"Generating a Hypothesis, Developing the Protocol, and Following It Through Produces the Most Rewarding Research, but Often Also Represents a ‘Loss-Leader’ for the Research Unit"

David Hildick-Smith, consultant cardiologist, Royal Sussex County Hospital, Brighton, UK, and director of cardiac research at Brighton and Sussex University Hospitals National Health Service Trust, talks to Jennifer Taylor, BSc, MSc, MPhil.

The impact of the global economic climate on the pharmaceutical industry means that researchers—particularly those in interventional cardiology—may have to look elsewhere for funding.

“Interventional cardiology has usually been viewed as a speciality where there is quite a lot of money from industry, and therefore the funding from the charitable bodies has probably not gone in that direction as much as it’s gone into basic science research,” says David Hildick-Smith, MD, FRCP, FSCAI, director of cardiac research at Brighton and Sussex University Hospitals National Health Service Trust, Brighton, UK. “That’s something that may have to change because all of the companies are under financial pressure now.”

Dr Hildick-Smith does much of his research to generate the £300,000 a year needed to pay the salaries of 7 full-time research nursing staff (i.e. senior nursing staff who have moved into research) and a full-time secretary. He explains, “Some of the research we do is of a cardiovascular nature but primarily to pay the bills. That may be multicentre, pharmaceutical-type research, hypertension, etc.”

The unit has also increasingly taken part in multicentre interventional research studies, often funded by companies that want to run the studies. “Those tend to be interesting but not particularly remunerative for the unit,” Dr Hildick-Smith says. And although research remains central to his job in Brighton, in reality he must shoehorn it into a week largely filled with clinical work and administration.

Some of the money raised enables the unit to follow up its own hypotheses, which Dr Hildick-Smith considers a fair trade-off because if money simply came from a central pot its recipients might waste it too easily. Dr Hildick-Smith and colleagues presented a recent example of this research, “The British Bifurcation Coronary Study: Old, New and Evolving Strategies,” as a late-breaking trial in October 2008 at the Transcatheter Cardiovascular Therapeutics conference, Washington, DC.

Dr Hildick-Smith and colleagues have several projects in the pipeline, including a European follow-up of the British Bifurcation Coronary Study and the Nordic Bifurcation trials with 6 colleagues from the European Bifurcation Club. They also have plans for a trial in chronic occlusion angioplasty.

Patent foramen ovale represents another area of interest. For the past 5 years, Dr Hildick-Smith has participated in a randomised trial comparing patent foramen ovale closure versus medical therapy in young people who have had strokes, and the group has now submitted an application to the British Heart Foundation to look at the impact of a patent foramen ovale on stroke incidents in older people.
An Unplanned Career Path Led to Interventional Opportunities at Papworth Hospital

Hildick-Smith’s mother and 3 older sisters all practised as doctors, but during his studies at Cambridge University, Cambridge, UK, he had more interest in playing in a band. But that changed after he qualified in 1989. He says, “When I was a medical student, I felt that I was a bit of a spare part. Whereas once I’d qualified, I suddenly found I was quite helpful, and that was really the first time I liked it.” He then took an unconventional career path, which included time off travelling in Spain and a stint in anaesthesiology. “It wasn’t necessarily the best curriculum vitae for getting a job in cardiology,” he says. But David Redwood, MD, consultant cardiologist at St George’s Hospital, London, UK, whom he had previously worked with as a senior house officer in 1993–1994, gave him a break by offering him a 6-month locum registrar post in 1994–1995.

This job provided the springboard to a post at Papworth Hospital, Cambridge, where Dr Hildick-Smith worked with Michael Petch, MD (now retired). “He was a very charming, grand, and impressive man who was a very, very good diagnostician. If you wanted a clinical opinion without necessarily using all sorts of fancy tests, he was extremely good at distilling just what was wrong with the patient and quickly establishing what should be done.”

