Lord Kakkar, professor of surgery, University College London, London, England, consultant surgeon, University College London Hospitals NHS Foundation Trust, chair for quality, University College London Partners, and director of the Thrombosis Research Institute, London, talks to Jennifer Taylor, BSc, MSc, MPhil.

Pioneer in Cardiology:
Lord Ajay Kakkar, BSc, MBBS, PhD, FRCS

“Modern Research Is Very Much About Collaboration, Ensuring We Deliver the Best Practices as Quickly as Possible, and Thereby Improving Clinical Outcomes for our Patients”

Lord Kakkar, professor of surgery, University College London, London, England, consultant surgeon, University College London Hospitals NHS Foundation Trust, chair for quality, University College London Partners, and director of the Thrombosis Research Institute, London, talks to Jennifer Taylor, BSc, MSc, MPhil.

Professor the Lord Kakkar has continued in this area of research in collaboration with a scientist he greatly admires, Wolfram Ruf, MD, professor of immunology at the Scripps Research Institute, La Jolla, CA.

“It Was Wonderful to Grow Up in an Environment Where We Always Had Many Committed, Caring, and Brilliant Doctors and Scientists Around the House”

Professor the Lord Kakkar was born in Dartford, England, in 1964, following his parents’ move from India in 1961. His grandfather was a doctor in India, and his father, Emeritus Professor Vijay Kakkar, FRCS, OBE, was professor of surgical sciences at King’s College Hospital, London, and one of the pioneers in the field of venous thrombosis; he developed the concept of fixed low doses of heparin to prevent venous thromboembolism, and did much of this pioneering work in the late 1960s to the 1980s. Kakkar’s mother, also retired, was a consultant anaesthetist in London, and his brother is also a doctor. He recalls, “I grew up in a house where there was enormous academic medical interest, and I much admire my father because of his incredible achievements in research. He was very creative in his thinking. Indeed, his ideas have helped to transform medical practice around the world.”

Through his father, Professor the Lord Kakkar met many other inspirational doctors based in North America, Europe, Asia, and elsewhere. He says, “It was wonderful to grow up in an environment where we always had many very committed, caring, and brilliant doctors and scientists around the house.” This sparked an interest in medicine, and he started attending thrombosis conferences from his early days in surgery.
teenage years onwards. He went to his first International Society on Thrombosis and Haemostasis congress, the main biannual thrombosis congress, in 1979, at the age of 15, and he has been to nearly every congress since. He remembers being “overwhelmed by it,” adding, “I thought it was so interesting, and it was then that I started to develop a real interest in the thrombosis area.” At the same time, he was a student at Alleyn’s School in Dulwich, England, where he had inspirational teachers, particularly a biology master, Chris Liffen, who strongly encouraged him to pursue medicine.

Professor the Lord Kakkar ended up going to King’s College Hospital Medical School, University of London. He had a wonderful time, and because he has “always been quite interested in things beyond medicine,” he became president of the Preclinical Students Society and then president of the Guild of Students when he went to the clinical school at the hospital. It was an early exposure to medical politics.

King’s College Hospital Medical School was an exciting place at that time, with a strong tradition of research in thrombosis, liver disease, obstetrics and gynaecology, cardiology, and chest disease. In addition, it provided high-quality clinical experience, and as a student and then a junior doctor in this large, busy hospital, Professor the Lord Kakkar relished his exposure to a wide variety of clinical cases.

During junior surgical training, Professor the Lord Kakkar met Robin Williamson, MD, professor of surgery at the Hammersmith Hospital, London, at what was then the Royal Postgraduate Medical School. Professor Williamson became one of Kakkar’s first bosses, and took a great interest in him. He encouraged Kakkar to apply for a Medical Research Council clinical training fellowship in 1992 at a time when it was uncommon for surgeons to receive that kind of training fellowship. Professor the Lord Kakkar was successful, and began working on a PhD in Professor Williamson’s department. His PhD, which he received from the University of London in 1998, was on the molecular biology of tissue factor, an initiator of blood coagulation in cancer. It was one of his first areas of interest in thrombosis, and from then on he was hooked on investigating thromboembolic disease and coagulation biology in cancer.

After his PhD, Kakkar was again supported by Professor Williamson when he applied for a clinician scientist fellowship from the Medical Research Council, which allowed him to complete his surgical training and also to establish his own lab in the Department of Surgery at the Hammersmith Hospital, by which time it had become part of Imperial College.

Professor the Lord Kakkar finished his surgical training in 1999 and was then appointed senior lecturer and consultant surgeon at the Hammersmith Hospital. At this point, he started to broaden his research interests into venous thromboembolism prevention more generally, and then into the development and evaluation of novel antithrombotic agents. In 2004, he was appointed to a chair at Barts and The London School of Medicine and Dentistry, and he took the title of Professor of Surgical Sciences.

