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Editorial

Welcome to the April 2003 issue of *The* Bulletin!

This issue includes two review articles. The first, *'ACE2, a novel homologue of Angiotensin Converting Enzyme. Potential functional roles.'*, has been written by Dr Gillian Rice and collgues of the Cardiac Medicine Proteolysis Research Group, School of Biochemistry and Molecular Biology, University of Leeds. Dr Rice and collegues provide a fascinating insight into the functional role of a novel homologue ACE2. The second review, written by Dr Bashir Matata and Professor Manuel Galiñanes of the Department of Integrative Human Cardiovascular Physiology and Cardiac Surgery at the University of Leicester, focuses on the involvement of reactive oxidant species in the pathophysiology of open heart surgery.

As highlighted by Dr Barbara McDermott in the Secretary's Column, the Society's Autumn meeting is being held jointly with the Scottish Cardiovascular Forum at the University of Edinburgh. Full details of the meeting programme are included in this issue.

Finally, we bring you the latest details of grants awarded to researchers in the Cardiovascular field, by the British Heart Foundation and the Wellcome Trust.

Helen Maddock and Nicola Smart

Articles for *The* Bulletin

Would you like to write a Review or Laboratory Profile for the BSCR Bulletin? These articles provide an excellent opportunity to let BSCR members know about your research activities and also provide an insight into your research field.

We are keen to hear from anyone in cardiovascular research who would be willing to write for *The* Bulletin.

If you are interested, please contact the Bulletin editors with your ideas: Helen (h.maddock@coventry.ac.uk) or Nicola (N.Smart@ich.ucl.ac.uk)

ACE2, a novel homologue of Angiotensin Converting Enzyme. Potential functional roles.

Gillian I. Rice*, Anthony J. Turner*,
Peter J. Grant† and Nigel M. Hooper*

* Proteolysis Research Group, School of Biochemistry & Molecular Biology, University of Leeds

†Academic Unit of Molecular Vascular Medicine, G-Floor, Martin Wing, Leeds General Infirmary.

The renin-angiotensin system plays a key role in regulating blood pressure and fluid and electrolyte homeostasis on a systemic level, but also has a more chronic localised role in the cardiovascular system. Angiotensin converting enzyme (ACE) is involved in determining local levels of angiotensin II, and ACE inhibitors are an important treatment for hypertension and cardiovascular disease. A novel homologue of ACE, ACEH or ACE2 was recently identified, that may also have an important role to play in the regulation of the renin-angiotensin system. In this article, recent advances in our knowledge of ACE2 and its role in the renin-angiotensin system are discussed. Data include ACE2 substrate specificity, and potential functional roles of ACE2 identified by the study of mouse knockout and over-expression models. The question of whether angiotensin II is a substrate for ACE2 *in vivo* is discussed in the light of recent experimental data.

Introduction

The renin-angiotensin system (RAS) mediates numerous effects in the cardiovascular system and is believed to operate on two levels, a circulating level and a local tissue level. In humans, the circulating RAS plays a crucial role in regulating blood pressure, fluid and electrolyte homeostasis (1). In contrast, the tissue RAS may provide a more chronic, localised influence on regulation of vascular tone or renal, cardiac, neuronal, adrenal or intestinal function (2). Kidney derived renin, a proteolytic enzyme, catalyses the conversion of the large globular protein angiotensinogen to the decapeptide angiotensin I (Ang I) (3) (**Fig. 1**). At the circulating level of the RAS, renin represents the rate-limiting step in production of angiotensin II (Ang II) from Ang I (4). However, at the tissue level of the RAS, it is the level of another enzyme, angiotensin converting enzyme (ACE) that is important in determining local levels of Ang II. ACE generates Ang II by cleaving the carboxy-terminal dipeptide His-Leu from Ang I (5).

Ang II is a bioactive peptide with a crucial role in the RAS, mediated by binding to the angiotensin II type 1 and 2 (AT_1 and AT_2) receptors. The binding of Ang II to the AT_1 receptor mediates many components of cardiovascular regulation including regional blood flow and vascular smooth muscle cell proliferation and migration (6). The binding of Ang II to the AT_2 receptor is thought to oppose several functions mediated by the AT_1 receptor (7,8) including inhibition of cell proliferation, promotion of cell differentiation and possibly mediation of apoptosis (7). There is cross-talk between the AT_1 and AT_2 receptors in mediating the physiological effects of Ang II, and the balance between vasodilation and vasoconstriction will depend on the local AT_1 and AT_2 receptor density.

Ang (1-7) is the predominant peptide generated from Ang I in the vascular endothelium (9), as opposed to formation of Ang II by ACE. Ang (1-7) opposes the actions of Ang II by causing vasodilation (10,11), antiproliferation (12,13) and apoptosis (14). The major enzyme involved in the formation of Ang (1-7) from Ang I *in vivo* is neprilysin (NEP, neutral endopeptidase 24.11) (9,15). Evidence suggests that there may be a

