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Laboratory Profile
University Department of Cardiac Surgery at Bristol

In 1993, the University of Bristol appointed Gianni Angelini to a British Heart Foundation Chair in Cardiac Surgery. He was shortly joined by a secretary and a clinical research registrar. This team of three has now grown to become a main centre for cardiovascular research at Bristol with more than 30 people (clinical, non-clinical and supporting staff) and attracting substantial research funding. In addition to this, laboratories were refurbished and essential equipment was purchased and a purpose designed building was erected. This effort was the natural outcome of Prof. Angelini’s commitment to basic research and his conviction that clinical and non-clinical interaction is vital for the advancement of clinical research. The following highlights the on-going research in the Department.

Research into saphenous vein graft failure has been Prof. Angelini’s main interest for more than a decade (started in Cardiff in collaboration with AC Newby). The team involved in this programme includes clinical (AJ Bryan & B Izzat) and non-clinical (K Southgate, S George & J Jeremy) staff members. Recent work has established that proliferation and migration of vascular smooth muscle cell in response to endogenously generated growth factors underlies graft wall thickening. We have also shown that smooth muscle cell proliferation is stimulated by increased wall stress, which may reduce fluid flux through the vessel wall leading to the accumulation of growth factors and hypoxia or interruption of vasa vasora. Consistent with this idea, we have investigated the effect of a

Front: Emma Warwood, Sonia Birkett, Gianni Angelini, Emily Alexander, Dawn Wallace, Anne Moffatt
Middle: Nicola Merrell, Isaac Kadir, Katherine Walker, Saadeh Suleiman, Kay Southgate, Sarah George, Susan Watts, Jane Robbins, Elizabeth Gardiner
high-porosity, non-restrictive external polyester stent on luminal size and on the degree of medial and intimal thickness and proliferation in our pig saphenous vein graft model. Four weeks after graft implantation stented grafts had a larger lumen and a far thinner media and neointima than paired unstented grafts in the same animal. Cell proliferation was virtually abolished by stenting in the neointima and in the medial layer. The type of stenting material and procedure used here are readily applicable to human saphenous vein grafts. The impact of the stent on wall thickness and patency needs now to be tested directly in a clinical study, and the commencement of this is planned for June 1995. Direct evidence has also been obtained that matrix-degrading metalloproteinases are produced by cells of the vessel wall in pig vein grafts and in human saphenous vein in culture. Strategies aimed at inhibiting the proliferation of vascular smooth muscle cells and subsequent intimal proliferation are being evaluated and these include the use of specific antibodies and antisense oligonucleotides.

Research into vascular cell biology has also been extended (C Jackson) to studying the control of smooth muscle migration and proliferation in injured arteries, processes which play a major role in the late failure of such techniques as coronary angioplasty. The aim of this research will be mainly on the role of extracellular matrix and its interactions with growth factors and smooth muscle cells.

Recent interest has focused on the application of normothermic perfusion during open heart surgery as opposed to more traditional methods involving systemic cooling. To define the place of normothermic systemic perfusion in clinical practice, the department (GD Angelini, AJ Bryan, B Izzat, I Regragui, I Birdi) has embarked on a major prospective randomised trial to compare bypass perfusion at 28°C, 32°C or 37°C. The aim of this trial is to evaluate outcome in terms of both clinical and economic endpoints, and also to investigate the influence of perfusion temperature on end-organ dysfunction. In the last 12 months 200 patients have been recruited with overall excellent clinical results, and only 2 deaths. Interim analysis of clinical outcome has demonstrated only minimal differences between the 3 groups. Investigation of subsystem dysfunction has shown that there is no apparent influence of perfusion temperature on postoperative renal or respiratory dysfunction, but there is indication that neuropsychological changes are more marked in those undergoing normothermic perfusion. Further investigations of myocardial protection and release of inflammatory mediators are still under way.

An early collaboration between the Departments of Cardiac Surgery and Physiology in the University of Bristol provided evidence for a fall in intracellular free amino acid pool in heart cells during open heart surgery. This fall was interpreted in terms of activating a Na-dependent amino acid cotransporter(s) as well as metabolism. During open heart surgery, the heart is arrested using cold cardioplegic solution, conditions known to provoke a rise in intracellular sodium. We (SSuleiman, GD Angelini, AJ Bryan, WDihmis) have now expanded on this preliminary study and are looking at the effects of both temperature and different cardioplegic solution media on changes in amino acids during surgery so that strategies can be formulated to improve myocardial preservation and functional recovery of the heart. In addition to monitoring changes in free intracellular amino acids pool, we are also looking at a variety of pre-, intra- and post-operative parameters which include tissue levels of adenosine nucleotides, lactate and pyruvate. As recent evidence suggests that ischaemic preconditioning may also protect the heart, we are carrying out preliminary work where human hearts are preconditioned prior to cardiopulmonary arrest and the levels of cellular metabolites monitored.

