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Contents

Editorial

Welcome to the October issue of *The* Bulletin. Apologies for a small issue this time - we would like to include articles such as laboratory profiles and 'Careers in Cardiovascular Research' as regular features. In the past, these articles have been of particular interest to our readers. If you would like to contribute an article of this kind, we would be delighted to hear from you.

The review article for this issue on nitric oxide in the vasculature, was kindly written by Dr Valerie O'Donnell from the Wales Heart Research Institute.

Sadly, Dr Gary Baxter writes his last column as the BSCR Secretary. As editors, we are very grateful to Gary for his continued co-operation and assistance in obtaining items required for inclusion in *The* Bulletin. In his column, the secretary announces the result of the recent election for membership of the BSCR Committee. We look forward to working with the new Committee members in future issues.

'Mitochondria and Cell Death' is the subject of this issue's book review. As always, we finish with listings of grants awarded, by the British Heart Foundation and Wellcome Trust, to scientists in Cardiovascular research.

If you have any suggestions or items that you would like us to publish in The Bulletin, please do not hesitate to contact us.

Helen Maddock and Nicola Smart

Where does nitric oxide go in vascular disease?

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Introduction

Nitric oxide (NO) is a free radical gas formed in the vasculature through oxidation of L-arginine by NO synthase enzymes (NOS). Under physiological conditions, NO maintains vascular homeostasis through inhibiting leukocyte and platelet activation, and causing smooth muscle relaxation. These activities are mediated through activation of soluble guanylate cyclase (sGC) to generate guanosine 3':5'-cyclic monophosphate. In the vasculature, NO is synthesised by numerous cell types, however the major sources of NO under basal conditions are endothelial cells and platelets.

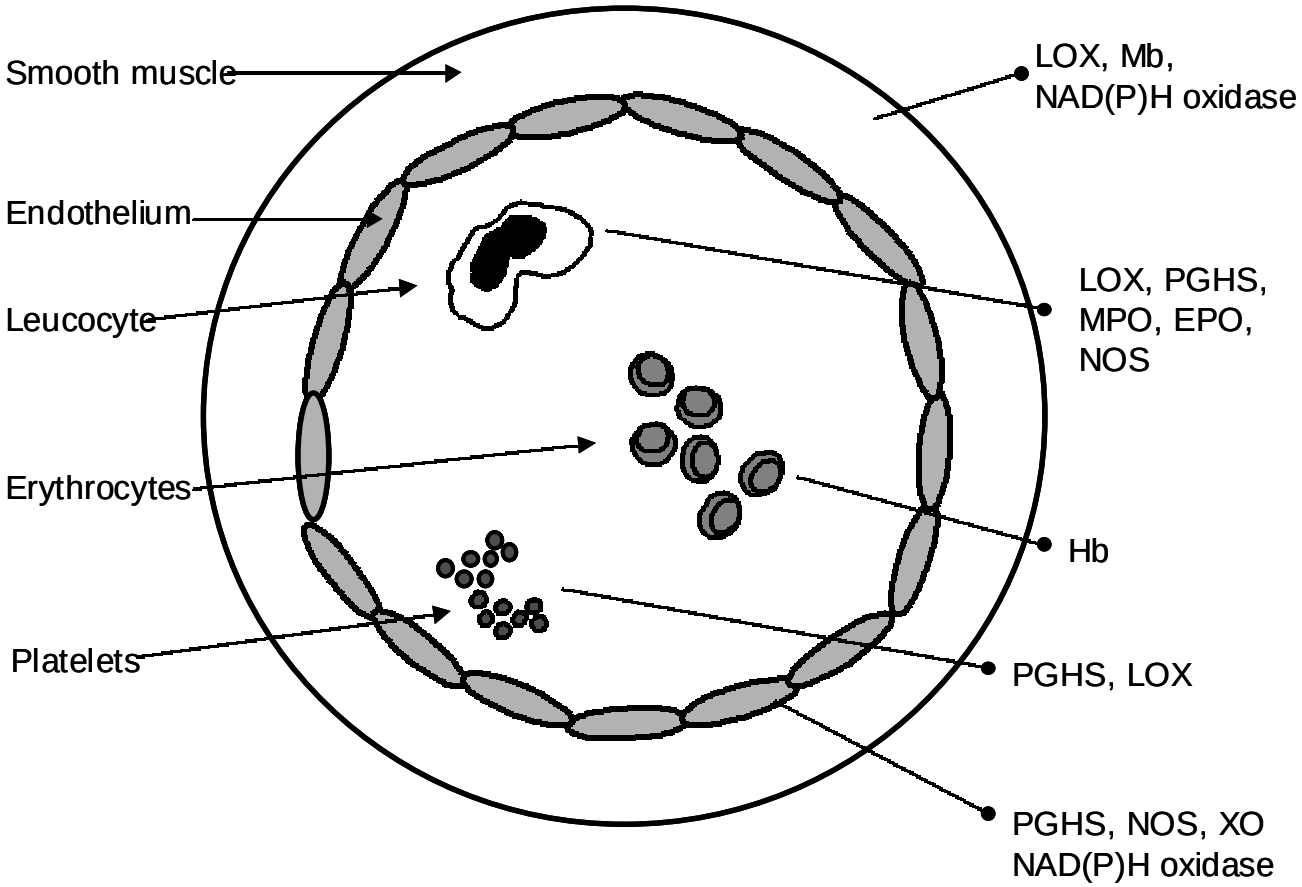
In vascular disease, impaired NO signalling through its accelerated removal, is consistently observed. For example, loss of agonist-induced vasodilatation in humans is associated with both hypertension and hypercholesterolaemia (1-3). These patients typically have elevated plasma NO metabolites, indicating that the loss of NO bioactivity is not due to decreased NO generation (4). Accelerated removal of NO results in attenuation of its vasorelaxant and anti-thrombotic activities. Also, the suppressive effects of NO on leukocyte adhesion and margination, and smooth muscle proliferation are lost. This enables progression of atherosclerosis and contributes directly to initiation of thrombosis. Under physiological conditions, oxyhaemoglobin (Hb) and oxymyoglobin (Mb) react with NO generating nitrate (NO_3^-). However, these reactions are not expected to participate in accelerated NO removal in atherosclerotic vascular disease, since the levels of Hb and Mb will be relatively unchanged.

