Most studies of cardiovascular disease in general, and in epidemiology in particular, have been carried out in men. Over the next few years, the gender balance is likely to be repaired through work being carried out at the University of Oxford, Oxford, England, based on huge datasets that were initially collected to investigate links between breast cancer and hormonal contraception and hormone replacement therapy. The first fruits of this initiative are 2 articles in *Circulation*, which have clarified risk of venous thromboembolism as a result of surgery and the additional risk of smoking. The findings are a product of the Million Women Study led by Professor Dame Beral, MD, DBE, AC, FRS, who since 1989 has been director of the Cancer Epidemiology Unit housed in the Richard Doll Building at Oxford, together with the Clinical Trial Service Unit, directed by Professors Sir Richard Peto, MA, MSc, FRS, and Sir Rory Collins, MSc, FRCP, FMedSci (see http://circ.ahajournals.org/content/117/25/f145).

"The Million Women Study Is the Biggest Prospective Cohort Study of Women in the World"

"The Million Women Study has full electronic linkage to the UK National Health Service datasets for 1.3 million women from recruitment through all hospital admissions, cancer registrations, and deaths," says Professor Beral. "It is the biggest prospective cohort study of women in the world at the moment. Studies of this kind, where the population is electronically linked to national health data, started in the Scandinavian countries, but we have been able to look at larger numbers because of the greater population of the United Kingdom. We have also collected much detailed information on lifestyle and other personal information from every study participant. The Chinese are not far behind with respect to record linkage to hospital admission data, and in a decade or two, we might be seeing even larger studies from China.

"The virtue of operating at this scale is that the confidence intervals narrow down and the uncertainties of smaller studies can be addressed. This approach has been strongly advocated here at Oxford, largely by my colleague Richard Peto: the bigger the study, the more reliable the findings can be; you don’t need fancy statistics and people generally don’t argue with the results. The bigger the numbers, the more transparent and less sophisticated you have to be when presenting your results."

On other pages...
“We Showed That Venous Thromboembolism Events Were More Likely in Smokers and ≈50% of All Venous Thromboembolic Events Were Linked to Surgery”

“Venous thromboembolism is the first aspect of cardiovascular disease we have looked at because it has long been linked with hormone replacement therapy,” explains Professor Beral. “We had a good look at the quality of the data and found that in over 90% of cases, the hospital diagnostic data are reliable, and the same results were found for heart attacks and stroke. In the case of body mass index as a risk factor for venous thromboembolism associated with surgery,1 we have been able to look at the risk, with and without surgery, and they go up and up at every level of body mass index.

“In the case of smoking and venous thromboembolism,2 previous studies had many inconsistencies and provided no clear answer, but we showed that venous thromboembolic events were more likely in smokers, both in those who had had surgery and in those who had not. About 50% of all venous thromboembolic events were linked to surgery, which was a much greater risk than we thought would be the case. The excess risk peaked at 3 to 4 weeks after surgery, with a relative risk [surgery-associated venous thromboembolism vs nonsurgical venous thromboembolism] greater than 100, and the excess risks lasted for up to 12 weeks postoperatively. Operations on the lower limbs, such as joint replacements and hip fractures, carried an even greater relative risk of about 200.”

“We Have Been Able to Look at Fine Divisions of Body Mass Index and the Risks of Heart Disease, and They Go Up and Up at Every Level—It’s a Simple, Linear, Relationship”

In future studies, the Million Women Study data will be used to quantify the risk factors in women for heart disease and stroke.

Professor Beral comments, “For women in their 50s, the most common serious illness is breast cancer, in their 60s and 70’s, it is cardiovascular disease, and in their 80s, it is hip fracture, and, of course, dementia. The average age of women in the Million Women Study is now 70 years, so we are able to look in detail at cardiovascular disease. I don’t think we are going to make major breakthroughs in heart disease, which has already been extensively studied. However, previous studies had suggested nonlinear relationships with body mass index—J-shaped, U-shaped curves, and the like. We have been able to look at fine divisions of body mass index and the risks of heart disease, and they go up and up at every level—it’s a simple, linear relationship. This tends to be our finding for many risk factors from large datasets—there are few examples where relationships with disease are more complicated than simple straight lines. We don’t understand the causes of stroke very well, but I think we will be able to clarify the risk factors in women, especially for haemorrhagic versus ischaemic stroke, where there are clear differences in their aetiology.”
The Million Women Study was started almost by accident in the mid-1990s when uncertainties about the risks of oral contraceptives and hormone replacement therapy meant that Professor Beral and her colleagues decided to study a set of 5000 women from the United Kingdom who had breast cancer. Most data on hormone replacement therapy came from the United States, where an oestrogen-only product was used, in contrast to Europe, where oestrogen–progestogen combinations were preferred. At the time, widespread breast screening within the National Health Service had just begun.