Len Shapiro, MD, a consultant cardiologist who specialised in intervention, served as Dr Hildick-Smith’s official mentor. Dr Shapiro’s colleagues considered him the person to go to with difficult interventional problems, and he allowed Dr Hildick-Smith to perform techniques that many registrars in other centres did not get the opportunity to do. “He is somebody who has great visual, spatial awareness,” says Dr Hildick-Smith. “He can do things that other people can’t. His grasp of the 3-dimensional structure of the heart is very good, and he has what people call good hands.” Dr Hildick-Smith worked at Papworth Hospital for 6 years and received his certificate of specialist training in 2001. He moved to Brighton in 2002 when a job came up. He comments, “I had to chase it pretty hard.”

Cardiologists in the United Kingdom “Will Probably End Up Becoming Cardiovascular Interventionists”

Dr Hildick-Smith believes that the government in the United Kingdom has damaged the strategic planning of cardiac services by introducing the system of payment by results for hospitals. “A lot of the spirit of collaboration between hospitals recognising each other’s strengths has diminished because each hospital now has a financial imperative to generate its income by doing procedures.” Patients come out as the losers because centres with low-volume activity produce less impressive outcomes. And, because hospitals get paid for each procedure, patients may have procedures that only provide borderline benefit to them, or hospitals might stage procedures unnecessarily.

However, Dr Hildick-Smith describes the current time as an exciting one to enter the specialty. “Aortic technology is excellent and is developing very fast. It’s quickly going to be followed by mitral valve technologies, some of which are already present, but there will be new and more sophisticated versions quickly in development,” he adds. Researchers also are advancing tricuspid valve technologies to reduce tricuspid regurgitation.

And, in the United Kingdom, cardiologists could see changes in their roles. As an increasing number of centres begin to carry out more primary angioplasties, cardiologists’ working patterns will have to change to cover nights. With stroke medicine currently about 20 to 25 years behind heart attack medicine, Dr Hildick-Smith says this new arrangement will likely bring about interventional management of stroke. He says, “That may well come into the hands of cardiologists if they’re the ones that are up at night. So, I foresee that cardiologists will probably end up becoming cardiovascular interventionists.”

Jennifer Taylor is a freelance medical journalist.
Pioneer in Cardiology: Attilio Maseri, MD, FRCP, FACC

Asking the Questions That Others Don’t Ask and Challenging the Conventional Models of Ischaemic Heart Disease, and Renowned for Characterising Spasm in Coronary Artery Disease

Professor Attilio Maseri, president of the Italian Heart Care Foundation, Florence, Italy, talks to Barry Shurlock, MA, PhD.

Attilio Maseri, MD, FRCP, FACC, receives credit from many cardiologists as an inspirational mentor and an influential cardiologist, and has worked in Pisa, Italy; New York, NY; Baltimore, Md; London, UK; Rome, Italy; Milan, Italy; and now Florence. Challenging new thoughts pour out of him like a torrent. Yet, after more than 40 years of puzzling and experimentation, the mechanisms of acute coronary instability and the biology of myocardial damage still haunt his waking hours.

Professor Maseri not only practises as a cardiologist, but also trained in nuclear medicine and thereby gained a head start, having the foresight to realise the power of radioisotopes for exploring the circulation. His insights into early ischaemic heart disease (IHD) now permeate textbooks, notably the role of vascular tone and vasospasm, the importance of “primary angina” (often called “Pisa angina”), and the significance of silent ischaemia. And no fewer than 12 former pupils and coworkers have chairs of cardiology—in the United States, the United Kingdom, Australia, and Italy.

Until the final year of his baccalaureate, Professor Maseri planned to train as a naval architect, and he still keeps the small plywood models he constructed as a teenager growing up in the country in the Friuli region of northeast Italy. But his schoolteachers recognised a very bright pupil and steered him toward medicine. As a result, he took up medical training at the closest medical school, in Padua, Italy, a city where some of the greatest anatomists of the Renaissance worked, including Falloppio and Fabricius, whose celebrated pupils shared the prize with a Columbia coworker, Dickinson Richards, MD, and a German surgeon, Werner Forssman, MD, who, as a 25-year-old trainee working at Eberswalde near Berlin, Germany, had shown how one could insert a catheter into the cubital vein and advance it 65cm into the right atrium by placing the tube in his own forearm!