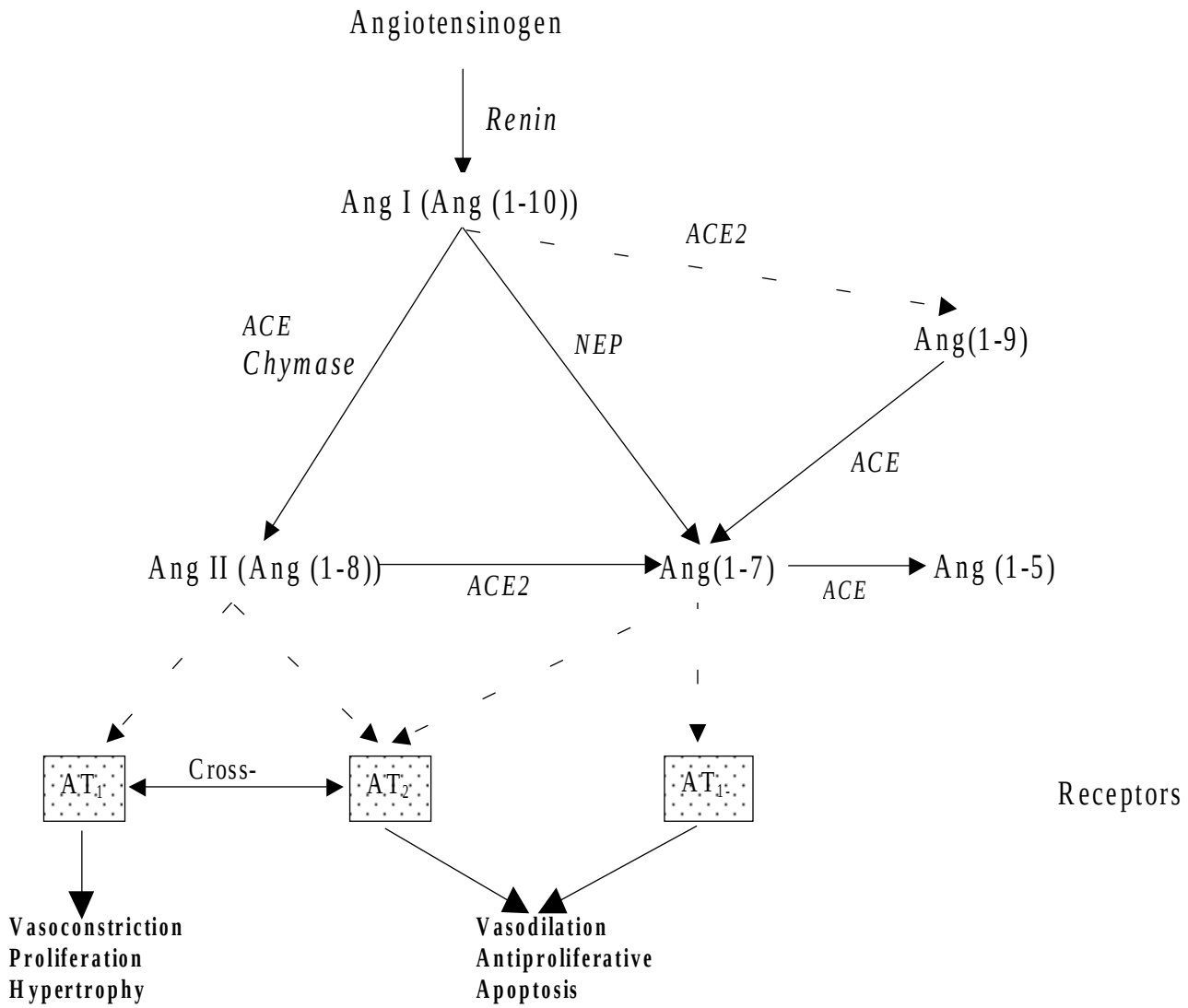

Figure 1. Schematic diagram of the renin-angiotensin system illustrating where ACE2 is believed to have a role.

distinct Ang_{1-7} receptor (16) but this has not been isolated and characterised.

Thus it can be seen that the RAS is a very complex enzyme cascade with balances and counter-balances at every step. The balance of the system between coronary risk factors (vasoconstriction, cellular proliferation and hypertrophy) and coronary protection (vasodilation, antiproliferation and apoptosis), will depend on the levels of individual peptides, enzymes and their inhibitors in each local system. The RAS has also been reviewed in more depth in two recent papers (17,18).

ACE 2

The most recently reported member of the ACE family, which may prove to be a novel player in the renin-angiotensin system, is the ACE homologue ACEH or ACE2. The identification of human ACE2 was first reported in 2000 by two independent groups; ourselves (19) and Donaghue et al. (20). The full length cDNA sequence for ACE2 was obtained from a human kidney library (19) and a human cardiac left ventricle library (20). A comparison of the structure and characteristics of ACE and ACE2 is shown in **Table 1**. ACE2 is more localised in its tissue expression, being found mainly in the testis, kidney, heart and intestines, in comparison to ACE which is considered to be virtually ubiquitous (19). Immunohistochemical studies have shown that ACE2 is localised to the endothelium of most of the intramyocardial vessels of the heart; and is also present in the endothelium and proximal tubule epithelial cells of the kidney (20).

Table 1. Comparison of ACE and ACE2.

	ACE	ACE2
Expression	Ubiquitous, lining endothelium of conduits	Testis, kidney, heart, intestines
Active site(s)	2 active sites	1 active site
Protein size	1306 amino acids	805 amino acids
Structure	Membrane bound, cleaved by secretase	Membrane bound, possibly cleaved by secretase
Inhibitors	Inhibited by ACE inhibitors	Not inhibited by enalaprilat, lisinopril, captopril when Ang II is substrate
Substrates	Cleaves Ang I, bradykinin	Cleaves Ang II, des-Arg^9 bradykinin
Cleavage site	Cleaves C-terminal dipeptides	Cleaves 1 amino acid from C-terminus
Role in fertility?	Role in fertility	No apparent role in fertility

A comparison between the structures of somatic ACE, single domain testicular (germinal) ACE, ACE2 and collectrin is shown in figure 2. ACE2 is a 805 amino acid protein, consisting of a C-terminal transmembrane anchor, a 17 amino acid N-terminal signal sequence and the HEXXH zinc metalloprotease active site domain. Recently, collectrin, a novel homologue of ACE2 was identified. It comprises 222 amino acids with an apparent signal peptide and transmembrane domain. Human collectrin has 47.8% identity with part of the extracellular, transmembrane and cytosolic domains of ACE2, but has no similarity with ACE. Collectrin mRNA transcripts are expressed exclusively in the kidney and this developmentally regulated renal protein is reported to be highly localised to collecting ducts. Isolation of the cDNA encoding ACE2 from a human cardiac left ventricle library (20) and the up-regulated expression of collectrin after renal ablation, suggests that the collectrin domain of ACE2 may regulate tissue response to injury, whereas the catalytic domain is involved in peptide processing events.

ACE2 substrate specificity

ACE cleaves C-terminal dipeptides from substrates such as Ang I, Ang (1-9), bradykinin, and kallidin. It can also act as an endopeptidase on substrates that are amidated at the carboxyl terminus, such as substance P and Luteinizing hormone releasing-hormone. In contrast ACE2 acts as a carboxypeptidase cleaving a single amino acid from the C-terminus of peptides. ACE2 hydrolyses efficiently most substrates with a penultimate proline residue followed by a hydrophobic amino acid (21). It cleaves Ang II with high catalytic efficiency (**Fig 1**), but Ang I is a poor substrate for ACE2 (21). Ang (1-9), Ang (1-7) and Ang (1-5) are not cleaved by ACE2. ACE2 also efficiently hydrolyses des-Arg^{9}bradykinin and Lys-des-Arg^9-bradykinin but cannot cleave bradykinin itself (21). Of interest, it has also been shown to hydrolyse apelin-13 and apelin-36. Apelin is an endogenous ligand of the human orphan APJ receptor, which is closely related to the AT_1 receptor (22). Apelin is synthesised as a 77 amino-acid pre-prohormone, which is processed into the 36 amino acid peptide apelin-36; further proteolytic cleavage generates apelin-13 (23). Apelin-13 has been shown to promote vasoconstriction in endothelium-denuded coronary arteries (24) therefore this is a second system in which ACE2 might have a role in blood pressure regulation. ACE2 has also been shown to cleave Dynorphin A 1-13 and b-casomorphin, opioid peptides which activate G-protein-coupled k and d opioid receptors (21). Thus ACE2 may have multiple functions in different systems. The true substrates of ACE2 *in vivo* have yet to be identified, but the following model systems may help to illustrate possible roles for ACE2.