Professor the Lord Kakkar says that clinical practice is a “great privilege,” and that doctors are in a unique position to work with patients and help them through serious problems. He believes that everything a doctor does, whether it be clinical practice, education, or research, has to be directed towards improving the outcome, safety, and experience of patients. He comments, “Ultimately, although we can perform huge studies, it all comes down to individual human beings. We have got to try to improve their health so that we reduce the burden to them and their families and society more generally.” He adds that, although all medical disciplines are equally important, surgeons are in a special position because not only do they make diagnoses and plan treatments, but they also need the technical skills to deliver them. On top of that, they must be good at building teams, because surgery is all about teamwork. Over the years, Professor the Lord Kakkar has enjoyed making sure that surgical teams are working effectively and in a way that they can best benefit patients.

**Collaborative Research That Led to New Guidelines on the Treatment of Recurrent Venous Thromboembolism in Cancer Patients**

Professor the Lord Kakkar’s group has made an important contribution to evaluating the potential role of antithrombotic therapy in the management of cancer patients. They have conducted some of the first trials in the world using low molecular weight heparin in these patients to determine whether it has an impact on survival. Their first article resulting from this work, and one of the first in this field, was a negative study, but it stimulated a huge amount of interest because it suggested that there may be a group of patients who have malignant disease who can achieve an important survival benefit from chronic exposure to low molecular weight heparin. They, and other groups around the world, are now conducting studies to test this hypothesis.

Professor the Lord Kakkar’s group also collaborated in investigating the treatment of venous thromboembolism in cancer patients with a group at McMaster University in Hamilton, Canada, led by Mark Levine, MD, an early mentor.
of Kakkar’s, who encouraged his interest in clinical research. Publication in 2003 of the CLOT study led to new guidelines around the world, which focus on providing low molecular weight heparin for up to 6 months rather than vitamin K antagonists to treat thrombosis in cancer patients because it results in a much lower rate of recurrent venous thromboembolism.4

More recently, they have been involved in the phase II studies and clinical phase III programme evaluating the factor Xa inhibitor, rivaroxaban, for the prevention of venous thromboembolism in high-risk surgical patients.5 The studies form part of a continuum of research looking at oral factor Xa inhibitors as antithrombotic agents to replace warfarin.

Professor the Lord Kakkar has been involved in the steering committee for a large programme of studies, the first of which was published at the end of 2009, looking at the direct oral thrombin inhibitor, dabigatran, as a replacement for warfarin, in this case for treating venous thromboembolism.6 They found that warfarin safely and effectively can be replaced with a fixed dose unmonitored orally active thrombin inhibitor. It is an exciting finding, and while Professor Kakkar’s work on dabigatran has focused on venous thromboembolism, other groups are investigating additional indications.

In his research career, Professor the Lord Kakkar considers himself fortunate to have worked in many good collaborations. He explains, “Most of my meaningful research has been done in partnership with colleagues around the world. Modern research is very much about collaboration, ensuring we deliver the best practices as quickly as possible, and thereby improving clinical outcomes for our patients.”

Looking back, Professor the Lord Kakkar is proud of his group’s willingness to work with other scientists internationally. He has learned over the years that the best research is often delivered in partnership, because when groups of committed and intelligent people are brought together, each of them will have different insights and will often bring something special to the discussion. He says, “It is difficult to know exactly how people look at what we do, but my sense is that colleagues think we are open, collaborative, and that we try to bring people together.”

Although Kakkar’s group brings people together to stimulate thinking and ideas, on some occasions the work may be taken forwards and published by another group, but that does not concern him. He comments, “What I really want to do is ensure that the research gets done by the best people. Where we have a contribution to make, I am absolutely delighted that we do that; and where others are stronger, then they should lead, because ultimately the work needs to get done.”

In the cardiology world, Professor the Lord Kakkar has collaborated with numerous exceptional people, such as those on the steering committee of the Global Anticoagulant Registry in the Field (Garfield), which is looking at management and outcomes in 50,000 patients with newly diagnosed atrial fibrillation. Kakkar has been impressed by what they and others have achieved in transforming the care of patients with arterial thrombosis. “It has been an inspiration to me, how cardiologists have come together and looked at the whole thrombosis problem, defining in a very exact way the appropriate role of antithrombotic and antiplatelet therapies in improving clinical outcomes in acute coronary syndromes,” he says. “In the period from the late 1970s through to today, there has been a dramatic
impact on improving survival after myocardial infarction as a result of several landmark clinical trials and the clinical insights that have been derived from them.”