Maseri sailed through medical school, a feat he explains by analogy with football. “I was often asked how I did it, without apparently doing much work. I said, ‘It’s easy—you remember the soccer results you hear on a Saturday afternoon, because you’re interested.’ I was interested in medicine. I loved it.” And a month after graduating, Maseri married. His wife Francesca, with whom he shared his life for 40 years, was his “musa inspiratrice” until her death in 2000.

“To Achieve Something, You Have to Change!”

For his postgraduate boards in cardiology and then nuclear medicine, Maseri packed his bags and left Padua for Pisa, Italy (he felt impressed by textbooks written by authors from the university). This move set the typical pattern he would follow for most of his life. Every few years, then after a decade or so, he moved on, following his motto: “If you want to achieve something, you have to change!”

Maseri found the cardiology training at Pisa excellent, but, even more than that, he came under the influence of a mentor he would never meet: Paul Wood, MD, FRCP (1907–1962), director of the Institute of Cardiology, National Heart Hospital, London, UK. At the time, Dr Wood seemed a Goliath of a cardiologist, with an international reputation based largely on his single-author textbook, Diseases of the Heart and Circulation, published in London in 1950 by Chapman & Hall. At a time when he did not yet feel comfortable with English, Maseri obtained a copy of Dr Wood’s book and devoured it. Fellow trainees in Pisa could not understand where he got his ideas. He admits, “I was always quoting Paul Wood. This was the book from which I learned my cardiology. It was so far ahead of others. Italian cardiology texts were like British books of 30 years before! I also admired the books of [Professor Dame] Sheila Sherlock [MD, FRCP, FR Soc, Royal Free Hospital, London] on liver disease.”

In 1965, 2 years after passing the cardiology board with full honours, Maseri moved to Columbia University, New York, NY, where he held a public health research fellowship for a year. There, he came under the influence of André Cournand, MD, who in 1956 had received the Nobel Prize for Medicine for his work on “catheterisation and pathological changes in the circulatory system.” He had shared the prize with a Columbia coworker, Dickinson Richards, MD, and a German surgeon, Werner Forssman, MD, who, as a 25-year-old trainee working at Eberswalde near Berlin, Germany, had shown how one could insert a catheter into the cubital vein and advance it 65 cm into the right atrium by placing the tube in his own forearm!

Recalling his time in New York, Professor Maseri says, “André Cournand was always called ‘the old man,’ and he had a strong French accent. He was a curious scientist—in the proper sense of the word—and each week we had to present a case for discussion. Curiosity had been instilled into me by Paul Wood’s writings, but Cournand was always stimulating, and I was still clay that could be moulded!”

After Columbia, Maseri spent another year on a National
In 1967, Maseri returned to Pisa, then a major centre in Europe for nuclear medicine, which would play a key role in much of his future work. Although at first it seemed as if an absence of 2 years away had scuppered Maseri’s chances of a good job, he went on to set up the Coronary Research Group.

Professor Maseri recalls, “When I came back from the United States, others had taken over what I had started in the department, so my boss, Professor Donato, suggested I set up a coronary care unit and catheter lab, which I did. I went to Goteborg, Sweden, to learn angiographic techniques. I wanted to find out what caused symptoms in people with coronary disease, to understand what was wrong and to make them feel better. I realised that measuring total or average coronary flow was no good and that what we needed to do was to measure regional blood flow. Nuclear medicine was the most important innovative tool at the time, and Pisa was a strong centre for it in Europe. It was not a ‘technique in search of a question’—I had the questions, and I borrowed the technique! Gamma cameras became available and enabled us to carry out the first measurements of regional blood flow in the world, using xenon washout techniques during pacing-induced angina.

In 1971, we held an international meeting on coronary disease, to understand what was wrong and to measure regional blood flow in the world, using xenon washout techniques during pacing-induced angina. “They Didn’t Believe Me [About Spasm]!”