ACE2 over-expression model

Transgenic mice with cardiac-specific over expression of human ACE2 were generated (25). These mice exhibited complete atrioventricular block from 3 weeks of age, and as a result showed a high propensity for premature sudden cardiac death compared with their wild-type littermates. The condition was detectable at 1 week of age, and worsened progressively. Treatment with an atrioventricular blocker worsened the condition and in 6 week old mice, ventricular tachycardia could

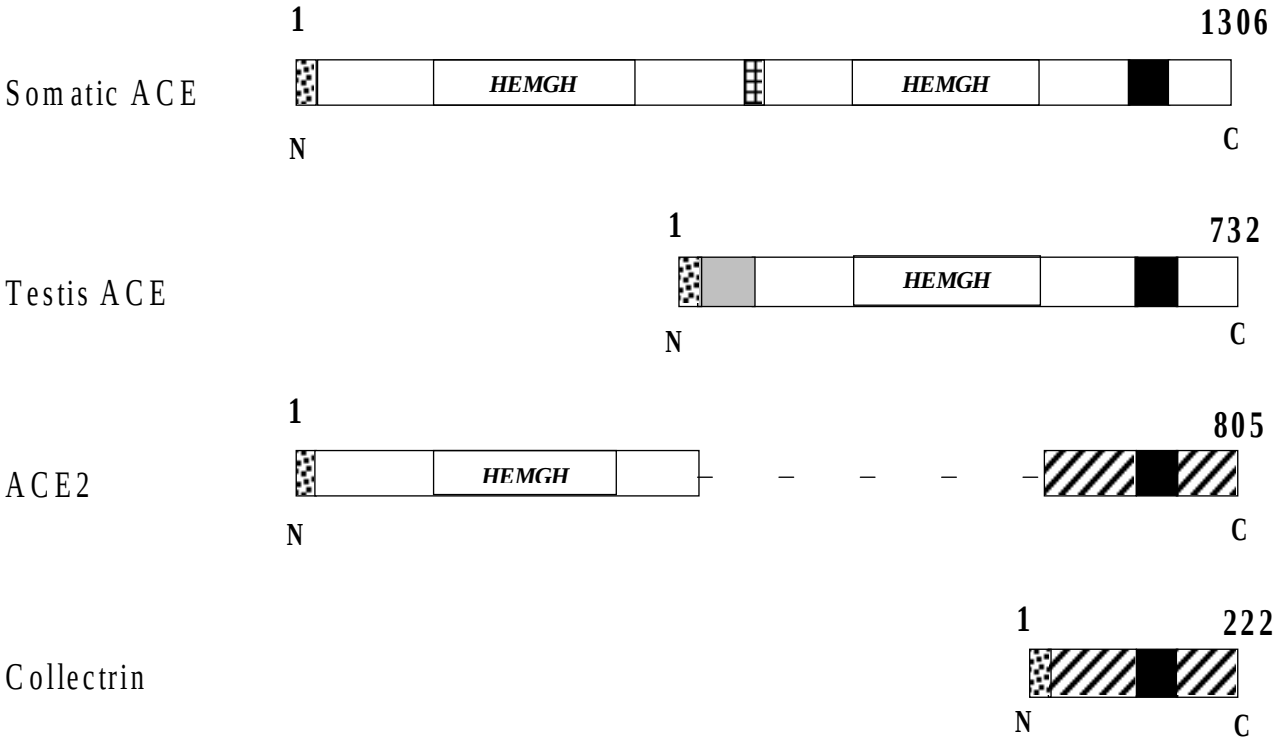

Figure 2. **A comparative diagram of ACE2 and homologous proteins.** Somatic ACE, testis ACE, ACE2 and collectrin are shown. Signal peptides are indicated by a dotted box, transmembrane domains by a black box, and the bridge region of somatic ACE by a hashed box. The unique N-terminal testis-ACE specific sequence is shown as a grey box. Regions of homology between ACE and ACE2 are denoted by white boxes, and between ACE2 and collectrin by diagonal lines.

easily be induced. Thus over-expression of ACE2 may contribute to cardiac arrhythmogenesis. These data add support to the existing idea that peptides in the renin-angiotensin system may contribute to cardiac arrhythmogenesis. No mention was made of whether Ang peptides were measured in these mice, but if Ang II is a substrate of ACE2 *in vivo*, then it would be expected that Ang II levels would be reduced and Ang (1-7) levels raised in these mice compared with healthy controls. It would be very interesting to establish whether this was the case and therefore whether Ang II is implicated in the pathogenesis displayed.

ACE2 knockout model

Another group of investigators recently created ACE2 knockout mice by homologous recombination, disrupting the ACE2 gene by replacing the active site, exon 9 with the neomycin resistance gene cassette in the reverse orientation (26). ACE2 null mice were born at the expected mendelian frequency, and in contrast to male ACE knockout mice that display significantly reduced fertility (27,28), both female and male ACE2 knockout mice were fertile. This suggests that despite ACE2 expression in the testis, it doesn't appear to have a role in fertility.

At 3 months of age, loss of ACE2 had no influence on blood pressure or kidney structure (26). It was shown that ACE2 maps to a QTL for hypertension on the X chromosome of hypertensive rats. ACE2 mRNA and protein expression were reduced in hypertensive rats compared with control rats fed a similar diet, and the downregulation was found to be independent of blood pressure regulation (26). These data suggest that ACE2 plays a role in the pathogenesis of hypertension, but the mechanisms by which ACE2 regulates blood pressure remain unclear. Ang II raises systemic blood pressure by peripheral vasoconstriction and by promoting sodium reabsorption in the kidney (1). ACE inhibitors are highly beneficial in the treatment of hypertension (29), reducing blood pressure by reducing Ang II levels in plasma. ACE2 cleaves Ang II to Ang (1-7) which is itself a vasodilator, therefore it would be expected that knocking out ACE2 would result in raised Ang II levels and therefore raised blood pressure. In the knockout mice, kidney, heart and plasma Ang II levels were indeed raised (26), but this did not appear to have any influence on blood pressure. Ang (1-7) can also be generated by the enzyme NEP. Unfortunately NEP and Ang (1-7) levels were not

measured in this study, but it would be interesting to establish whether NEP levels are up-regulated in the ACE2 knockout mice, compensating for the loss of ACE2 by maintaining Ang (1-7) levels.

ACE inhibitors are also very beneficial in the treatment of heart disease (30,31). However, neither ACE (27,28) nor angiotensinogen knockout mice (32) develop any overt heart disease. In contrast, the hearts of ACE2 knockout mice showed slight wall thinning of the left ventricle and increased chamber dimensions (26). They also demonstrated a severe reduction in cardiac contractility, resulting in reduced blood pressure in 6 month old male mice. This condition was shown to be progressive, and worse in male mice. These heart defects may have been caused by raised Ang II levels in the heart. It is known that raised Ang II levels cause cardiac remodelling, pathological hypertrophy and myocardial fibrosis (33). However, no evidence of such pathologies could be identified in these mice. The severe contractile dysfunction and mild dilation in the absence of hypertrophy or cardiac fibrosis resembles cardiac stunning and hibernation seen in human and animal models. These responses tend to be adaptive responses to chronic hypoxia seen in situations such as coronary artery disease or following bypass surgery. Loss of ACE2 could cause vasoconstriction due to the raised plasma Ang II levels, resulting in hypoxia. In favour of this theory, several genes known to be upregulated by hypoxia were shown to be upregulated in these mice (26). This suggests that the cardiac dysfunction seen in the ACE2 knockout mice was due to an indirect effect of Ang II causing vasoconstriction and hypoxia rather than a direct effect of raised Ang II levels on the tissues of the heart.

One interesting observation from this study was that ACE/ACE2 double knockout mice had no heart dysfunction (26). In the absence of ACE2, Ang II levels will be raised, and knocking out ACE in addition, will prevent the formation of Ang II in the first place (**Fig 1**). This suggests that the raised Ang II levels are causative in producing the cardiac dysfunction seen in the knockout mice. This suggests that ACE2 is an important regulator of heart function *in vivo*.