In animal models, a role for superoxide ($O_2^{\cdot-}$), reacting with NO to yield peroxynitrite ($ONOO^-$), accounts for some, but not all, of the accelerated NO removal in vascular disease (5). This has been proposed to involve a novel "NAD(P)H oxidase" related to the phagocyte NADPH oxidase, utilising a homologue of the heme-binding gp91*phox*, termed nox1 (6). However, other studies have implicated xanthine oxidase, released from the liver and binding to the luminal membrane of the endothelium, as the source of $O_2^{\cdot-}$ (7,8). In humans however, the mechanisms have not been established, and a role for $O_2^{\cdot-}$ reacting with NO *in vivo* has not been shown. Recent work has explored the possibility that NO removal in the vasculature may occur through its reaction with free radicals formed during turnover of enzymes that are upregulated as part of the disease process. In particular, we and others have shown that 15- and 12/15-lipoxygenases, prostaglandin H synthase-1 and myeloperoxidase, enzymes that play central roles in vascular homeostasis and disease, can catalytically consume NO and impair its bioactivity in isolated human and animal vascular cells (9-12). The contribution of these processes to accelerated NO removal in atherosclerotic vascular disease has not yet been established.

Elucidating mechanisms of NO removal under both physiological and pathophysiological conditions in the vasculature is a major clinical goal. Understanding these processes will provide new therapeutic strategies for vascular disease. In this review, current knowledge regarding the candidate mechanisms of NO consumption, and their contribution to atherosclerosis and hypertension are summarised. Finally, the potential implications of restoring NO bioactivity in the vasculature will be discussed.

Superoxide generating enzymes

A role for $O_2^{\cdot-}$ in mediating NO removal in vascular disease was originally suggested by observations of angiotensin (ang) II-stimulated lucigenin-enhanced chemiluminescence in isolated cells and aortic rings (13-15). Stimulation with NADH or NADPH and inhibition by the flavoenzyme inhibitor



Scheme 1. Localisation of NO consuming pathways in the vasculature. PGHS: prostaglandin H synthase, LOX: lipoxygenase, Hb: haemoglobin, NOS: nitric oxide synthase, XO: xanthine oxidase, MPO: myeloperoxidase, EPO: eosinophil peroxidase, Mb: myoglobin

diphenyleneiodonium (DPI) led to suggestions that this activity was related to the phagocyte bacteriocidal enzyme, NADPH oxidase. However, lucigenin can generate $O_2^{\cdot-}$ in biological samples rendering this technique unreliable (16,17). Also, DPI inhibits additional flavoenzymes that generate $O_2^{\cdot-}$, including xanthine oxidase (XO) and NOS, both of which are candidate $O_2^{\cdot-}$-generating enzymes in vascular disease (see later).

While the identity of the $O_2^{\cdot-}$ generating enzyme(s) are disputed, there is still good evidence for a role of this radical in causing at least some of the NO removal in vascular disease. In particular, adenoviral infected, liposomal encapsulated- or lecithinised-superoxide dismutase (SOD) enhances relaxation in cholesterol-fed or diabetic rabbits by approximately 50% (5,18,19).

The following section will describe the most likely participants in $O_2^{\cdot-}$ mediated NO removal in vascular disease, along with the clinical evidence to date implicating these.

1. "NAD(P)H oxidases"

The neutrophil NADPH oxidase is a multi-subunit enzyme system highly expressed by phagocytic leukocytes for bacterial killing. The oxidase consists of both membrane-bound and cytosolic components which include the complex of p22*phox* and gp91*phox*, and the cytosolic proteins p67*phox*, p47*phox*, Rac2, p40*phox* and Rap1A. On phagocyte stimulation, phosphorylation of the cytosolic components causes their membrane association where they bind with p22*phox* and gp91*phox* leading to enzyme activation.

In the early 1990's, several non-phagocytic vascular cells including endothelial cells, fibroblasts and smooth muscle cells were found to express components of NADPH oxidase leading to suggestions that this enzyme was a ubiquitous source of $O_2^{\cdot-}$ (20-22). Also, ang II induces several NADPH oxidase components in non-phagocytic vascular cells, including p67*phox*, and gp91*phox*. To date, evidence for a role for non-phagocytic "NADPH oxidase" in vascular disease is conflicting (23-26). For example, when apolipoprotein E -/- mice (which spontaneously develop atherosclerosis and hypercholesterolaemia) were crossbred with p47*phox* -/- or gp91*phox* -/- mice, no alteration in macrophage infiltration or lesion development was found (25,26). In contrast, deletion of gp91*phox* abolishes the increased lucigenin-enhanced chemiluminescence seen in isolated vascular rings following *in vivo* infusion of ang II, while p47*phox* deletion attenuates hypercholesterolaemia-induced leukocyte adhesion and emigration (27,28).

In many vascular cells, only some components of NADPH oxidase are present. For example, umbilical vein endothelial cells do not possess detectable cytochrome b_{558} (20). Recently, homologs of the haem-binding gp91*phox* subunit, termed nox1 and nox4 have been identified in human vascular cells (6,29,30). These have been suggested to replace the leukocyte haem-binding subunit, reconstituting $O_2^{\cdot-}$ generation in gp91*phox*-deficient cells, although functional interactions with other NADPH oxidase subunits have not yet been shown. The non-phagocyte "NAD(P)H oxidase" utilises both NADH or NADPH with relative preference depending on cell type and $O_2^{\cdot-}$ generation assay (31). This is somewhat unusual for a pyridine-nucleotide oxidising enzyme, since most exclusively utilise either NADH or NADPH, with little or no oxidation of the other. The reasons for this lack of preference are unclear and so far, have not been resolved by enzymology studies of the gp91*phox* homologs.

2. Xanthine oxidase

Xanthine oxidase (XO) is a molybdenum, iron and flavin-containing enzyme derived from proteolysis of the hepatic enzyme xanthine dehydrogenase, that generates $O_2^{\cdot-}$ through oxidation of several substrates including NADH, pterin and xanthine. Early studies on "NAD(P)H oxidase"-dependent lucigenin chemiluminescence in vascular disease ruled out a role for XO, through lack of inhibition by allpurinol. However, it has since been shown that oxidation of NADH by XO leads to $O_2^{\cdot-}$ generation that is inhibitable by DPI, but not by allopurinol (32). This is in contrast to XO oxidation of other reducing substrates, including xanthine. Clearly, XO is a good candidate enzyme for mediating NO removal in atherosclerosis where $O_2^{\cdot-}$ generation may be stimulated extracellularly by non-pyridine nucleotide reducing substrates.