Parallel to the above described clinically based research, methods are being to study the effect of cardiac insults in isolated perfused animal hearts and cells (S Suleiman). Perfused heart and isolated myocytes will be subjected to experimental protocols that are similar to those seen during cardiac surgery. Recent evidence suggests that the transition from reversible to irreversible damage during cardiac insults is determined by the extent of damage to the mitochondria. Work (S Suleiman, E Griffiths, AP Halestrap in Biochemistry) is currently underway to assess the role of different inhibitors of mitochondrial calcium transport systems using isolated heart cells. It is hoped that this study in parallel with work on isolated hearts and animal hearts subjected to cardiopulmonary bypass will help in the development of an optimal cardiopulmonary solution media.
We (S Suleiman, GD Angelini, S Birkett) have recently shown that metabolic damage associated with surgical preparation of human saphenous vein for coronary artery bypass grafting is accompanied by a fall in the intracellular free amino acid pool. This may have important implications for the functional recovery of the grafted vein and is being currently investigated.

Transoesophageal Echocardiography (TOE) model of imaging has become routine in our department, both intraoperatively and postoperatively. We have shown that TOE can be used as a haemodynamic monitor of cardiac output by measurement of pulmonary artery flow in patients undergoing coronary artery surgery. Using TOE we have also discovered that severe segmental ischaemia occurs during mobilisation of the internal mammary artery and a study is now in progress to identify the causes of this as well as means to prevent it from occurring. Echocardiography was recently used in combination with dobutamine stress to evaluate small valve prostheses in the aortic position. This is, to our knowledge, the first time that such a methodology has been successfully used in this context.

An important part of ongoing research in the department is to investigate the interaction of mother–children with congenital heart disease and to study the pre- and postoperative mental health of patients undergoing elective coronary artery bypass surgery (F Gardner, AJ Bryan, GD Angelini, I Regragui). An increased level of distress was found in infants. Significant numbers of cardiac infants showed low levels of positive affect in engagement and interaction with their mothers and this was present from before surgery. This suggests that the cardiopathy per se is the cause of this disturbed interaction. The mother also showed depressed levels of positive affect and engagement and were significantly psychologically depressed. These were not influenced by the surgery. It is now our intention to study the possible effect of two forms of therapy, psychological intervention or counselling for mother–infant pairs prior to surgery in order to assess whether this will raise the level of positive interpersonal engagement in interaction. The mental health of patients undergoing elective coronary artery bypass surgery was assessed using self-report questionnaires and a semi-structured interview. A significant number of those patients, more than 40%, were found to be depressed preoperatively and also at six weeks after surgery, and this was independent of successful clinical outcome. A long-term follow-up at six months and one year is planned in order to assess the long term psychological function of these patients.

As part of a joint effort with the Department of Materials Engineering and Design, University of Nottingham, we have succeeded in developing a new composite material to be used for the manufacture of heart valve prostheses. This is based on a titanium substrate covered with a thin diamond-like carbon layer. A valvuloplasty ring made of this material is at present being evaluated in a clinical trial. A novel bileaflet mechanical heart valve prosthesis is also being tested in vitro and a plan of in vivo implants is expected to start at the beginning of 1996. Further progress has also been made on a device to allow endoscopic removal of the saphenous vein at operation. This project was recently supported by a development grant from the Department of Trade and Industry.

Research activity in the Department is considered as an integral part of the ongoing research at Bristol. Therefore we have been active in developing collaborative research links with other groups particularly with A Halestrap (Biochemistry), CGarland (Pharmacology) and A Levi (Physiology). We also hope to extend such collaborative links to other clinical and pre-clinical groups in order to advance cardiovascular research in the region.

Finally, we would like to acknowledge the support of The British Heart Foundation, the Garfield Weston Trust and the Wellcome Trust who among other research funding bodies, must be given the credit for this development.

M-Saadeh Suleiman, Senior Lecturer