His advice for achieving a successful career in academic medicine is to have the right values and keep the ultimate purpose of the work focused on accomplishing the best results for patients. In clinical research, that means conducting studies that help inform how we improve patient care. Another quality observed in many successful peers is mutual respect.

“We Want to See What Is Happening in the Real World”

Professor the Lord Kakkar’s most exciting new area of research is thromboembolic stroke. His group has established Garfield—the largest prospective global registry of patients who have been newly diagnosed with atrial fibrillation. Unlike other work in this area, they are including patients in 5 consecutive cohorts, each of 10000 patients, regardless of whether they have been treated according to the guidelines or are receiving an anticoagulant or aspirin to prevent stroke. “We want to see what is happening in the real world,” says Professor the Lord Kakkar.

The methodology differs from other research because they are randomly selecting sites around the world. Professor the Lord Kakkar explains, “Often in performing outcomes research, one tends to go to centres of excellence, where colleagues who perform clinical trials are based. The problem is, of course, that centres of excellence manage patients very well because they are enthusiastic, so we do not know the true burden of disease for many illnesses where thrombosis is a problem.”

To date, ~600 centres are enrolled, and the aim is to involve 1000 centres in up to 50 countries. Professor the Lord Kakkar hopes that collecting these data will improve understanding of how patients are managed and where new interventions, both antithrombotic therapy and other interventions to manage the heart rhythm disorder, can have the greatest impact. They will look at clinical outcomes such as stroke, other thrombotic events, bleeding, and the overall cost of interventions. In so doing, they will be able to determine the value that is added by introducing different therapies for the management of patients at high risk of stroke.

Professor the Lord Kakkar believes the study is important because, as new discoveries are made, it is essential to ensure that this information is adopted responsibly. He adds, “We also want to make sure that we understand practice patterns in other countries around the world, so that we can better help those countries adopt new knowledge in the most effective and cost-effective way.”

Other areas of ongoing research for Professor the Lord Kakkar include a continuing interest in cancer-associated thrombosis and coagulation biology in cancer. His group is also leading studies aimed at determining whether thromboprophylaxis in acutely ill medical patients in hospital can impact their mortality, something that has been established in surgical but not medical patients.

In addition to a broad base of clinical research, Professor the Lord Kakkar’s group is becoming particularly interested in identifying novel biomarkers based on microparticles shed from the endothelium and elsewhere that might help predict thrombosis risk in different clinical situations.

As the lead group on the lab work in this collaborative programme, they are testing the hypothesis that some of these shed microparticles may help them to understand stroke risk at an individual level rather than for large groups of patients, and therefore better understand how to improve the use of antithrombotic therapy. They will also look at thrombosis risk and the ability to predict whether prophylaxis should be provided to medical oncology patients. It is another area of interest, in which they will test whether they can use advances in understanding at the molecular level to identify novel biomarkers that can progressively be adopted in clinical practice. However, Professor the Lord Kakkar believes that the real opportunity for all scientists in cardiovascular research is to ensure that new interventions and strategies that have been appropriately evaluated are adopted as quickly as possible to improve clinical outcomes.

In the future, clinicians will increasingly need to understand how the interventions they are proposing add value to healthcare generally. They are already accustomed to demonstrating that interventions improve clinical outcomes and safety, enhance patient experience, and can be delivered at a certain cost, but with the increasing demands on healthcare expenditure, it will no longer be possible to evaluate interventions in isolation. “We will have to look at them in the totality of the management of patients with a particular disease—myocardial infarction, acute coronary syndrome, atrial fibrillation,” says Professor the Lord Kakkar. “This challenge is not insurmountable, but requires us to consider value, patient adherence and education.”

Professor the Lord Kakkar’s research has been supported by research councils, charities, and industry. For the Thrombosis Research Institute, one of the most important sources of charitable funding has been the Garfield Weston Foundation, but from a personal point of view, Professor the Lord Kakkar says, “I would not have been able to start my research career if it were not for the two substantial fellowships from the Medical Research Council.”

On top of his clinical and research work, Professor the Lord Kakkar is involved in education and administration. Since 2005, he has been dean for external relations at Barts and The London School of Medicine and Dentistry, a post in which he has gleaned an understanding of how complex it is to deliver a successful medical school.

Professor the Lord Kakkar received two prizes early in his career. In 1996, he won the David Patey Prize from the Surgical Research Society for a paper given at their annual meeting. In 1997, he was made a Hunterian Professor of the Royal College of Surgeons of England. Both are awards for surgical trainees in the United Kingdom, but for Professor the Lord Kakkar it had extra meaning because his father was made a Hunterian Professor in late 1969, and he
received the David Patey Prize in 1970. He says, “At the time I received it, he and I were the only father and son who had received the David Patey Prize, so those are very meaningful to me.” Later in his career, in 2009, he was honoured to be appointed the Wellcome Memorial Lecture at the Royal Society of Medicine, because he greatly admires the work of the Royal Society of Medicine and the people involved in it. Most recently, he has been elected an honorary fellow of Harris Manchester College, University of Oxford.