Plasma levels of XO increase following diverse tissue insults, including ischaemia-reperfusion to the splanchnic system, or following hypovolaemic shock, with further increases found following infusion of high concentrations of heparin (1,000 U/hr) (33-35). Treatment of rabbits with Allopurinol or tungsten (inactivates XO) protects against injury to lung vascular barrier function secondary to splanchnic ischaemia-reperfusion (33,36). Intriguingly, allopurinol protects against both rabbit and human myocardial ischaemia-reperfusion injury, despite several reports that these hearts have low or undetectable XO levels (37-41). Lung-associated XO rises following infusion with effluent from reperfused liver, an organ rich in XO (42). This indicates that XO can be released from tissues, circulate in the vascular system and bind to endothelium at remote sites normally devoid of activity. Observations of increased XO in the vasculature of atherosclerotic patients and cholesterol-fed rabbits, and that allopurinol can restore acetylcholine-induced relaxation of aortic rings from cholesterol-fed rabbits by 35-40% indicates that this $O_2^{\cdot-}$-generating enzyme can interfere with NO bioactivity *in vivo* (7,43,44). Vascular XO may originate either from increased local expression, or binding of plasma XO (45-47). A recent study showed that exogenous XO binds (K_d 6 nM) to cultured endothelium through interactions with chondroitin sulphate proteoglycans (8). This leads to internalisation of the enzyme, and $O_2^{\cdot-}$ generation in an intracellular compartment where it can effectively attenuate NO activation of sGC (8).

3. Nitric oxide synthase

NO is generated in mammalian cells by NOS enzymes, of which there are three isoforms. In the vasculature, NO is generated by endothelial NOS (eNOS). This constitutively-expressed enzyme produces NO in response to agonists for maintenance of vascular homeostasis. The second NOS enzyme, neuronal NOS (nNOS) is expressed mainly in neuronal cells. Nitric oxide is produced by nNOS mainly as a

neurotransmitter, but is also utilized for muscle tone regulation. The third NOS isoform, iNOS, is inducible in virtually all mammalian cells by a variety of proinflammatory stimuli. All three purified isoforms of NOS can generate $O_2^{\cdot-}$ in the absence of the essential co-factor, tetrahydrobiopterin (BH_4) (48-51). Also, NOS enzymes are "NADPH oxidases" that are inhibitable by DPI (52). Recently, evidence has emerged that BH_4 depletion may cause NOS-dependent $O_2^{\cdot-}$ generation in cultured cells and *in vivo* under certain conditions (53-55). For example, in smokers but not healthy subjects, infusion of BH_4 improves forearm blood flow (53). This suggests that NOS may be a source of $O_2^{\cdot-}$ in vascular disease.

Enzymes that consume NO *via* catalytic turnover intermediates

1. Lipoxygenases

Lipoxygenases (LOX) are non-haem iron-containing enzymes expressed ubiquitously in the vasculature that catalyse unsaturated fatty acid oxidation (56,57). Several mammalian LOX isoforms are known, including 5-, 12-, 12/15- and 15-LOXs. LOXs are named by the site of oxygen insertion into arachidonic acid (AA). For example, leukocyte-type 12/15-LOX inserts oxygen primary at C12 of AA forming 12-S-hydroperoxy-5Z,8Z,10E,14Z-eicosatetraenoic acid [12(S)HPETE] (56,58). Unique among LOXs, 12/15- and 15-LOXs can oxidise linoleate and also membrane-bound fatty acids (59). These isoforms play a central role in atherosclerotic vascular disease, since (a) their products, mRNA and protein are found in atheroma, (b) inhibition of 15-LOX in rabbits slows atherosclerosis and (c) inactivation of the 12/15-LOX gene attenuates lipid deposition in apo E-deficient mice (60-65). In addition, 12/15-LOX inactivation prevents neointimal thickening in balloon-injured rat aortae (66,67). Finally, 12/15-LOX is elevated in angiotensin (ang) II-dependent hypertension, and ang II upregulates 12/15-LOX *in vitro* via the AT_1 receptor (67-72).

15- and 12/15-LOXs can catalytically consume NO in the presence of lipid substrate, through its reaction with an enzyme-bound lipid peroxyl radical (EredLOO·). In primary porcine monocytes expressing 12/15-LOX, or fibroblasts transfected with human 15-LOX, this causes depletion of mM NO, and significantly attenuates NO activation of sGC (9,10). 12/15-LOX inhibition by non-specific inhibitors reduces blood pressure in hypertensive rats through unknown mechanisms (73-75). Observations of catalytic NO consumption in primary mammalian cells suggests a novel pro-hypertensive mechanism for LOX, although this has not yet been definitively proven *in vivo*.

2. Prostaglandin H synthase

Prostaglandin H synthase (PGHS) is a haem enzyme that catalyses the initial steps of arachidonate oxidation required for prostaglandin biosynthesis. PGHS has two distinct activities, peroxidase and cyclooxygenase, both of which are required for successful generation of prostanoids. PGHS isoforms play essential roles in the maintenance of vascular homeostasis, and the pathophysiology of vascular disease. The constitutively expressed isoform, PGHS-1 generates precursors for thromboxane biosynthesis, products that are centrally involved in promoting thrombus formation. In contrast, the formation of the anti-thrombotic mediator prostacyclin in the healthy vasculature predominantly requires PGHS-2 turnover (77-81). In vascular disease, significantly elevated levels of metabolites from both isoforms are found (82-85).

The potent anti-thrombotic effects of aspirin *in vivo* indicate a central role for PGHS in promoting fatal vascular events (86,87). With clinically utilised regimens, aspirin selectively inhibits PGHS-1, since it is exclusively localised in enucleated platelets. The low half life of aspirin *in vivo* (20 min) allows nucleated cells to re-induce PGHS-2, resulting in a virtually complete inhibition of thromboxane synthesis, with little or no effect on prostacyclin.

It has long been assumed that the effects of PGHS on vascular function are mediated solely through the bioactivity of its prostanoid products, however this is not clearly established. For example, inhibiting thromboxane receptor signalling does not alter blood pressure in spontaneously hypertensive rats (88). We have recently shown that PGHS-1 can catalytically consume NO through peroxidase turnover, with NO acting as a reducing substrate. In human platelets, this prevents activation of sGC attenuating the anti-thrombotic effects of NO (11). Catalytic NO consumption by PGHS-1 thus represents a novel pro-thrombotic function for this enzyme and may provide an explanation for the restoration of agonist-induced vasodilatation by aspirin previously observed by several studies (89-90).