Is Ang II a substrate of ACE2 *in vivo*?

As discussed above, ACE2 may be an important regulator of hypertension, but the mechanism involved does not appear to be due to any alteration in systemic Ang II levels to an extent that causes alteration in blood pressure. Over-expression of ACE2 would be expected to result in a reduction of Ang II levels, and in mice, this resulted in atrioventricular block i.e. disrupted electrical signalling in the heart. It is known that Ang II in cardiac myocytes causes reduced cell coupling and conduction velocity, and controls inward Ca^{2+} current (34,35). Is it likely then that reduced Ang II levels could cause atrioventricular block? In ACE2 knockout mice, Ang II levels in the heart, kidney and plasma were raised, and severe contractile dysfunction and mild dilation of the heart were identified. However this was found in the absence of hypertrophy or cardiac fibrosis, suggesting that if raised Ang II levels were in involved, it was via an indirect effect on vasoconstriction locally in the heart, rather than via any direct effects on systemic blood pressure or heart tissue. So is Ang II the true substrate of ACE2 *in vivo* or is there another, as yet unidentified, substrate that causes all the effects seen?

Two recent reports may go some way to answering these questions. In a separate ACE2 knockout mouse model (36), Ang II was infused into ACE2 knockout mice or control mice at a level that does not cause hypertension in the control mice. Blood pressure was increased in the ACE2 knockout mice compared to controls, and this was accompanied by a significant reduction in heart rate. Ang II levels were found to be much higher in the ACE2 knockout mice than in controls following the infusion, suggesting that ACE2 is an important regulator of Ang II levels *in vivo*, and is required to prevent Ang II levels from becoming dangerously high. The increase in blood pressure may only become apparent when Ang II levels become so high that other compensatory mechanisms can no longer maintain the equilibrium. In a second study (37), chronic administration of omapatrilat, an ACE/NEP inhibitor was shown to reduce blood pressure, increase Ang (1-7) levels in urine and induce ACE2 expression in the kidney. This data suggests that ACE2 has an important role in regulating Ang II and Ang (1-7) levels *in vivo*, and that feedback mechanisms regulate enzyme levels, in order to be able to compensate for loss of one or more enzymes from the system.

Taken together, these data suggest that Ang II clearly is a substrate of ACE2 *in vivo*, and that ACE2 has an important role in regulating Ang II and Ang (1-7) levels. However, the RAS is a very complex enzyme cascade with many feedback and compensatory mechanisms, that are able to cope with the loss of one component. It is only under severe stress that the loss results in a visible phenotype. As a result, the phenotypes that are seen in the mouse models tend to be the result of indirect local effects, rather than due to the direct influence of large scale alterations in Ang II

levels. The result of the loss or up-regulation of ACE2 in a particular system will depend on the concentration of the various enzymes of the RAS and the Ang peptides in the localised tissue, rather than systemic concentrations and levels.

Concluding remarks

The RAS is clearly a very complex system which we are only beginning to fully understand. The discovery of a novel ACE homologue, ACE2, that appears to have an important role in the regulation of the RAS is an exciting prospect. Many experiments need to be carried out to clarify the role of ACE2 in the regulation of the RAS, but already there is the possibility for novel therapeutics aimed at treating hypertension and heart disease. The recent development of ACE2 inhibitors (38) will help to elucidate the exact role of ACE2, and aid in the study of its regulation. Identification of polymorphisms or functional mutations in the ACE2 gene might demonstrate whether ACE2 does indeed have a role in the pathogenesis of hypertension or heart disease in humans. Ultimately up-regulation of ACE2 might prove to be beneficial in certain disease situations.

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Correspondence to:
Dr Gillian Rice
School of Biochemistry and Molecular Biology,
University of Leeds, Leeds. LS2 9JT, UK.

Telephone: 0113 343 3132
Facsimile: 0113 343 3167
Email: bmbgir@bmb.leeds.ac.uk

For up to date information on forthcoming meetings,

workshops and symposia,

please remember to check the new BSCR Website:

http://www.bcs.com/affiliates/bscr.html

Secretary's Column

I am back at my desk, having just returned from the very successful Glasgow meeting on 'Molecular therapy for cardiovascular disease'. The out of town location and all in package at the Kelvin Conference Centre provided the environment for a wonderfully focused meeting. We escaped only briefly to the patio outside the poster exhibition space to appreciate the glorious sunny weather which prevailed for the two days. The Committee also met and we were able to progress the plan to transfer the contents of the BSCR website to the British Cardiac Society site. The new URL is http://www.bcs.com/affiliates/bscr.html. The opportunity has been taken to include downloadable forms for BSCR meeting registration, abstract submission and application for student bursaries. These are now available for the next main meeting, which is the joint BSCR / Scottish Cardiovascular Forum meeting, scheduled for 8-9 September at the University of Edinburgh. Full details of the programme and arrangements are included in this issue. Further ground breaking activity for the BSCR at this meeting will be the publication of the presented abstracts in Heart Online, but this will not replace their inclusion in the Bulletin. Lastly, in further pioneering fashion, the Edinburgh meeting will see the first presentation of 'BSCR Meeting Prizes', one for a best oral communication and one for the best poster. The age limit for the competition is 30, so hopefully more young scientists will be encouraged to participate. In the meantime, our only other event is the BSCR symposium to be held at the annual meeting of the British Cardiac Society on Tuesday 29th April at 09.00 - 10.30h in the Scottish Exhibition and Conference Centre (SECC) in Glasgow. I hope to see many of you there.

Barbara McDermott

Reactive oxidant species and the pathophysiology of open-heart surgery

Bashir M. Matata and Manuel Galiñanes

Department of Integrative Human Cardiovascular Physiology and Cardiac Surgery, University of Leicester, Clinical Sciences Centre, Glenfield Hospital, Leicester.

Introduction

Cardiac operations under cardiopulmonary bypass (CPB) trigger a chain of events that may induce a temporal change in the patient's own immune system [1-3]. The complex role played by the immune system in the CPB-mediated pathophysiology is not yet fully understood although several interlinked mechanisms are known to play a role. CPB-mediated pathophysiology may be triggered by a wide range of factors including the exposure of blood to nonphysiological surfaces and mechanical shear stresses, surgical trauma, anaesthesia, changes in body temperature, increased intestinal permeation by endotoxins and ischaemia-reperfusion injury. The combined action of these factors results in a complex immunological reaction commonly termed "the systemic inflammatory response", which includes the activation of complement [4,5], the release of proinflammatory cytokines [6,7], endothelium and leukocyte activation along with the expression of adhesion molecules[8,9], and the production of various noxious substances such as oxygen free radicals[10-12], arachidonic acid metabolites [13,14], endothelins [15], and platelet activating factor[16,17] among others. The clinical manifestations of the systemic inflammatory reaction are thought to include prolonged in-hospital stay and postoperative complications such as wound infections, respiratory failure, myocardial damage causing cardiac contractile dysfunction and even heart failure, renal impairment, coagulopathy, neurological dysfunction and altered liver function [18], and even increase mortality [19-23].