The initial idea was to carry out a case–control study of 5000 women with breast cancer, but it morphed into a prospective study of 1 million women. Between 1996 and 2001, and predominantly in 1998, 1.3 million women between 50 and 64 years of age were recruited. As time goes by the cohort therefore has the potential to provide data on many aspects of disease in the ageing woman.

Professor Beral works in a setting that owes much to the late Sir Richard Doll, MD, CH, OBE, FRS, the epidemiologist who is best known for proving the link between smoking and lung cancer. He revolutionised the subject and put it on a footing that has created what some people call the “Oxford statistical truth machine,” which has spawned a succession of major studies that have influenced medical practice worldwide.

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Professor Beral heads a team of 50 people, many of whom are involved in “cleaning and tidying” the data and computer processing. Despite the daunting prospect of handling a dataset involving more than 1 million subjects, it has proved possible to enter and clean the data with a team of only 10 using page-scanning and character recognition techniques that Professor Beral first encountered in the early 1990s when helping one of her sons with his homework. Although Professor Beral has a long list of articles, she and her group prefer to produce a few substantial articles each year rather than an avalanche of minor contributions.

Commenting on her move to Oxford in 1989, Professor Beral says, “I’m a medic, but my natural skills are mathematical. I like numbers, I like looking at pages covered with numbers. I was fortunate to be invited to come to Oxford and see the real greats in the field. Being around the people here who were absolute leaders in their field and seeing how good they were had a big influence on me. Their rigourousness sits in my consciousness. They speak to me. I would not like to let Doll down. I am also fortunate with the people who do the technical work in the unit, some of whom worked with him in the 1960’s.”

Professor Beral has been showered with honours, among which she especially rates the Companion of the Order of Australia and her Fellowship of the Royal Society. She says, “I was very pleased to get the Australian honour, from my home country, though I’ve been away from it for so long. With the FRS [Fellowship of the Royal Society], I couldn’t believe it! Most of the people at the award ceremony felt the same, I think: that we were not quite good enough to be there. It was absolutely terrific to be admitted and sign the same book as Isaac Newton.”

References

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Awards: British Cardiovascular Society

Michael Davies Early Career Award

Recognising Recently Established Independent Investigators Who Have Made and Are Making Outstanding Contributions to Cardiovascular Science

Recipients of the British Cardiovascular Society Michael Davies Early Career Award in 2012 and 2009 describe their research to Jennifer Taylor, BSc, MSc, MPhil.

The British Cardiovascular Society Michael Davies Early Career Award honours clinical and nonclinical researchers who have recently established themselves as independent investigators and who have made and are making, an outstanding contribution to cardiovascular science.

Michael J. Davies, MD, FRCPath, FRCP, who died in 2003, was a leading cardiovascular pathologist who published seminal articles on atherosclerosis and cardiomyopathy. He is described in his obituary in Circulation1 as “a leading exponent of the concept of plaque rupture” by Professor Peter Libby, MD, and Adriano M. Henney, PhD. They go on to explain, “Michael Davies’ observations, thought, and articulate advocacy led a major shift in the concepts of the mechanisms of acute myocardial infarction that have transformed contemporary cardiology.”

Professor Davies was appointed the first British Heart Foundation (BHF) chair of cardiovascular pathology in 1981 and became assistant medical director for research at the BHF. He was given a Lifetime Achievement Award, presented in absentia, at the American Heart Association meeting in 2001. “Few transform the field as decisively as Michael J. Davies did,” conclude Professor Libby and Dr Henney.

The Michael Davies Early Career Award of the British Cardiovascular Society is open to applicants involved in cardiovascular research who have an affiliation with a UK institution. They should be clinical or nonclinical researchers who have shown sustained outstanding productivity over several years, resulting in a significant contribution to cardiovascular medicine. Applicants are expected to be within 5 to 10 years of achieving their higher degree and on track to continue a successful clinical and/or academic career.