3. Haem peroxidases: myeloperoxidase and eosinophil peroxidase

Myeloperoxidase (MPO) and eosinophil peroxidase (EPO) are abundantly expressed peroxidases in phagocytic leukocytes, with MPO comprising up to 5% of total neutrophil protein (92). Classically their role has been considered one of host defence, generating hypochlorite (HOCl) from hydrogen peroxide (H_2O_2) and chloride (Cl^-) (93,94). Similar to PGHS, purified MPO and EPO catalytically consume NO as a reducing peroxidase substrate (12,95). This reaction may play a role in host defence responses when both high levels of neutrophil activation and NO generation co-exist. For example, incubation of purified MPO with either aortic or bronchial rings attenuates NO signalling *in vitro* (96,97).

Conclusions

Loss of NO bioactivity is a hallmark of atherosclerotic vascular disease. Current research has identified several pathways that can catalyse NO removal in vascular cells, and work is now in progress to identify which of these are responsible for NO removal *in vivo*. Due to the multifactorial nature of atherosclerosis, it is likely that more than one will be simultaneously involved, depending on stage and type of disease, and also the level of associated inflammation.

A major question remains as to whether restoration of NO bioactivity *in vivo* will be vascular protective. Increasing NO bioactivity through L-arginine supplementation has been successful at restoring vascular function in hypercholesterolaemic rabbits (98-100). In humans, results have been mixed, with i.v. L-arginine infusion acutely improving coronary vasodilatation, but being without effect on microvascular endothelial function in hypercholesterolaemic patients (101). NO plays a major homeostatic role *in vivo* through attenuating leukocyte and platelet activation, and preventing smooth muscle proliferation. It is likely therefore that any restoration of NO bioactivity in atherosclerosis will be of benefit. Currently, clinical inhibitors for the pathways so far implicated are limited to aspirin (and other PGHS inhibitors) and allopurinol. Aspirin undoubtedly has beneficial effects *in vivo* that are consistent with preserving vascular function, although its ability to restore NO bioactivity has not been examined in detail. Finally corresponding studies on allopurinol have not been reported.

In summary, loss of NO bioactivity is likely be a causative factor in both the development of atherosclerosis and the acute thrombotic events that occur in advanced disease. It is likely that strategies designed to prevent NO loss and restore its signalling will become of major importance in the fight against this devastating condition, and its associated pathologies.

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Valerie B. O'Donnell is a Wellcome Trust RCD Lecturer at the Wales Heart Research Institute, University of Wales College of Medicine, Cardiff.

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Review Articles for *The* Bulletin

Would you like to write a review for the BSCR Bulletin? Review articles are an opportunity to let members know about your partiular research area and also provide an overview of the current 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@ucl.ac.uk) or Nicola (N.Smart@ich.ucl.ac.uk)

Secretary's Column

In May this year I received six nominations for election to membership of the Committee from January 2002. A postal ballot of members was held during the summer. Eighty-seven ballot papers were returned by the due date (17 August) and a total of 260 votes were cast as follows:

Gavin Brooks	52
Gillian Gray	53
Hugh Montgomery	24
Ajay Shah	59
Saadeh Suleiman	39
Peter Weinberg	33

Since there are four vacancies, Professor Shah, Dr Gray, Dr Brooks and Dr Suleiman have been elected to serve for the period 1 January 2002 to 31 December 2004. Formal announcement of the election result was made at the Society's Annual General Meeting in Oxford on 14 September. I would take this opportunity to congratulate the successful candidates and to thank all of them for so generously allowing their names to go forward for election. Great strengths of the Society are the diversity of its membership and the democratic processes by which the Society's course is steered.

The Society's Spring meeting is due to take place at the University of Reading on 11-12 April 2002. Organised by Dr Gavin Brooks and Dr Michael Shattock, the subject is "Ion Channels and Transporters in Cardiovascular Cell Growth". As usual, I would urge interested members to register in good time for this meeting.

Although the society ran two very successful workshops this year (one in Liverpool on QT interval and the other in Bristol on mitochondrial function) there are presently no workshop proposals for the 2002 calendar year. Could I remind you that the Society is willing to consider proposals for one day workshops on any suitable topic. If the prospect of organising a full two day meeting in your research field is too daunting, why not consider organising a small workshop, with the aim of getting together 20-30 interested people to discuss a more focused research problem? BSCR workshops play a key role in the Society's mission and have always been extremely popular with both organisers and members. Please do consider submitting proposals for workshops to me or any Committee member.

With this column, my last as secretary, I take the opportunity to say farewell to the many members of the Committee I have worked with during the last six years, first as an ordinary committee member and then as Secretary. First of all, I would like to pay tribute and public thanks to Andrea Burdus who has assisted me so reliably and cheerfully in the day-to-day office tasks such as agenda- and minute-typing and Bulletin-mailing. I am fortunate also to have had such personable and dependable colleagues on the Committee and I am especially grateful to Chairman Metin Avkiran and Treasurer Michael Curtis. I would also single out the Treasurer's assistant Tony Cavalheiro who has made a superb job of managing the Society's database. Tony is the very paragon of organisation. I have been fortunate, too, in working closely with kind and sympathetic Bulletin Editors. When copy deadlines drew near and then passed, their indulgence and patience have been exemplary! Thanks are due then to Nicola and Helen and to their predecessor, James Mockridge.

As I mentioned in my previous column, I am handing over the reins with great confidence to Dr Barbara McDermott in Belfast. She and I will be working closely during the next few months to ensure a seamless transfer of functions and I have the pleasant prospect of rounding off my term of office with a trip to Belfast to transfer the Society's key documents and paperwork. I am grateful to have received the confidence of members when they elected me to the Committee in 1995 and it has been a singular privilege for me to serve the BSCR as Secretary.