Professor Maseri feels passionate about the need to constantly question the “established paradigm.” He cites as an example his work in Pisa in the early 1970s, when most others viewed coronary artery spasm as an artefact induced by coronary catheterisation. He and his coworkers, in a study of patients with angina at rest (variant or Prinzmetal angina), showed that during episodes of rest pain, they also could detect areas of massive ischaemia, from the initial distribution of thallium 201, in the absence of catheterisation. He recalls how in 1974 he showed the first 3 cases in a packed lecture hall at the World Congress of Cardiology held in Buenos Aires, Argentina. The audience seemed sceptical, and when he got back to Pisa, he said to his wife, “They didn’t believe me!”

But, within a few years, as a result of a series of articles by the Pisa Group,1–4 the medical community had changed its opinion. An editorial published in 1979 in the British Medical Journal5 acknowledged the work of Professor Maseri and his group and concluded that “the weight of probability in favour of spasm occurring without catheterisation is now so great that the hypothesis must be taken as proved ... [the Pisa group’s] conclusion seems irrefutable: in some patients spasm may precipitate infarction.”

Professor Maseri says, “We had proved convincingly that spasm is important, but only in a selected group of patients. We then showed that nitrates, and later calcium antagonists, dilated the vessels and prevented spasm in this group, but then they were prescribed for all cases. It’s an abuse of the idea! Like our later work on the role of inflammation in patients threatened with infarction—that idea has also been abused, and now you find “inflammation” everywhere in cardiovascular research.

“We have not yet shown what causes spasm, why arteries respond excessively to constrictor stimuli. In the 1990s, we worked with Professor Sasaiama’s group in Japan, and we have just begun working with Professor Shimokawa’s group in Japan, on the molecular mechanisms of spasm, which is common in that country.”

The New England Journal of Medicine First Rejected an Article Proving That “Intracoronary Injection of This Drug [Streptokinase] Could Reopen the Artery and Abort the Effects of the Infarction” and Then Accepted the Article Without Changes

Twelve years after returning to Pisa from the United States, Professor Maseri left for London, where he became Sir John McMichael Professor of Cardiology at the Royal Postgraduate School of Medicine, universally know as the “Hammersmith” after its major affiliated hospital. There, funded by the UK Medical Research Council, he used positron emission tomography to develop techniques for studying perfusion and metabolism in the myocardium.

Emphasising the power of the well-designed, small-scale clinical experiment to answer a specific question—and relatively quickly—Professor Maseri recalls, “When I was at the Hammersmith in the early days of thrombolysis...
with streptokinase, it was not clear, if you injected the drug to dissolve the thrombi, whether the resulting infarction was smaller than it would otherwise have been. So, we selected patients whose symptoms of the heart attack had started no more than 2 hours before, so the myocardium was not yet dead, and we proved that intracoronary injection of this drug could reopen the artery and abort the effects of the infarction. We sent a paper based on 9 cases to the New England Journal of Medicine, and it was rejected. I wrote back to the editor—the only time I’ve ever done it—saying that the reviewers had not understood the importance of what we had done and that he must be mad not to publish such an important finding! By return, it was accepted without changes and published in 1984 in the Medical Intelligence section.”

In London, Professor Maseri’s international reputation grew as he continued to uncover many key features of IHD, including the role of distal coronary vessel constriction in chronic stable angina, the mechanisms of ischaemic cardiac pain, and the frequent absence of preexisting stenoses in the infarct-related coronary arteries. He started courses on European and American cardiology at the Hammersmith, with a prestigious international faculty, that attracted as many as 400 participants from all over the world—a unique forum for discussion!

In 1991, Professor Maseri packed his bags again and left the British capital for Rome, Italy, where he became professor of cardiology at the Catholic University and director of the Institute of Cardiology at the Agostino Gemelli Polyclinic and continued to characterise the minutiae of IHD. With his group, he showed elevation of circulating inflammatory markers, in particular C-reactive protein, in unstable patients evolving toward acute infarction and the activation of leukocytes across the coronary bed in these patients.