Molecular events in CPB-induced inflammation

The molecular events that trigger CPB-induced complications have remained difficult to unravel owing to the broad variety of techniques used for CPB such that comparison of findings is often difficult and conclusions confusing. It is not until recently, that investigators[24] have shown that the pertubation of the immune response system by cardiac operation may occur in two phases. The first phase (postoperative day 1) represents the proinflammatory and antiinflammatory reaction of the innate immune system that returns to baseline on postoperative day 3. The response is characterized by the activation and release of proinflammatory factors such as complement, cytokines, adhesion molecules, arachidonic acid metabolites, endothelins, and platelet activating factor[5-17], as well as antiinflammatory factors such as interleukin 10[24,25]. In addition, there is a release of heat-shock protein 70, monocyte CD14 and Toll-like receptor-4[26]. Monocyte CD14 and Toll-like receptor-4 are molecules involved in the heat shock 70-mediated activation of the innate immunity. The second phase that occurs on postoperative day 5 may represent the response of the adaptive immune system and is characterized by an antiinflammatory type of reaction and a period of increased infection [24]. Other studies [27] have also shown that CPB increases the activity of matrix metalloproteinases and nitric oxide synthase in human myocardial tissue, enzymes known to mediate acute inflammation and organ injury and a possible cause for delayed postoperative heart complications. Although the magnitude of the inflammatory reaction varies from patient to patient, it is reasonable to conclude that the persistence of any degree of inflammation during and after surgery is potentially detrimental to the cardiac patient.

Reactive oxygen species, and CPB-mediated injury

In tandem with the release of inflammatory factors, CPB induces deleterious effects triggered in part by reactive oxygen species, although their direct involvement in the course of surgery has remained largely undetermined. There is indirect evidence in the literature

that CPB induces reactive oxygen species but the type, identity, origin and magnitude of this production remain unknown [27-45]. Factors such as severe stresses on blood leukocytes and endothelial cells induced by CPB and the reperfusion of organs such as the heart and lungs after variable periods of ischaemia may trigger the release of reactive oxygen species. Several potential cellular components can be the source of the reactive oxygen species and these include the xanthine/xanthine oxidase system, the NADH/NAD(P)H-dependent electron transport chain, the cyclooxygenases and others [46-49]. Oxygen free radicals can be generated during cardiac surgery at several stages of the operation. It has been shown that extracorporeal bypass is the major source of free radical production, and that levels are much greater than those produced by the reperfusion of the ischaemic myocardium, in studies using spin trap techniques [50]. Other experimental models have shown that reactive oxidant species such as hydrogen peroxide, superoxide radical, hydroxyl radical and peroxynitrite are increased upon reperfusion of the heart following a period of ischaemia [51-56]. It is well known that the increased production of reactive oxidant species during ischaemia/reperfusion of the heart affects the intracellular redox state. This may lead to a series of detrimental events such as arrhythmias, microvascular damage, myocardial stunning and cell death [57-61].

For the past 20-30 years, researchers have employed various strategies, mainly free radical scavengers, for reducing the damage that occurs during ischaemia/reperfusion due to oxidative stress. However, discrepant results have been reported from the attempts to deliver antioxidants during and after myocardial ischaemia/reperfusion [58,62] and during cardiopulmonary bypass [33,63]. Exogenous antioxidants may be restricted to the interstitial space and this may limit their ability to protect intracellular proteins against reactive oxygen species. Hydroxyl free radical for example, is believed to be the main agent for oxidative damage, is highly reactive with all cell components, but with a half-life of $7x10^{-10}$ seconds at 37^0C [64], may only act within the cell. Other studies have suggested that the reaction between peroxynitrite and its biological targets, particularly enzymes with metal centres, is faster (e.g. 10^4-10^8 M^{-1} S^{-1}) than between peroxynitrite and antioxidants such as ascorbate and glutathione (e.g. 10^2 M^{-1} S^{-1}) [65]. In contrast, the formation of peroxynitrite from nitric oxide and superoxide occurs at nearly diffusion-controlled rates of $4.3\text{-}6.7x10^9$ M^{-1} S^{-1} [66,67]. It is therefore difficult to envisage that the administration of exogenous antioxidants can prevent peroxynitrite or hydroxyl-radical-induced tissue damage. Recent data from our laboratory have shown [44] that infusion of nitroglycerin at moderate concentrations during CPB significantly reduces oxidative stress in individuals with diabetes mellitus, a group of patients known to have high levels of oxidative stress [68]. The recent introduction of new cardiac surgery techniques has allowed surgeons to perform beating heart surgery to accomplish multi-vessel coronary revascularization without the need for CPB. We [69] and others [70-72] have shown that off-pump surgery significantly reduces but does not abolish oxidative stress and inflammation, and that despite this, the overall morbidity, cost of care, and mortality are reduced [21-23]. A more effective strategy may be to minimize or to prevent the production of powerful radical oxidants. To this end, experimental models have shown that over-expression of catalase, superoxide dismutase, or glutathione peroxidase are protective against oxidative stress [73-75] and that the beneficial effect of antioxidant enzymes can be potentiated by the upregulation of stress proteins [76-78]. Clearly, the importance of this strategy requires further investigation in humans.

Traditionally, oxidative stress has been viewed as a pathological process that contributes to cell damage. Recently,however, it has been shown that reactive oxygen species are widely used as second messengers that propagate proinflammatory and growth-stimulatory signals [79-83]. Researchers have now realised that oxidative stress and chronic inflammation are related and perhaps inseparable [84]. Therefore the design of novel interventions that allow supplementation of antioxidant defences while antagonizing redox-sensitive signal transduction may prove to be an important approach to improved clinical outcome in patients undergoing heart surgery.

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Correspondence to: Professor Manuel Galiñanes, Department of Integrative Human Cardiovascular Physiology and Cardiac Surgery, University of Leicester, Clinical Sciences Centre, Glenfield Hospital, Leicester, LE3 9QP, UK.

Cardiovascular Related Meetings

XXIII Congress of the European Society of Cardiology, together with Heart Failure 2003 (ESC). June 21-24, 2003, Strasbourg, France. Enquiries: ESC, 2035 Route des Colles, BP 179 - Les Templiers, 06903 Sophia Antipolis Cedex, France. Tel: +33 4 9294 7600; Fax: +33 4 9294 7601; Website: www.escardio.org

International Society for Heart Research, XXV Annual Meeting of the North American Section. Mystic, Connecticut. Enquiries: Gerald Cordis, Cardiovascular Research - L1086, Department of Surgery, University of Connecticut, School of Medicine, 263 Farmington Avenue, Farmington, CT 06030-1110, USA. Fax: +1 860 679 4606; E-mail: scientificconferences@amhrt.org; Website: www.americanheart.org

Scientific Sessions of the American Heart Association. Orlando, Florida. Enquiries: American Heart Association, Meetings and Councils, 7272 Greenville Avenue, Dallas, TX 75231. Tel.: + 1 214 706 1543; Fax: +1 214 373 3406; E-mail: gcordis@neuron.uchc.edu; Website: http://ishr2003.uchc.edu

XVIII World Congress of the International Society for Heart Research, August 7-11, 2004, Brisbane, Australia. Enquiries: ISHR 2004 Congress, PO Box 164, Fortitude Valley QLD 4006, Australia. Tel +61 7 3854 1611; Fax +61 7 3854 1507; E-mail: heart2004@ozaccom.com.au; Website: www.baker.edu.au/ISHR

Keystone Symposia: 'Molecular Biology of Cardiac Disease' and 'Cardiac Development and Congenital Heart Disease'. March 7-12, 2004, Keystone Resort, Colorado, USA. For further information: www.keystonesymposia.org; 221 Summit Place #272, Drawer 1630, Silverthorne, CO 86498; Tel: +1 970 262 1230; info@keystonesymposia.org.