Gary F Baxter

Cardiovascular Related Meetings

American Heart Association ***Scientific Sessions 2001*** will be held in Anaheim, California, November 11-14. Further Information: Telephone 214/706-1543; Fax 214/706-5262 E-mail: sessions@heart.org http://www.scientificsessions.org/

The Eighth International Symposium on Adenosine, Cardioprotection and Its Clinical Application. 'Adenosine Receptors, Physiologic Actions and Its Clinical Applications'. November 10, 2001 (Just prior to the A.H.A. meeting in Aneheim) H.M.S. Queen Mary Long Beach CA. Buses will run from the conference site to the convention center after the conference. Contact Robert M. Mentzer, Jr., MD in Lexington, KY Tel: (859) 323-6013, Fax: (859) 323-1045. mentzer@pop.uky.edu

22nd Annual Meeting of the ISHR - European Section, Szeged, Hungary, July 3-6, 2002. For further details, contact Prof. Dr. Ágnes Végh, University of Szeged, Faculty of Medicine, Department of Pharmacology and Pharmacotherapy, Dóm tér 12. H-6720 Szeged, Hungary. Tel: +36-62-545-673 Fax: +36-62-544-565, E-mail: vegh@phcol.szote.u-szeged.hu. Web Site: http://www.cardiovasc.com/ishr2002/

The Failing Heart: From molecular mechanisms to clinical applications A satellite symposium to the 22nd annual meeting of the European Section of the ISHR, will be held at Stara Lesna, the High Tatras Slovak Republic (Dr. J. Styk, Chairman). Further information about the Meeting is available from Dr. Tanya Ravingerova, Secretariat, Institute for Heart Research,Slovak Academy of Sciences, Dubravska cesta 9, 84233 Brataslava, SlovakRepublic usrdravi@savba.savba.sk tel+4217 5477 4405, FAX +4217 5477 6637 http://nic.savba.sk/sav/inst/usrd/usrdconfer

Translational Approaches to Cardiovascular Disease, the 24th Annual Meeting, ISHR, North American Section, will be held in Madison, Wisconsin, July 24-27, 2002. The abstract deadline is February 1, 2002. Organizer: Richard L. Moss, Ph.D., Director, UW Cardiovascular Research Center, Professor and Chair, Department of Physiology, Telephone: 608-262-1939, Fax: 608-265-5072, email: rlmoss@physiology.wisc.edu

NewEra Cardiac Care 2002, January 4-6, 2002, St. Regis Monarch Beach, Dana Point, CA Program Co-Chairs: W. Randolph Chitwood MD & Mehmet C. Oz MD Rregistration: Aligned Management Associates, Inc.,1835 South Centre City Parkway, PMB 513, Escondido, CA 92025 U.S.A. Phone - 760.839.1200 Fax - 760.839.1250 Email - newera@amainc.com

The 22nd Annual San Diego Cardiothoracic Surgery Symposium: Pathophysiology and Techniques of Cardiopulmonary Bypass: February 21 - 23, 2002 San Diego Marriott Hotel & Marina, San Diego, California Course director: Julie A. Swain MD. Information: Aligned Management Associates, Inc. South Centre City Parkway, PMB 513, Escondido, CA 92025 U.S.A., Phone - 760.839.1200, Fax - 760.839.1250 1835 cref@amainc.com

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

Travel Reports for *The* Bulletin

The Bulletin regularly publishes travel reports written by members. These are up to 3 pages in length including 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!

BSCR Bulletin Book Review: Mitochondria and Cell Death

Edited by G.C. Brown, D.G. Nicholls and C.E. Cooper
Portland Press, London 1999 £65.00 ISBN 1 85578 125 5

reviewed by Nicola Smart, Molecular Medicine Unit,
Institute of Child Health

Mitochondria and Cell Death is derived from the July 1998 Biochemical Society Symposium held at the University of Sheffield. Interest in this field of research has recently flourished since mitochondria were implicated in apoptosis, ageing and a wide variety of disease conditions. With the wealth of recent literature, an overview of mitochondria and their role in cell death is timely. In this respect, the book fulfils the role of providing a synopsis of "all you need to know" about mitochondria. It would be particularly useful for the many non-specialists who have found that their areas of research have suddenly become mitochondria-orientated. However, the book assumes a considerable level of prior knowledge and understanding, but most chapters are well referenced for this purpose. My main criticism of the book is that some points, in my view, could have been more clearly explained.

The book addresses the key areas of current mitochondrial research, namely: i) mitochondrial permeability transition; ii) apoptosis; iii) excitotoxicity and neurodegenaration; iv) mitochondrial DNA diseases; v) free radicals and nitric oxide and vi) hypoxia/ ischaemia. Whilst some chapters focus on individual aspects of mitochondrial physiology, others integrate multiple aspects, usually in the context of a pathophysiological condition (notably sepsis, ischaemia, ageing and neurodegenaration).

The first chapter sets the scene by summarising the involvement of mitochondria in apoptosis. An outline of the basic principles of mitochondrial physiology would be expected in the opening chapter of a book such as this and its omission presumably reflects the nature of the symposium. As a book in its own right, *Mitochondria and Cell Death* would be infinitely improved by the inclusion of a more comprehensive introduction.

The key players in apoptosis are introduced in the earlier chapters: nitric oxide (chapters 2 and 5), ceramide (chapter 3) and calcium cycling (chapters 4, 6, 13 and 14). Their role in activating the apoptotic machinery and, in particular in effecting cytochrome C release, is addressed in some detail. The common themes and differences between apototic and necrotic cell death are discussed in chapter 7, a chapter which complements the introductory chapter and could possibly have been combined as one, especially as both are disappointingly short.

The mitochondrial permeability transition pore (MPTP), central to all aspects of cell death is elegantly described in chapters 15,16 and 17 by the experts in MPTP research, Martin Crompton (chapter15) and Andrew Halestrap (chapter 16). Chapter 17 (by J. J. Lemasters) stands out as the most useful for those wishing to start experimental work studying mitochondrial function. It beautifully describes a range of approaches for the use of confocal microscopy to study various mitochondrial parameters, for example, membrane potential and calcium concentration.

Much attention is devoted to discussion of the role of mitochondria in neurodegeneration (chapters 5, 6, 8, 9 and 10, with chapter 9 focussing on Parkinson's disease). This reflects not only the importance of this area of research, but also that excitotoxicity remains one of the main models for the study of mitochondrial function.

The order of the chapters is not ideal, presumably as they reflect the order of the talks at the Symposium. As an example, chapter 8, which introduces MPTP is separated by 6 unrelated chapters from the other 3 chapters on MPTP. The editors and authors have, however, suitably cross-referenced between chapters.

