Are you developing a drug for the general good whereby maybe a small percentage of people are going to suffer, but the great majority of people are going to benefit, or do you say that the drug must be absolutely safe before anyone can benefit?" Unless this question is addressed and resolved, drug development is likely to stagnate, according to Sir Richard Sykes, who is also chair of the WHO International Advisory Board that oversees the International Clinical Trials Registry Platform, and received a knighthood in 1994 for services to the pharmaceutical industry.

He believes that the future must lie in identifying sections of the population most likely to suffer adverse effects from a drug, so they can be excluded, and in identifying those people most likely to benefit so that they can be actively targeted. It costs US $500 million to US $800 million to develop a novel compound to launch, so it is vital for researchers and drug companies to confirm the safety and efficacy of drugs as early as possible.

“The first thing you want to do is to identify a target, and the next one is to validate that target,” Sir Richard said. “This can be done by animal models and tissue culture, but eventually it has to be put into man.”

Obtaining permission to test potential compounds in humans in a phase 1 study is now much harder, Sir Richard said, and as a result it now takes 4 to 6 years to prepare a compound from the laboratory for testing in humans. Of the most extreme examples of an adverse incident in a phase 1 trial occurred earlier this year at Northwick Park Hospital in London. Six patients were injected with a compound being developed to treat rheumatoid arthritis, leukaemia, and multiple sclerosis, and experienced multiple organ failure.

“I have never, never seen that, one does not understand what has gone on,” Sir Richard said. “For this to occur in a phase 1 clinical study is absolutely unique. Compounds fall out normally in phase 1, not because they are dangerous toxic chemicals, but because the pharmacokinetics are not correct and the compound did not appear in the urine or in the blood.” He continued, “Even this would be unusual, because they would have already been tested in animals.”

Sir Richard explained that drugs were more likely to be abandoned when safety and efficacy were tested during phase 2 and 3 trials, and even then it was impossible to identify all possible risks, because the total number of patients tested would only be about 3000.

“If you have an incidence of an adverse event of 1 in 1000, you need 3000 patients to find 1 case,” Sir Richard said. “If you have an incidence of an adverse event of 1 in 10 000, which is not unusual, you would have to look at 65 000 patients to pick it up.”

As a result, it is often only once a drug is launched and larger numbers of patients are exposed to it that many adverse effects are noted. “You can go through trials, market the drug for 1 to 2 years, and then it has to be withdrawn, and that happens with some frequency,” Sir Richard said.

He added that increasing concerns about risk and litigation in recent years had meant that some good drugs, such as COX-2 inhibitors, had been withdrawn unnecessarily. COX-2 inhibitors were withdrawn because they were found to be associated with an increased level of cardiovascular events. But Sir Richard does not believe that there was “any real evidence that COX-2s were any more dangerous than any other NSAID. It is just that they have been tested under different conditions and different regulations,” he said. “We are comparing apples and oranges. If you have taken an NSAID and bleed badly, then a COX-2 is going to be of great benefit to you. So for some patients that COX-2 is going to give them a much greater benefit than there is risk.”

No drug is ever going to be risk free, and at the end of the day it is a matter of whether a compound confers significant benefits over risks. One of the best ways to minimise risk is to introduce novel drugs slowly and then watch for potential adverse events, according to Sir Richard. “If they occur, you can try to understand them and then make sure that they...
A View From Athens

Harisios Boudoulas, MD, PhD, president of the Hellenic Cardiological Society, considers the past, present, and future of cardiology in Greece.

It is difficult to describe the feelings and emotions experienced while walking into the Plaka, the Market of Athens, seeing the Acropolis with the Parthenon, and the places where Socrates, Plato, Aristotle, Pericles and other remarkable men, the fathers of Western civilisation, created their great ideas. Besides philosophy, art, and democracy, Greece also has a rich history in medicine. Generations of physicians worldwide, from antiquity to the present, have taken the oath of Hippocrates, the father of medicine. Some may be wondering what Greek medicine has had to offer since the days of Hippocrates, Galenos, and other great physicians of that time, so it is worth emphasising that Greeks have contributed to the progress of medicine in general and to cardiology in particular during recent years.

The introduction of L-DOPA, the single most effective agent in the treatment of Parkinson’s disease, by Georgios Kotzias, MD (1918–1977), and the Pap test by Georgios Papanicolaou, MD (1883–1962), are just a few contributions. Likewise, Greek cardiology has stood at the frontiers of international clinical research during the last 30 years.