North American Society of Pacing and Electrophysiology : 24th Annual Scientific Sessions, 14th-17th May, 2003, Washington D.C. For further information, please contact: Tel: 001-508-647-0100; E-mail: info@naspe.org; Website: http://www.naspe.org

National Meeting of the French Society of Cardiology (ESC), 22nd – 24th May, 2003, Brest, France. Further information: Prof. N. Danchin, tel: +33 (0)1 4322 3333; E-mail: contact@cardio-sfc.org; Website: http://www.webcardio.com/main.asp

Travel Reports for *The* Bulletin

The Bulletin regularly publishes travel reports written by members. These are up to 3 pages in length, may include photographs and can be on any conference, course or laboratory visit of interest to other members. If you are planning on travelling to a cardiovascular-related meeting and would like to write a report for the Bulletin, please contact the editors. A bursary of **£100** is available towards the cost of your visit, and this will be provided on receipt of the report. Bon voyage!

British Society for Cardiovascular Research

Autumn 2003 Meeting

'Oxidative stress: from measurement to management'

held jointly with the

Scottish Cardiovascular Forum

8th-9th September, 2003

John MacIntyre Conference Centre, Pollock Halls of Residence, University of Edinburgh

Organising Committee:
G.A. Gray, S. Maxwell, I.L. Megson, I. Rahman (Edinburgh), A. Shah (London)

Monday 8th September:

Scottish Cardiovascular Forum/BSCR Symposium (Prestonfield Rm)

9.00-10.00:	Coffee, registration (Conservatory) and poster mounting (Holyrood Room)
10.00-10.30	Local Keynote lecture: Rudolph Reimersma, University of Edinburgh: 'Fish oils: cardioprotective or not?
10.30-12.00	SCF/BSCR Oxidative stress - related free communications
12.00-14.00	*Lunch, Posters and exhibitions*

BSCR meeting (Prestonfield Room)

14.00:	Welcome: Professor David Webb, Head, Centre for Cardiovascular Science, University of Edinburgh.
14.10-15.00	**British Cardiac Society Lecture** Professor Barry Halliwell, National University of Singapore
15.00-16.00	**Session 1: Oxidative Stress: CV sources, targets and measurement**

- Dysfunctional NOS — Keith Channon *(Oxford)*
- NADPH oxidase/NO pathways — Valerie O'Donnell *(Cardiff)*
- Cytochrome P450 2CP — Ingrid Fleming *(Frankfurt)*

16.00-16.30 *Tea/coffee*

16.30-17.30 **Session 1** (continued)

- Vascular oxidative stress/statins — Ralf Brandes *(Frankfurt)*
- Isoprostanes as markers — Sandy Hill *(Dundee)*
- EPR — Jurg Muller *(Magnatech, Berlin)*

17.30-18.00 BSCR AGM

19.30 **BSCR/SCF Reception & Dinner: National Trust for Scotland, Charlotte Square**

Tuesday 9th September

9.00-11.00 **Session 2: Oxidative Stress: CV targets & disease processes**

- Lipid peroxidation — Irfan Rahman *(Edinburgh)*
- Heme oxygenase 1 — Roberto Motterlini *(Imperial)*
- Neurovascular injury — Mary Cotter *(Aberdeen)*
- Reperfusion injury & protein thiolation — Phil Eaton *(KCL)*
- NADPH oxidase & cardiac hypertrophy — Ajay Shah *(KCL)*

11.00-11.30 *Tea/coffee*

11.30-12.30 **Session 3 Oxidative Stress: Management**

- Vit E trials in pre-eclampsia — Lucilla Poston (GKT, *London)*
- Allopurinol in heart failure — Justine Davies *(Dundee)*
- Arterial SOD gene transfer — Julia Brosnan *(Glasgow)*

12.30-14.30 Lunch, posters and exhibition

14.30-15.20 **Session 3 (continued) Oxidative Stress: Management**

- Polyphenolic compounds/cardioprotection — Dipak Das *(Connecticut, USA)*
- Uric acid — Simon Maxwell *(Edinburgh)*

15.20-16.00 **National Heart Research Fund Lecture**:
Dr Jane Armitage, Oxford CTSU 'Antioxidant trials and epidemiology'

16.00: Prize presentations & wine reception

End of Meeting

BRITISH HEART FOUNDATION GRANTS

Project Grants Committee: January 2003

DEFERRED APPLICATIONS AWARDED

Dr J P Greenwood, Leeds General Infirmary. "Pathophysiological mechanisms of hypertensive left ventricular hypertrophy optimising regression": (2 years) £93,645.

Dr T J Mohun, National Institute for Medical Research. "The role of HAND1 in cardiac morphogenesis" (3 years) £143,775.

Dr A H Gershlick, University of Leicester. "A scoring system to stratify risk in patients undergoing percutaneous coronary intervention" (3 years) £105,046.

NEW APPLICATIONS AWARDED

Dr P K MacCallum, Queen Mary, University of London. "Air travel and venous thromboembolism" (1.25 years) £176,010.

Professor A K Campbell, University of Wales College of Medicine, Cardiff. "Novel genetically-engineered probes for monitoring nitric oxide in living cells" (3 years) £142,620.

Professor M R Boyett, University of Leeds. "Inward rectification of cardiac K+ channels-a new twist" (3 years) £158,993.

Dr A Owen et al, Canterbury Christ Church University. "The effects of 24 weeks' high-and moderate-intensity exercise on physical fitness and selected coronary heart disease risk factors" (1.5 years) £6,580.

Dr C M Shanahan, Addenbrooke's Hospital, Cambridge. "Functional interactions of nesprins in sarcomere of cardiomyocytes" (3 years)£149,387.

Dr D E Newby, Royal Infirmary, Edinburgh. "Vascular and anti-inflammatory effects of fish oils in patients with a recent myocardial infarction" (2 years) £114,032.

Dr T A McDonagh, Royal Infirmary Glasgow. "Neurohormonal predictors of prognosis in advanced heart failure" (1 year) £37,088.

Dr B L Ellis, University of Manchester. "The pre-clinical evaluation of novel radioactive tracers for myocardial perfusion imaging (Tc-99-tricarbonyl halides)"(1 year) £53,340 .

Dr Q Xu, Middlesex Hospital, London. "Intracellular low density lipoprotein accumulation induced by hypoxia and retinoic acid: identification of potential targets for amelioration of atherosclerosis" (2 years) £98,809.

Dr J N Townend, Queen Elizabeth Hosp, Birmingham. "Does the acute administration of L-arginine and tetrahydrobiopterin(BH4) to patients with heart failure result in improved cardiac vagal control due to stimulation of nitric oxide synthesis?" (6 months) £34,935.

Dr A Clerk & Professor P H Sugden, Imperial College, London. "Gene profiling in cardiac (ventricular) myocyte hypertrophy using microarray analysis" (3 years) £211,411.