For the interested researcher, the book represents a wealth of current knowledge by many leaders in the field. Much of the information remains up-to-date, despite the passage of time since the symposium; however, this will certainly change over the coming years, now that a growing number of researchers are studying mitochondria. Since the majority of chapters are highly specialised, this is not a book for the average undergraduate, or indeed anyone without a reasonable background knowledge

BRITISH HEART FOUNDATION GRANTS

Chairs and Programme Grants Committee, June 2001

Programme Grants

Prof J E Deanfield et al, Great Ormond Street Hospital, London "Genetic and environmental influences on the atherogenic phenotype in the young: a population based study" (5 years) £762,751

Prof S Salmons et al, University of Liverpool "Conditioned skeletal muscle ventricles for permanent cardiac assistance" (3 years) £421,580

Prof N J Samani et al, University of Leicester "Genetic regulation of arterial pressure of humans in the community: The GRAPHIC study" (4 years) £594,442

Prof M L Rose & Dr M J Dunn, Harefield Hospital, Middlesex "Role of endothelial cells in graft vasculopathy following cardiac transplantation" (3 years) £547,973

Prof P J Scambler, Institute of Child Health, London "Analysis of the developmental, genetic and biochemical basis of the congenital heart defects associated with deletion 22q11 syndrome" (5 years) £955,760

Prof P H Sugden & Dr A Clerk, National Heart & Lung Inst, London "Modulation of cardiac myocyte growth and death by oxidative stress: a proteomics approach" (5 years) £562,320

Prof D C Crossman, Northern General Hospital, Sheffield "An investigation of the effects of IL-1 and endothelial cell IL-1 receptor antagonist upon the vessel wall response to injury and atherogenesis" (5 years) £926,992

Basic Science Lectureships

Dr A J Workman, Royal Infirmary, Glasgow "Atrial fibrillation-induced remodelling of ion currents and mRNA levels in the human atrium" (5 years) £229,424

Dr C S Redwood, University of Oxford "Functional analyses of novel classes of mutations in thick filament proteins that cause hypertrophic cardiomyopathy" (5 years) £281,526

Dr D O Bates, University of Bristol "Vascular endothelial growth factor, microvascular permeability and angiogenesis" (5 years) £235,250

Project Grants Committee, July 2001

DEFERRED APPLICATIONS AWARDED

Dr S J Mitchinson & Prof N Standen, University of Leicester "Regulation of HERG and IKr channels by intracellular second messengers" (3 years) £106,492

Dr P A Swift & Prof G MacGregor, St George's Hospital Medical School, London "Double blind, randomised controlled crossover trial comparing the antihypertensive effects of amiloride and spironolactone in black hypertensives with and without the T594M mutation" (2 years) £89,744

Dr D Carling, Hammersmith Hospital, London"Characterisation of AMP-activated protein kinase in heart: role of the γ2 subunit in the development of arrhythmia and cardiac hypertrophy" (3 years) £77,163

Dr A W Trafford, University of Manchester "The regulation and role of cardiac collagen turnover in the progression of left ventricular hypertrophy and heart failure" (3 years) £163,936

Dr S A M Thom et al, St Mary's Hospital, London "Relationship between mechanical forces and wall thickening in femoral bypass grafts – a combined clinical and numerical simulation study" (2 years) £172,747

NEW APPLICATIONS AWARDED

Professor J Cleland & Dr A Clark, Castle Hill Hospital, Kingston-upon-Hull "What is the role of stress-echocardiography and colour Doppler myocardial imaging in the evaluation of patients with suspected heart failure" (2 years) £53,478

Dr M Hillsdon et al, London School of Hygiene & Tropical Medicine "A systematic review of physical activity interventions for adults" (1 year) £24,449

Professor R Hainsworth et al, University of Leeds "Could nocturnal baroreceptor resetting protect against hypertension? Studies in normal subjects, hypertensives and patients with sleep disordered breathing" (2 years) £63,749

Professor A M Lever et al, University of Cambridge"Lentivirus based gene delivery to cardiac tissue" (2 years) £146,433

Dr M A Laffan, Hammersmith Hospital, London"The mechanism of thrombophilia in patients with elevated factor VIII" (2 years) £107,910

Professor M R Bennett & Mr A J Ritchie, Addenbrooke's Hospital, Cambridge "Mechanism of cell senescence in atherosclerosis" (3 years) £140,520

Dr A Dorling, Hammersmith Hospital, London "Transplant accommodation, a paradigm of acquired resistance against vascular inflammation – defining the factors initiating the protective response" (3 years) £157,888

Dr J H Walker & Dr S Ponnambalam, University of Leeds "Cytosolic phospholipase A2 in the human endothelial cell line EA.hy.926 – regulation by association with specific binding proteins" (2 years) £66,032

Mr T J Spyt et al, Glenfield Hospital, Leicester "Use of pulmonary vein isolation by radiofrequency ablation to reduce atrial fibrillation after mitral valve surgery-randomised prospective assessment" (2½ years) £115,476

Dr S E Harding et al, National Heart and Lung Institute, London "Functional effects of $Na^+/Ca2^+$ -exchanger overexpression in adult cardiomyocytes" (2 years) £34,762

Professor T S J Elliot et al, Queen Elizabeth Hospital, Birmingham "Serodiagnosis of bacterial endocarditis" (3 years) £142,654

Professor C C Ashley & Dr I P Mulligan, University of Oxford "Mechanism of action of calcium sensitizers" (3 years) £99,776

Dr N G MacFarlane, University of Glasgow "Inspiratory muscle fatigue in chronic heart failure" (2 years) £89,896

Dr A J Hobbs & Dr R J MacAllister, University College London "Regulation of cardiovascular homeostasis via interplay of soluble and particulate guanylate cyclases" (3 years) £110,585

Dr J Wharton & Prof MR Wilkins, Hammersmith Hospital , London "Role of phosphodiesterase enzymes in regulating cyclic nucleotide signalling and growth of human pulmonary artery smooth muscle cells" (3 years) £137,144

Dr C E Austin, Manchester Royal Infirmary, Manchester "Influence of extravascular pressure on isolated coronary artery reactivity" (1 year) £42,202

Fellowships Committee, July 2001

Intermediate Research Fellowships

Dr C F Lawson & Prof M L Rose, Harefield Hospital, Middlesex "Molecular analysis of ICAM-1: a multi-functional molecule" £134,544

Dr E M Diaz & Prof D A Eisner, University of Manchester "What causes the heterogeneity of the systolic Ca release in isolated cardiac ventricular myocytes: the effects of inotropic manoeuvres" £128,410

Junior Research Fellowships

Dr S Robinson, Dr D E Newby & Dr N A Boon, Edinburgh Royal Infirmary "Influence of genetic factors on the impaired release of tissue plasminogen activator in cigarette smokers" £72,700

