventional approaches work well with minimal untoward events; however, chronic total occlusions are still a big problem, and treatment of bifurcation lesions still does not give the results one obtains for nonbifurcation lesions. These are areas in which there is a lot of thought and research going on in an attempt to solve these issues. Once they are solved, especially chronic total occlusions, then we will reach a point where very few people will need bypass surgery; most people will undergo a percutaneous approach.

A third area is the repair of the myocardium, such as with stem cells. This has turned out to be a much more difficult problem than people had anticipated. If the current problems can be solved, and repair of a damaged myocardium could be achieved by a percutaneous approach, it would be a major step forward. I am not totally optimistic regarding this at the current time, but I know there are a lot of good people working on it and if it is possible, it will happen.

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Bibliography