Dr G E Rainger, University of Birmingham. "Platelet adhesion to endothelial cells cocultured with smooth muscle cells" (2 years) £109,464.

Professor A M Shah, King's College School of Med & Dent London. "Role of NADPH oxidase-derived reactive oxygen species in cardiac remodelling after myocardial infarction" (3 years) £148,452 .

Dr D E Newby, Royal Infirmary, Edinburgh. "The effects of air pollution on vascular vasomotor and fibrinolytic function in patients with ischaemic heart disease" (2 years) £194,433.

Dr S J George, Bristol Royal Infirmary "Regulation of cell cycle genes by the cadherin-catenin complex in smooth muscle" (2 years) £86,731 .

Dr T L Shaw & Professor Q Xu, St George's Hospital Medical School, London "Jumonji gene expression in smooth muscle cells that have been stimulated by mechanical stress" (3 years) £123,016.

Prof A K Soutar & Dr R Naoumova, Hammersmith Hospital, London. "Characterisation of the role of ARH1 in the LDL-receptor pathway" (2 years) £83,808.

Prof D I Wilson & Dr N A Hanley, Southampton General Hospital "An investigation into the differentiation of the primordial germ cell- embryonic germ cell lineage to a myocardial phenotype" (2 years) £103,100.

Dr J A Pizzey, Guy's Hospital, London. "The role of the transcription factor GATA-6 in regulating early cardiomyocyte differentiation" (3 years) £146,399.

Dr P K Luther, Imperial College, London. "Three-dimensional structural analysis of MyBP-C protein in cardiac muscle: implications for familial hypertrophic cardiomyopathy" (3 years) £271,079.

Dr R M Reynolds, Western General Hospital, Edinburgh. "Birthweight and adrenocortical responsiveness in women" (3 months) £12,420.

Professor B M J Foxwell, Charing Cross Hospital, London. "Analysis of IL-10 receptor structures involved in macrophage inactivation" (3 years) £175,803.

Prof J A Mitchell & Prof T Evans, NHLI, London "The signalling of gram-negative bacteria in macrophages and blood vessels diverge at the level of toll like receptor 4: implications for tissue selective intervention in the treatment of shock" (3 years) £153,545.

Professor J A Goodship, University of Newcastle upon Tyne "Investigation of the function of EVC and LBN, genes that play a role in atrioventricular septation" (3 years) £199,025.

DEFERRED AWARDS

Intermediate Research Fellowship

Dr J S O'Donnell, Hammersmith Hospital, London. "Significance of the N-linked glycans of Von Willebrand Factor in determining clearance of the vWF-FVIII complex"(3 years) £245,951.

Junior Research Fellowship

Dr K M Goode, Hull Royal Infirmary. "Improving the accuracy of brain natriuretic peptides for the efficient detection of heart failure using artificial neural networks" £58,579.

Dr B Datta, University of Wales College of Medicine. "Nitric oxide metabolism and regeneration - a pathological role for glycosylated haemoglobin?" £86,309.

Clinical PhD Studentship

Dr J R Davies, Addenbrooke's Hospital Cambridge. "Quantification of atherosclerotic plaque inflammation by positron emission tomography" (3 years) £138,061.

NEW APPLICATIONS AWARDED

Intermediate Research Fellowship

Dr S.J. Mundell, University of Bristol. "Molecular mechanisms underlying the regulation of $P2Y_1$ and $P2Y_{12}$ receptors: an investigation of how platelets control their response to ADP" (3 years) £143,934.

Junior Research Fellowship

Dr D.J. O'Keeffe, Addenbrooke's Hospital, Cambridge. "Neutralisation of clot-bound thrombin by Heparin Cofactor II: a target for more effective antithrombotic therapy" (2 years) £98,638.

Dr N.F. Kelland, Western General Hospital, Edinburgh. "Role of the endothelial cell endothelin B receptor in the heart" (2 years) £86,214.

Dr A.C. McCulloch, Glasgow Royal Infirmary. "Left ventricular diastolic dysfuction - a radionuclide approach" (2 years) £81,626.

Dr R. Das, Leeds General Infirmary. "Risk assessment and quality of care of patients with redefined acute myocardial infarction. A second evaluation of methods and management of acute coronary events study: EMMACE-2" (2 years) £72,847.

Dr S. Sen-Chowdhry, Royal Brompton Hospital, London. "Investigation of arrhythmogenic right ventricular cardiomyopathy in probands and first degree relatives using cardiovascular magnetic resonance" (2 years) £84,757.

Dr Y. Ismail, Bristol Royal Infirmary. "Targeting plaque-specific inflammation: a genomic approach" (2 years) £88,266.

Dr M. Jones, Barts and The London NHS Trust. "Do patients in primary care with angina have better clinical outcomes if managed according to expert panel ratings of appropriateness" (1 year) £34,361.

PhD Studentship

Miss L. Macdonald, University of Aberdeen. "Role of sphingosine 1-phospate-induced signalling pathways in the activation of transcription factors from vascular smooth muscle"(3 years) £65,168.

Unnamed and Dr A. E. Pickering, University of Bristol. "The baroreflex arc: diverging autonomic pathways within the nucleus tractus solitarii" (3 years) £66,667.

Miss N. Sunak, Cardiff University. "Regulation of the

CCAAT-enhancer binding protein-d gene transcription by cytokines" (3 years) £66,252.

Unnamed and Dr S. Ali, University of Newcastle upon Tyne. "Examination of the role of MCP chemokines during cardiac allograft rejection" (3 years) £68,502.

Miss L.C. Preston, University of Oxford. "The use of site-specific mutants to determine the impact of phosphorylation of human cardiac troponin T on contractility"(3 years) £78,105.

Mr A. Hussain, Coventry University. "The role of A3 adenosine receptors in protecting the mycardium from myocardial ischaemia / reperfusion injury" (3 years) £71,423.

Unnamed and Professor S. D. Brain, Guy's Hospital, London. "The influence of adrenomedullin, calcitonin gene- related peptide(CGRP) and their receptors on mechanisms involved in sepsis"(3 years) £76,101.

Unnamed and Dr C. Ettelaie, University of Hull. "Investigation of the influence of tissue factor expression and activation on vascular restenosis" (3 years) £65,739.

Miss F.K. Andersson, Addenbrooke's Hospital, Cambridge. "Induction of mesoderm differentiation in pluripotent stem cells"(3 years) £71,001.

Ms S. Becker, Guy's Hospital, London. "Mechanism of K^+ current inhibition by hypoxia in rat pulmonary artery" (3 years) £72,385.