Dr M Westwood, Dr D Pennell, Dr J M Walker & Dr B Wonke, Royal Brompton Hospital, London "Assessment of myocardial iron using magnetic resonance T2* relaxometry: optimisation of chelation therapy in thalassaemia for prevention of cardiac mortality" £96,357

Dr S Chia, Dr D E Newby & Prof K A A Fox, Edinburgh Royal Infirmary "Effects of inducible nitric oxide synthase on vascular function in inflammation and heart failure" £56,261

Dr T Stanton, Prof J M C Connell & Prof A F Dominiczak, Western Infirmary, Glasgow "Genetic determinants of left ventricular mass - the role of beta-1 adrenoceptor variation" £101,237

Dr A Quraishi, Prof W J McKenna & Dr D J Pennell, St Georges' Hospital Medical School, London "Cardiovascular magnetic resonance (CMR) features of arvc in probands and the diagnostic sensitivity of these features in asymptomatic first degree relatives" £85,548

Dr M S Mussa, Dr K M Channon & Mr D Taggart, John Radcliffe Hospital, Oxford "Endothelial and smooth muscle function in the human radial artery: rational approaches to prevent vasospasm in radial artery coronary bypass grafts" £85,470

PhD Studentships

Mr B Shortt & Dr Smythe, University of Dundee "Regulation of clathrin-mediated endocytosis by phosphorylation" £61,155

Ms F I Marques & Dr Bhattacharya, University of Oxford "Control of cardiac development by p35srj" £65,860

Mr R J Potepa & Dr D P Ramji, Cardiff University "The role of the phosphatidylinositol-3-kinase signal transduction pathway in the regulation of macrophage lipoprotein lipase (LPL) gene expression" £61,209

Mr P H Milliken & Prof R Wadsworth, University of Strathclyde, Glasgow "Modulation and role of superoxide dismutase in pulmonary hypertension" £1,582

Ms N Strudwick & Prof N B Standen, University of Leicester "Fluorescence imaging studies of cellular correlates of ischaemic cardioprotection and K_{ATP} channel function in rat isolated ventricular trabeculae" £61,318

Unnamed, Dr J S Lymn & Prof A D Hughes, St Mary's Hospital, London "Mechanism of regulation of phospholipase C delta in vascular smooth muscle. The role of tissue transglutaminase II/ Gh. £66,502

Mr M S Crane, Dr I L Megson & Dr A G Rossi, University of Edinburgh "A study of the cGMP-independent effects of conventional and novel nitric oxide donor drugs in human platelets" £61,055

Unnamed, Prof M C Sugden & Prof P H Sugden, Queen Mary & Westfield College, London "Role of the GLUT1 glucose transporter and the ERK cascade in the cardiac response to hyperglycaemia. Significance for cardiac failure in the insulin resistance syndrome" £65,682

Ms D Balaska, Dr E J Griffiths &Dr M S Suleiman, University of Bristol "Developmental response of isolated myocytes to ischaemia/reperfusion injury: basic mechanisms and design of protective strategies" £52,140

Miss C W L Tam & Prof S Brain, King's College, London "CGRP-related peptides: release and receptors-mediated vasodilatation in the normal and genetically altered mouse" £74,557

Unnamed & Prof A Ahmed, University of Birmingham "Study of angiopoietin-tie2 signalling in endothelial and trophoblast cells" £61,645

Ms S J Dolling, Prof P J Grant, Dr B I Hudson & Dr A M Carter, Leeds General Infirmary" Characterisation of the transcriptional regulation of genetic variants of the receptor for advanced glycation end-products" £61,702

Miss S B Withers, Dr J Armstrong & Dr C M Holt, University of Manchester "Identification of the mechanisms involved in the induction of apoptosis following dyregulation of c-*myb*" £60,960

Ms F Barnes, Prof M K B Whyte, Dr C D Bingle & Prof D C Crossman, Royal Hallamshire Hospital, Sheffield "Modulation of endothelial cell lifespan and function by the Bcl-2 protein, Mcl-1" £61,305

PhD Studentships (Clinical)

Dr N Kukreja & Dr S E Harding, National Heart & Lung Institute, London "Dual coupling of the β2-adrenoceptor to stimulatory and inhibitory G-proteins in failing human heart: implication for beta-blocker therapy" £162,720

Dr R E Harrison & Prof R C P Trembath, University of Leicester "BMPR2 promoter cloning and molecular functional characterisation in primary pulmonary hypertension" £137,959

Dr I J Nadra, Dr R C Landis & Prof D O Haskard, Hammersmith Hospital, London "Effect of macrophage differentiation on the vascular inflammatory response to hydroxyapatite crystals" £151,660

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
15(1)	*Jan. 2002*	*Dec. 1st*
15(2)	*April 2002*	*March 1st*
15(3)	*July 2002*	*June 1st*
15(4)	*Oct. 2002*	*Sept. 1st*

Cardiovascular Related Wellcome Trust Grants

June 2001 to July 2001

Project Grants

Dr Susanna M O Hourani, School of Biological Sciences, University of Surrey, Guildford. Cardiovascular responses to adenosine in genetically-modified mice lacking the adenosine A2A receptor. 16 months £8,238

Dr A W Poole, Department of Pharmacology, School of Medical Sciences, University of Bristol.The role of the protein tyrosine phosphatases Shp-1 and Shp-2 in ITIM signalling in platelets. 36 months £136,246

Prof Thomas B Bolton, Department of Pharmacology & Clinical Pharmacology, Jenner Wing, St George's Hospital Medical School London. Functional and morphological investigations of ICC-like cells found in rabbit portal vein. 36 months £248,703

Prof A J S Coats, Department of Cardiac Medicine, Imperial College School of Medicine, National Heart & Lung Institute, London. Pathophysiology and treatment of the decreased ventilatory efficiency in patients with chronic heart failure. 18 months £82,073

Prof Michael S Marber, Department of Cardiology, Rayne Institute, St Thomas' Hospital, King's College London. The use of expression cloning to identify genes that increase myocardial resistance to ischaemia. 36 months £254,827

Prof Daniel S McQueen, Department of Neuroscience, University of Edinburgh, Scotland. Sensory innervation of blood vessels: physiological role in cardiorespiratory regulation and pharmacological characterisation. 18 months £95,865

Prof N Joan Abbott, Centre for Neuroscience Research, GKT School of Biomedical Sciences, Kings College London. Brain endothelial ion transport at the blood-brain barrier: molecular and cellular mechanisms of glial induction. 36 months £286,555