Over the last several decades many Greek cardiologists who went to the United States and other European countries for postgraduate studies brought their experiences from abroad back home. Most of these individuals have become directors of cardiology departments in Greece and leaders in the Hellenic Cardiological Society (HCS). Importantly, they continue to have close collaborations with those centres.
I believe that all these international collaborations have been important for the development of cardiology in Greece.

The Hellenic Cardiological Society, a nonprofit organisation, was established on September 7, 1948 (this was 1 year before the American College of Cardiology [ACC], and 2 years before the European Society of Cardiology [ESC], of which it is a founder member). The remarkable history of the HCS parallels the history of cardiology in Greece. Initially, there were just 28 members of the society, but today there are approximately 2500 members. The society’s state-of-the-art, 5-floor administrative building, located in Athens, is dubbed the “Hellenic Heart House.”

The major goals of the society include continuing education of Greek cardiologists and cardiology fellows, educating the Greek public about cardiovascular risk factors and prevention, advocating activities directly related to clinical practice, and supporting competitive cardiovascular research. Almost 2500 participants attend the annual congress of the HCS, the most important cardiological event in Greece, with international authorities as well as Greek leaders in cardiology actively involved with cutting edge lectures and panel discussions. Some 19 working groups are developing guidelines for practicing cardiologists, and regional meetings take place in several small towns throughout Greece.

Greek cardiologists have had leadership positions in the American Heart Association, ACC, ESC, and medical schools worldwide. World-class clinical research is performed enthusiastically in Greece. Important achievements include the intra-aortic balloon pump by Spyros Moulopoulos, MD; the pioneering work on the vulnerable atherosclerotic plaque by Christodoulos Stefanadis, MD; the hypersensitivity to adrenergic stimulation after β-blockade withdrawal and the continuation of β-blockade therapy during coronary bypass surgery by myself, Richard P. Lewis, MD, and colleagues, and the classification of floppy mitral valve/mitral valve prolapse and the mitral valve prolapse syndrome by Charles F. Wooley, MD, and myself.

We believe that the new generation will follow in the steps of our forebears and continue this progress. It is our duty, however, to keep alive the past of the HCS, and, for this reason, the society is in the process of publishing its remarkable history.

The future of cardiology belongs to the new generation, that is, to the cardiology fellows, and the HCS has started educational seminars to help them achieve their goals. The major topics of cardiology are covered within 2 years, while advances in the field will be included in subsequent seminars. The seminars aim to provide uniform education for cardiology fellows, to develop a standardised cardiology training programme in Greece, and to establish a close relationship between the fellows and their teachers. In addition, the HSC provides scholarships for young cardiologists to study in other well-known international medical centres, and has initiated a programme to support cardiovascular research with competitive grants.

Due to the vision, enthusiasm, and hard work of Gregorios Skalkeas, MD, the Foundation of Biomedical Research, Academy of Athens (see Figure below), opened in 2003. The foundation is a first-class research facility and one of the best in Europe.

Basic scientists and clinical investigators work very closely together, where findings from the laboratory bench can be applied to the clinic, and observations from the bedside can be tested in the basic research and/or the experimental research laboratories. Genetic variations in common cardiovascular diseases in the Greek population will be defined, and pharmacogenetics/pharmacogenomics will be applied in the near future.

Cardiology leaders and the HCS are actively involved in the education of cardiology fellows, and they hope they are well prepared for the future. As the pledge of young Spartans to their fathers says, “We will become much better than our ancestors.”

Dr Boudoulas is professor of medicine/cardiology and pharmacy (emeritus) at The Ohio State University, president of the Hellenic Cardiological Society, director of the Center of Clinical Research, and president of the Scientific Council Foundation of Biomedical Research, Academy of Athens.

What led you into a career as specialised as heart and lung transplantation?

As a trainee in cardiac surgery at Harefield Hospital, I came under the spell of Sir Magdi Yacoub, FRS, FRCS, who was a consultant surgeon there. This was in April 1983, and cyclosporine had only recently been introduced, with dramatic improvement in survival after transplantation.