Professor Maseri has just changed jobs again, this time taking on the presidency of the Italian Heart Care Foundation, based in Florence. Unlike many countries, which have single professional bodies for cardiology, Italy has 2—one for those in academia and the other for hospital cardiologists. Professor Maseri explains that in 1999 these 2 bodies came together to publish the Italian Heart Journal, and he served as its first editor-in-chief, but they did not manage to agree on a single foundation for increasing the strength of Italian cardiology and raising research funds.

The Heart Care Foundation began as an initiative by hospital cardiologists. Professor Maseri says, “I decided I didn’t want to be a professor any more, and the idea of being retired was scary, so I resigned in Milan [Italy] in December last year [2007], but then I was asked to stay on for a few months. The hospital cardiologists invited me to be the president of their foundation—I thought about it for a few months, found the people involved were very nice human beings ... and I didn’t want to overstay my welcome in Milan, so I accepted the job. I had always been tremendously impressed by the work of hospital cardiologists in their Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico studies, which have a unique potential—particularly if the focus of observation could be moved from the most prevalent average patient behaviour and response to that of the outliers on both sides of the mean—those really unusual cases which, in their network, could be found in sufficient numbers. The information provided by these cases, carefully characterised, regularly followed in databases, with biological material stored in biological banks, can provide useful fingerprints for the development of novel working hypotheses and therapeutic targets.”

**Wrestling With Accepted Views**

Professor Maseri’s IHD research has always challenged the accepted model on the basis of compelling clinical observations. It brings to mind those grand master anatomists who strutted the Paduan lecture theatres in the 16th century, though, paradoxically, Professor Maseri refuses to accept invitations to give “master lectures.” He prefers to reply to questions from his audience, to engage in a conversation, rather like the students in Rembrandt’s Anatomy Lesson of Dr Nicolaes Tulp in the Mauritshuis Museum, The Hague, The Netherlands. He is always wrestling with a problem, such as the accepted view that plaque fissures in coronary arteries lead to infarction. He rails, “My students often tell me this, but I forgive them; they have only read it in textbooks. In fact, fissures are common, but 25% of people with atherosclerosis die of noncardiac causes, and 25% to 45% of those who die after an infarction show no evidence
of fissure. Yet cardiologists, with a reductionist approach, continue to say that plaque fissure causes infarction. In some cases, this may be the case, but it appears too simplistic to be true!”

“We Need a ‘Renaissance of Clinical Observation’”

Professor Maseri seems scathing about the obsession of the contemporary medical community with the results of clinical trials, which he points out present “average” outcomes. He comments, “This is undoubtedly good but not good enough! Research and prevention have been focused on the same target for the past 25 years. Residual adverse events on current optimal therapy are still too many, and their reduction is reaching a plateau. Conversely, very many individuals with high levels of risk factors reach old age in good health—maybe we should not try to explain these common discrepancies only with what we have learned so far!”

Illustrating his point, Professor Maseri says, “Why would I ever want to wear the shoes of an average-sized Italian? Within each major cardiovascular syndrome, each subgroup of patients needs to be treated in the way that is appropriate for the group’s individual causal mechanisms! Just like anaemia! We need a ‘Renaissance of clinical observation.’ If you follow the [treatment] guidelines in a group of patients with coronary heart disease—reduce cholesterol, lower blood pressure, reduce weight, control diabetes, etc.—you will help some patients, but not others. Following guidelines makes it easy for cardiologists and protects them [from legal challenge], while the very broad spectrum of patients included in clinical trials is good for the industry. But this approach provides no incentive to search for the multiple causal components of each cardiovascular syndrome in specific subgroups of patients. You only learn by following up cases that do not fit the paradigm! In clinical research, looking at “the average” does not help—looking at outliers is the way to try and understand something that is still unknown.”

Professor Maseri has distilled the essence of his thinking and research into his textbook, Ischemic Heart Disease, published by Churchill Livingstone in 1995. A reviewer in the New England Journal of Medicine [January 30, 1997] called it “the most comprehensive book published on the subject.”

In an age when few textbooks are written by single authors, it “the most comprehensive book published on the subject.”


Barry Shurlock is a freelance medical journalist.

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References


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