Dr H S Fraser, Department of Medicine & Clinical Pharmacology, Chronic Disease Research Centre, University of The West Indies, Bridgetown Barbados.The incidence & outcome of stroke in black Caribbean populations in Barbados and south London. 24 months £155,034

Prof David S Latchman, Institute of Child Health, London. Role of caspase-8 and caspase-9 in ischaemia/reperfusion-induced injury in the intact heart. 3 years £277,670

Dr Margaret D Brown, School of Sport & Exercise Sciences, University of Birmingham. Haemodynamics and remodelling in the microcirculation of skeletal muscle after chronic flow reduction. 1 year £61,966

Dr B Therese Kinsella, Dept of Biochemistry, University College Dublin, Eire. Investigation of the differential roles of alpha and beta isoforms of the human Thromboxane A_2 Receptor in prostacyclin and nitric oxide (NO) regulated vascular hemostasis. 3 years £166,110

Dr C M P Rees, Nuffield Dept of Obstetrics & Gynaecology, John Radcliffe Hospital, University of Oxford. Adrenomedullin, calcitonin receptor-like, receptor activity modifying proteins and endometrial angiogenesis. 3 years £150,215

Prof M R Duchen, Dept of Physiology, University College London. Mechanisms of cardioprotection by mitochondrial ATP-dependent K+ channel. 3 years £14,865

Health Services Research Projects Grant

Dr Steven M Thomas Sheffield Vascular Institute, Northern General Hospital Sheffield. Cost effectiveness of fast track diagnostic services for stroke or threatened stroke. 12 months £59,066

Training Fellowships For Medical & Dental Graduates

Dr Javed Ehtisham, Wellcome Trust Centre For Human Genetics, Henry Wellcome Building of Genomic Medicine, University of Oxford. Genetic modifiers and phenotypic variation in hypertropic cardiomyopathy. 36 months £141,948

Four Year Phd Studentships

Ms Alison D McNeilly, Molecular Physiology Laboratory, Wilkie Building, University of Edinburgh Medical School, Scotland. Cardiovascular Research Initiative 4 yr PhD programme.48 months £72,114

Miss Catherine Shaw, Molecular Physiology Laboratory, Wilkie Building, University of Edinburgh Medical School, Scotland.Cardiovascular Research Initriative 4 yr PhD programme.48 months £72,114

International Prize Travelling Research Fellowships

Miss Linda Connelly, Department of Molececular & Medical Pharmacology, School of Medicine, University of California, Los Angeles, USA. Physiological and pathophysiological autoregulatory mechanisms governing nitric oxide signalling. 24 months £19,416

Dr H B Rossiter, Intracellular determinants of the angiogenic (vascular endothelial growth factor) gene response in skeletal muscle during exercise in health, ageing and chronically O_2-delivery-limited humans. 24 months £63,839

Dr Syed E A Haq, Molecular Cardiology Research Institute, Tufts University, New England Medical Centre, Boston, USA. The role of beta-catenin in cardiomyocyte hypertrophy. 24 months £15,330

International Research Development Awards

Dr S Kantachuvesiri, Department of Medical & Radiological Science, Medical School, University of Edinburgh, Scotland. Fine mapping of congenic regions in rats and characterisation of genetic polymorphisms of the rat ACE gene that contributes to malignant hypertension.36 months £7,269

Why Not Organise a BSCR Meeting or Workshop?

The most recent meetings of the BSCR were*Apoptosis in the Heart. Signalling, Mechanisms, Pathology and Protection* at St Thomas' Hospital, London (March 2001) and *Magnetic Resonance in Cardiovascular Research*at Oxford University (September 2001). A workshop entitled*Mitochondria and myocardial protection - from single cells to cardiac surgery*was recently held at the Bristol Heart Institute (September 2001). The format for BSCR events can range from a small gathering with a few speakers to a full meeting, as above. Please discuss your ideas with the BSCR Secretary Dr Gary Baxter (Tel.: 020 7380 9888/9881) or another Committee member in the first instance.

Grants of up to £1,000 are available for organising a Workshop, and £8,000 for a Meeting.

BSCR Spring Meeting 2002

ION CHANNELS AND TRANSPORTERS IN CARDIOVASCULAR CELL GROWTH

Dates: 11th and 12th April, 2002
Venue: : The University of Reading, Reading, Berkshire
Organisers: Gavin Brooks (Reading) and Michael J Shattock (KCL, London)

Meeting outline: the subject of how ion channels and transporters regulate, or themselves are regulated by, cellular growth processes in the cardiovascular system is of significant interest currently both from a basic science and a commercial viewpoint. This meeting aims to bring together scientists from the areas of ion channels, signal transduction and growth control in the cardiovascular system. The subject matter of this meeting is designed to target a broad range of cardiovascular researchers who have interests in cellular, molecular and electrophysiological aspects of normal and pathological cardiovascular cell growth.

Invited Speakers will include: Sir Michael Berridge (Cambridge), Jeffrey Molkentin (Cincinnati, USA), Karin Sipido (Leuven, Belgium), Metin Avkiran (London), Gary Baxter (London), Gavin Brooks (Reading), Lucie Clapp (London), Max Lab (London), Ken MacLeod (London), Oscar Petersen (Liverpool), Michael Shattock (London), Godfrey Smith (Glasgow), Michael Whitaker (Newcastle)

Communications: Part of this meeting will be devoted to the presentation of posters. Abstracts, on any relevant topic, are welcomed. **Abstract deadline: 28th February 2002.**

Travel & Accommodation: Reading is ideally situated for travel by car, rail, bus or air. Further details are available from the organisers. Accommodation will be available in Halls of Residence or local hotels.

Registration: Free to BSCR members, £50 for non-members. For further information contact: Gavin Brooks, School of Animal and Microbial Sciences, The University of Reading, PO Box 228, Whiteknights, Reading, Berkshire, RG6 6AJ. Tel: 0118-931-6363; Fax: 0118-931-6562; E-mail: g.brooks@reading.ac.uk. Deadline for registration is 15th March 2002.

Bursaries: The Society will consider awarding travel grants of up to £150 to *bona fide* PhD students. Application forms are available from Dr Gary Baxter at the address below.

Applications for membership and student bursaries are available from Dr Gary Baxter, Secretary of the BSCR, The Hatter Institute for Cardiovascular Studies, University College Hospital, Grafton Way, London WC1E 6DB.