It was all very exciting: I was helping to solve medical problems in patients for whom there was no other solution, and this was combined with riding helicopters in the middle of the night and dashing around the country in the back of police cars.
What was it like being a member of Sir Magdi Yacoub’s team?
He was a charismatic boss and had tremendous energy. He persuaded our team just to get on and do it, even if you had to make it up as you went along. I was eager to learn, and clearly remember my first donor organ retrieval. We arrived at a hospital in Coventry and when we arrived we found the donor heart was unusable, but that same evening there was a donor heart in Sheffield, and I was sent to recover it for the transplant procedure at Harefield. By February 1984, I was carrying out most of the donor heart retrievals in the UK and Western Europe.

Why did you leave for a research post in Canada after nearly 2 years with Sir Magdi?
When I arrived in Toronto University, Canada, in March 1985, it was the only place in the world doing lung transplants. The world’s first successful single-lung transplant was done here in 1983, and the first double-lung transplant in 1986. Personal contacts between Harefield and Toronto gained me the post. The team at Toronto needed someone experienced in cardiac surgery to do their laboratory work, and I was in the right place at the right time.

The work was equally exciting, but the whole set-up was very different from Harefield. Here, 2 highly qualified surgeons took the organs out and 2 highly qualified surgeons sewed them in again, with the whole team involved in the transplant. But at Harefield, Sir Magdi Yacoub did all the decision-making and often retrieved donor hearts and sewed them in himself. That seems to have been what was needed there at the time: To get things started, you often need the drive and ambition of one man.

What were the important factors in the set-up and success of the pioneering new transplant centre you have led in Newcastle since 1987?
In order to sustain a really active programme, you have to spread the talent, skill, and experience among a competent team. At Newcastle we have tried to ensure that all members of the team have responsibilities to the whole programme. In 1987, we became the first UK centre to do single lung transplants, and later that year performed the UK’s first bilateral lung transplant programme. In the mid-1990s we were doing 350 heart transplants per year; now we are doing about 150. But because the established donor system is geared to heart-beating donors, we had to set up a framework for retrieving non–heart–beating donors. The programme in Newcastle is now one of the most active in the world.

What is the main challenge for cardiopulmonary transplantation?
Most heart transplants are now in patients on inotropic drugs, patients who have had more prolonged heart failure, and in older patients often with relative contraindications such as diabetes. With the large drop in donors (mainly head-injured) from road traffic accidents, we are now relying more on donors who suffer from spontaneous intracerebral haemorrhage and subarachnoid haemorrhage. These are often older donors, many of whom have coronary artery disease or damaged valves. We are making more of the available organs: by doing valve replacements and using coronary stents to ensure adequate circulation, we have now achieved survival rates at 10 years that are just as good as those achieved with younger disease-free hearts. With these methods, we are managing now to make organs useable that would not have been useable a few years ago. We aim to at least halt the fall in donor organ numbers, and possibly even reverse it.

As a member of the UK’s Xenograft Interim Regulatory Authority, can you explain why have things gone so quiet in the UK recently, re: xenotransplantation?
It is true there is no ongoing animal work in the UK at present, and the UK regulatory atmosphere has made it difficult to extend experimental work over into clinical practice. But there have been big advances: the mean survival of the current pig to primate heart survival has gone up from 20 to 30 days to 80 to 120 days. However, things are being held up on 3 fronts: immunological problems remain to be resolved; extrapolation of findings to humans is limited by some physiological incompatibilities; and there are incompatibilities between the endothelium of human and pig coronary arteries. I believe these problems can be solved by refining genetic manipulation techniques, and the feared transmission of retroviruses does not appear to be happening.

Is there a single issue you can point to that has been important for the success of your career?
I’ve always believed that clinicians, particularly surgeons, need to go to the laboratory to solve specific clinical problems. For example, when we had difficulty with early dysfunction of the transplanted lung, we went to the laboratory and experimented with different techniques of preservation, and of modifying reperfusion injury. We showed that the pressure of reperfusion was important, and that some drugs were effective in reducing the damaging effects of white blood cells on the lining of blood vessels in the lung. It is very satisfying when you “complete the loop” by transferring findings from the laboratory to the clinical setting.

Which professional award are you most proud of?
The James IV Award presented by the Royal College of Surgeons of Edinburgh in 2003 for a presentation I gave entitled “Twenty Years of Lung Transplantation.” Why? Because it is a prestigious award from my favourite college.

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