Candidates should be nominated by 2 academic referees, 1 external. Applications should include a curriculum vitae with details of all awards and published, peer-reviewed articles, with the 5 most important articles highlighted in bold. In addition, a 4-page document should be submitted outlining the totality of a contiguous body of work undertaken or supervised by the applicant in the field of cardiovascular science. The roles of the applicant and other contributors should be specified.

The applications are judged by the Academic Committee of the British Cardiovascular Society. A single award is made each year. In 2013 the amount was £2000, plus a travel bursary of up to £1000 for visiting research collaborators overseas.

The award is presented at the British Cardiovascular Society Annual Conference, where the winner gives a 15-minute oral presentation of their work.

Reference


“I Am Exploring the Role of Thymosin β4 in the Maintenance of Vascular Stability and Looking at Ways to Enhance Epicardial-Based Therapy”

Nicola Smart, PhD, BHF Ian Fleming Senior Basic Science Research Fellow, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, England

Dr Smart received the Michael Davies Early Career Award in 2012 for her research on redeploying embryonic mechanisms for cardiovascular repair. The work was carried out under the mentorship of Professor Paul Riley, PhD, at University College London Institute of Child Health, London, England. Professor Riley is now chair of development and reproduction and BHF professor of regenerative medicine in the Department of Physiology, Anatomy, and Genetics, University of Oxford.

The human heart is unable to effectively repair itself following ischaemic injury; therefore, significant effort has been invested in the search for embryonic or adult progenitor cells that may replace damaged muscle cells and promote neovascularisation.1 An emerging paradigm in cardiovascular regenerative medicine is that studies of embryonic heart, including the identification of multipotent cardiovascular progenitors, might be instructive towards understanding how to manipulate an adult reparative response and this is the underlying basis of Dr Smart’s research.

Dr Smart and her colleagues identified thymosin β4 (Tβ4), an actin-binding peptide implicated in cell migration and angiogenesis, from a screen for mediators of murine cardiac development downstream of the transcription factor Hand1.2 They demonstrated that reduced levels of Tβ4 contribute to vascular defects in Hand1-null embryos and that these could be rescued by injection of pregnant females with Tβ4.3 Normal vascular gene expression was restored and suggested an involvement of transforming growth factor-β and Notch pathways in Tβ4-mediated vasculogenesis. Indeed, the group recently confirmed a wider role for Tβ4 in the development of the systemic vasculature, acting as an...
endothelial-secreted factor that functions synergistically with transforming growth factor-β to regulate mural cell differentiation.\textsuperscript{4}

To investigate a role for Tβ4 during cardiac development, Dr Smart and her colleagues generated embryos with heart-specific Tβ4 knockdown.\textsuperscript{5} These embryos displayed multiple cardiac defects indicative of impaired coronary vasculogenesis, the progenitors of which derive in large part from the epicardium. Epicardium-derived cells (EPDCs) invade the myocardium and give rise to coronary vascular smooth muscle cells and interstitial and adventitial fibroblasts, and arguably contribute a proportion of endothelial cells and cardiomyocytes to the embryonic heart, although this is intensely debated. Failure of EPDCs to migrate into the myocardium to form coronary vessels led to the identification of Tβ4 as a key instructive cue for EPDC migration and a potent activator of coronary vasculogenesis.\textsuperscript{5} Translation of the vascular developmental role for Tβ4 to that of vasculogenic therapy requires the release of the adult epicardium from a quiescent state, in which it resides from early postnatal stages onwards, and restoration of pluriotency.

Dr Smart’s studies identified Tβ4 as a therapeutic factor capable of reactivating adult epicardium, stimulating vasculogenesis and arteriogenesis in the ischaemic heart.\textsuperscript{6} Moreover, she recently demonstrated that Tβ4-mobilised adult EPDCs contribute de novo cardiomyocytes to the ischaemic adult heart that structurally and functionally integrate with resident myocardium to support cardiac regeneration and functional improvement.\textsuperscript{7} Dr Smart says, “The application of Tβ4-activated EPDCs, facilitating the replacement of destroyed myocardium, is a significant step towards resident cell-based therapy for acute myocardial infarction in human patients.”