A new dimension was added to Professor the Lord Kakkar’s life on March 22, 2010, when he was made a Life Peer in the House of Lords. He is independent of party, and sits on the cross benches. The experience is providing him with a fascinating opportunity to learn more about public policy across a range of areas outside medicine. The House of Lords is a house of experts, and Professor the Lord Kakkar hopes to provide useful input to debates on health, medical research, and education.

References

Jennifer Taylor is a freelance medical journalist.

The Thrombosis Research Institute, London, England

Established “To Drive Forward Research Specifically Related to Thrombosis and to Antithrombotic Therapy”

Lord Kakkar, BSc, MBBS, PhD, FRCS, professor of surgery, University College London, London, England, consultant surgeon, University College London Hospitals NHS Foundation Trust, chair for quality, University College London Partners, and director of the Thrombosis Research Institute, London, describes the Thrombosis Research Institute to Jennifer Taylor, BSc, MSc, MPhil.

The Thrombosis Research Institute, London, England, was built from the research programme of Emeritus Professor Vijay Kakkar, FRCS, OBE, which he started in 1965 at King’s College Hospital medical school. It was inaugurated in October 1990 by then-Prime Minister Margaret Thatcher, and its aims are to deliver excellence in research, teaching, and clinical practice in the area of thrombosis and related disorders. Professor Vijay Kakkar’s son, and director of the Institute since 2008, Professor the Lord Kakkar, BSc, MBBS, PhD, FRCS, professor of surgery, University College London, London, England, consultant surgeon, University College London Hospitals NHS Foundation Trust, chair for quality, University College London Partners, and director of the Thrombosis Research Institute, London, says, “It was
established because there was a growing recognition that thrombosis was a major problem, and there needed to be a focus and resource available to drive forward research specifically related to thrombosis and antithrombotic therapy.”

A Sister Thrombosis Research Institute in Bangalore, India: the Institutes “Effectively Work as a Single Institute Across Two Sites”

In 2006, Professor Kakkar senior founded and opened a sister Thrombosis Research Institute in Bangalore, India, which was inaugurated by the president of India at that time, His Excellency Dr A.P.J. Abdul Kalam. It grew out of the institute in London and an understanding that the epidemic of cardiovascular disease in India had the potential to have a devastating effect, because it affected both affluent and less affluent communities. There was also a realisation of the need to improve understanding of thrombosis and cardiovascular disease to determine whether the risk factors are different, and whether interventions need to be tailored to different populations to prevent a rapid explosion in cardiovascular disease in populations in India and globally.

Both institutes are charitable foundations. Over the years, the institute in London has received funding from the British Heart Foundation, the U.K. Department of Health, the Emmanuel Kaye Foundation, the Garfield Weston Foundation, the Medical Research Council, the Wellcome Trust, the Wolfson Foundation, and charitable bodies, individuals, and pharmaceutical companies. The Bangalore institute has received funding from the Garfield Weston Foundation, the Government of India, and the Sir Dorabji Tata Trust.

Professor the Lord Kakkar explains, “It was felt, why not go to the epicentre of the disease, start characterising the high-risk populations where there is early onset of cardiovascular disease, and then try to determine whether new therapies can be developed to prevent arterial disease or predict these risks.” Thus, the institute in India looks at ways to predict cardiovascular risk in different populations so that it is possible to intervene early. The main focus of its research is to look at the concept of a vaccine against heart disease in some form of immunotherapy. The research programme is common across both institutes, with parts of the work carried out in Bangalore and parts in London. Professor the Lord Kakkar says, “They effectively work as a single institute across two sites.”

The research in London specifically includes work on the vaccine, studies on biomarkers related to thrombosis risk, work on coagulation biology in cancer-associated thrombosis, clinical trials on venous thromboembolism prevention and treatment, and outcomes research in thromboembolic stroke. The clinical trials team at the Thrombosis Research Institute, London, is led by Iris Mueller, MD, working with Dr Gloria Petralia, MD, and the team conducting the lab-based research is led by Michael Scully, MD, Professor John McVey, PhD, Dr Xinjie Lu, and Dr Yunliang Chen.

Professor the Lord Kakkar’s father, an emeritus professor of the University of London, has retired to the Thrombosis Research Institute in India, where he is scientific chair and managing trustee and continues to have an active research interest, leading the work on the vaccine.

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