Cardiovascular Related Wellcome Trust Grants

November 2002 to February 2003

Wellcome Programme Grant

Dr B Therese Kinsella Dept of Biochemistry, Conway Institute Biomol & Biomed Res, University College Dublin Dublin 4 Eire. Mechanisms and regulation of intracellular signalling by the thromboxane A2 and prostacyclin receptors. 60 months Amount of Award: £512,768

Prof Michael A Geeves Dept of Biosciences, University of Kent at Canterbury, Canterbury. Mechanochemical coupling in the myosin super family of molecular motors. 60 months: £1,038,125

Postdoctoral Fellowship

Dr N M Morton Endocrinology Unit, Department of Medical Sciences, University of Edinburgh, Western General, Edinburgh. Dietary (lipid) regulation of the gluchcorticoid metabolising enzyme 11beta-hydroxysteroid dehydrogeanse type 1 and its implications for obesity and metabolic disease. 36 months £312,144

Project Grant

Prof Sian E Harding Dept of Cardiac Medicine, Imperial College School of Medicine, National Heart & Lung Institute London. B-blocker mediated coupling of the B2-adrenoceptor to Gi failing human heart: short and long term consequences. 0 months £131,712

Dr K J Buckler Laboratory of Physiology, University of Oxford, Oxford. An investigation of potential mechanisms for ischemia induced noradrenaline release from cardiac sympathetic nerves. 36 months £18,893

Dr A W Poole Dept of Pharmacology, School of Medical Sciences, University of Bristol, Bristol. Regulation of PKC isoforms by tyrosine phosphorylation: Functional cross-talk between phosphorylation signalling pathways in platelets. 36 months £187,778

Dr Cesare M N Terracciano Dept of Cardiothoracic Surgery, Harefield Hospital, National Heart & Lung Institute Middlesex. Cell transplantation to the failing

heart: functional studies on excitation-contraction and cell-to-cell coupling. 36 months: £389,135

Dr Mark A Pook Dept of Medical & Community Genetics, Kennedy Galton Centre, Level 8, Imperial College London Harrow. Generation of a Friedrich's Ataxia transgenic mouse model by using transformation-associated recombination cloning in yeast. 36 months: £205,927

Four Year Phd Studentships

Miss Catherine Shaw Molecular Physiology Laboratory, Wilkie Building, University of Edinburgh Medical School Edinburgh Scotland The role of nitric oxide-related species in protecting against atherogenesis. 36 months £39,410

Mr Charles Mayor Molecular Physiology Laboratory, Wilkie Building, University of Edinburgh Medical School Edinburgh Scotland. Gene transfer-mediated modulation of pro-inflammatory events in atheroma. 36 months £60,826

Advanced Fellowships For Medical Graduates

Dr Frank Wiesmann Dept of Cardiovascular Medicine, John Radcliffe Hospital, University of Oxford, Oxford. Morphological and functional MRI studes in human atherosclerosis. 24 months £134,569

University Awards

Dr Claire Harris Dept of Medical Biochemistry, Univ of Wales College of Medicine, Cardiff, Cardiff Wales. The role of complement and its regulators, CD46 and CD55, in cell activation in inflammation: molecular analysis of activation mechanisms. 60 months £307,709

High Cost Flexible Funding (HCFF)

Prof Lucilla Poston Dept of Obstetrics & Gynaecology, St. Thomas's Campus, UMDS of Guy's & St Thomas's Hospital London. A randomized controlled trial of vitamin C and E supplementation to prevent pre-eclampsia in women at risk. 34 months £1,320,357.

International Research Fellowships

Dr Vikram Sudarsan Dept of Biochemistry, School of Medicine, Stanford University Stanford USA. Regulation and function of the oxygen-controlled transcription factor, Shaved, in Drosophila tracheal branching. 36 months £128,180.

Collaborative Research Initiative Grants

Dr Robert Matthew Smith Department of Cardiology, The Hatter Institute, UCL Hospitals, London. Tumour necrosis factor-alpha activated cell survival signalling. 36 months £142,532.

Prof Gerardo Gamba School of Biological Sciences, G.38 Stopford Building, University of Manchester, Manchester. Structure-function relationships in the thiazide-sensitive Na-C1 cotransporter (TSC). 36 months: £145,836.

Dr Pablo Wappner Wellcome Trust Centre For Human Gen, Henry Wellcome Bldg of Genomic Med, University of Oxford, Oxford Regulation of hypoxia-dependent transcription in Drosophila melanogaster. 36 months: £176,783.

Equipment

Dr Eve Lutz Dept of Physiology & Pharmacology, University of Strathlcyde, Glasgow, Scotland. 'Quantitative analysis of the regulation of gene expression, changes in posttranlational protein modification and protein:protein interations'. 60 months £68,448.

Prize Studentships

Miss Rachel Simpson Dept of Pharmacology, University of Cambridge, Cambridge. Molecular and cellular studies of the stimulation of adenylyl cyclase type I by Ca2+/calmodulin. 36 months £78,588.

Mr Steven P Wilder Wellcome Trust Ctr for Human Genetic, University of Oxford, Oxford. Computational analysis of susceptibility genes for diabetes and cardiovascular diseases in animal models and translation to human genetics. 36 months £70,427.

Miss Nathalie L'Huillier Molecular Physiology Laboratory, Wilkie Building, University of Edinburgh Medical School, Edinburgh, Scotland. The physiological role of the pro-renin receptor. 36 months £124,387.

BSCR Autumn Meeting 2003

Oxidative Stress: from Measurement to Management

held jointly with the Scottish Cardiovascular Forum

Dates: 8th and 9th September, 2003

Venue: John MacIntyre Conference Centre, University of Edinburgh

Organisers: Gillian Gray, Ian Megson, Simon Maxwell, Irfan Rahman & Ajay Shah

Overall Aims:

- To consider the sources of oxidative stress and cellular targets in cardiovascular disease.
- To discuss the pros and cons of the techniques used for measurement of oxidative stress.
- To examine different approaches to the management of oxidative stress.

Invited Speakers include: Barry Halliwell (*Singapore*), Rudolph Riemersma *(Edin)*, Ingrid Fleming (*Frankfurt*), Sandy Hill (*Dundee*), Jurg Muller (*Magnatech*), Valerie O'Donnell (*Cardiff*), Keith Channon (*Oxford*), Roberto Motterlini (Imperial) Irfan Rahman (*Edin*), Philip Eaton *(KCL*), Mary Cotter (*Aberdeen*), Ajay Shah (*KCL*), Ralf Brandes (*Frankfurt*), Lucilla Poston (GKT), Julia Brosnan (*Glasgow*), Justine Davies (*Dundee*), Dipak Das (Connecticut), Jane Armitage (*Oxford CTSU*).

Travel & Accommodation: The conference centre is located adjacent to Holyrood Park and close to Edinburgh city centre. En-suite rooms and parking are available on site.

Communications: Part of this meeting will be devoted to oral presentation of selected abstracts, and posters. Prizes will be given for the best oral and best poster presentation given by young investigators.

Registration: Free to BSCR members, £40 for non-members.

Bursaries: The Society will consider awarding travel grants of up to £150 to bona fide PhD students.

Deadline for submission of abstracts, registration and application for student bursaries: 1st August

The abstract pro-forma, meeting registration form, and forms for application for BSCR membership or student bursaries can be downloaded from: http://www.bcs.com/affiliates/bscr.html

***Any further enquiries to*:** Dr Gillian Gray, University of Edinburgh, SBCLS, Hugh Robson Building, George Square, Edinburgh EH8 9JZ; Tel 0131-650-6817; FAX 0131-650-6527; gillian.gray@ed.ac.uk.

or: Dr Barbara McDermott, BSCR Secretary, Department of Therapeutics and Pharmacology, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL; Tel 02890-272242; FAX 02890-438-346; b.mcdermott@qub.ac.uk