In June 2012, Dr Smart moved to the University of Oxford and she has just been awarded a BHF senior research fellowship. She says, “I am exploring the role of Tβ4 in the maintenance of vascular stability and looking at ways to enhance epicardial-based therapy in the hope of advancing towards a treatment for patients who have heart failure.”

References

“We Are Particularly Interested in MicroRNAs, Epigenetics, and Nerve Growth Factor-Based Therapies, and at Exploiting Embryonic Stem Cells for Vascular Regeneration”

Costanza Emanueli, PhD, BHF senior research fellow, professor of vascular pathology and regeneration and deputy head of research, School of Clinical Sciences, Faculty of Medicine and Dentistry, University of Bristol, Bristol, England, and visiting professor, National Heart and Lung Institute, Imperial College London, London, England

Professor Emanueli received the British Cardiovascular Society award in 2009. She comments, “I had the opportunity to work in different labs and with several outstanding mentors during the first part of my career.”

Professor Emanueli started as a research assistant and then PhD student at the University of Florence, Florence, Italy, working with Professor Pierangelo Geppetti, MD, a clinical pharmacologist who is well known for his work on neurogenic inflammation. Professor Emanueli’s major project focused on elucidating the role of bradykinin and tachykinins in plasma extravasation. This research led to a travel fellowship to work with Professor Nigel Bunnett, PhD, at the University of California in San Francisco, where Professor Emanueli contributed to characterising one of the first mouse knockout models. She explains, “We elucidated the control of microvascular permeability and blood pressure by the enzyme neutral endopeptidase, which metabolises both bradykinins and tachykinins.”

Development of these studies led to an introduction to Paolo Madeddu, MD (see http://circ.ahajournals.org/content/126/7/f37), a cardiologist doing basic research in hypertension at the University of Sassari, Sassari, Sardinia. Professor Madeddu provided Professor Emanueli with bradykinin B2 knockout mice for her permeability studies.\textsuperscript{2–4} Professor Emanueli says, “This initiated a long-term collaboration in the lab as well as in life [Professor Emanueli and Professor Madeddu are now partners and...
Professor Madeeddu is chair of the Division of Experimental Cardiovascular Medicine, Bristol Heart Institute and head of the Regenerative Medicine Section, School of Clinical Sciences, University of Bristol, initially resulting in a series of articles in Hypertension elucidating the contribution of kinins to blood pressure regulation in different hypertensive models.”

Professor Emanueli’s first postdoc was in Rome, Italy, with Professor Maurizio Capogrossi, MD, who had just returned to Italy after many years at the National Institutes of Health in Baltimore, PA. Professor Emanueli says, “In his American-style lab, I thrived as a vascular scientist and learned the basis of angiogenesis research.” In this new research area, Professor Emanueli published the first evidence of the angiogenic actions of the kallikrein–kinin system5 and its therapeutic potential in models of limb ischaemia,6 including when associated with hypertension7 or diabetes mellitus8 and in diabetic microangiopathy.9

Professor Emanueli then identified more proangiogenic mediators, including nerve growth factor.10 “I am still studying nerve growth factor today and aim to translate it to the treatment of patients who have cardiac ischaemia,” she says.

Professor Emanueli’s final mentor was Professor Jeff Isner, MD, who died prematurely in 2001. Professor Emanueli says, “In his lab at the Saint Elisabeth Medical Centre, Boston, MA, I spent the most exciting although short period of my career and I was privileged to be in the same space with scientists such as Professor Doug Losordo, MD, and Takayuki Asahara, MD, PhD.”

Professor Emanueli moved to Bristol in 2005, where she has established a lab aimed at better understanding the pathogenic molecular mechanisms responsible for vascular suffrage and ischaemia, particularly in the context of diabetes mellitus, and at developing new regenerative approaches.

She says, “We are particularly interested in microRNAs, epigenetics, and nerve growth factor-based therapies, and at exploiting embryonic stem cells for vascular regeneration. Our work is translationally oriented and we work in close contact with our clinical colleagues, especially the Bristol academic cardiac surgery team established by the British Heart Foundation chair, Professor Gianni Angelini (with whom I also share a lab at Imperial College London), and wonderful collaborators and friends.”

References


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