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Contents

Editorial

Welcome to the October 2002 issue of *The* Bulletin!

Our review article for this issue, '*Infections and Atherosclerosis: Role of Heat Shock Proteins*' has been written by members or Professor Qingbo Xu's group at Department of Cardiological Sciences, St. George's Hospital, London.

In the Secretary's Column, Dr Barbara McDermott announces the result of the recent election of Committee members. We congratulate the successful cadidates and look forward to working with them from next year.

After it's postponement from last September, a successful "Autumn 2001" meeting of the Society was held in Oxford earlier this year and an interesting account of the proceedings has been provided by Andrew Murray.

We always look forward to hearing of your travels and we are especially keen to receive a report from anyone attending the American Heart Association meeting in Chicago. This is an ideal opportunity to raise money towards your travel costs. If you are interested in writing on this, or any other cardiovascular meeting, please contact us before you travel.

Finally, may we draw your attention to the request on page 16 for BSCR members to inform us of their current e-mail addresses. We feel this would be of considerable use in improving communication with society members and will facilitate discussion of society issues.

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)

Infections and Atherosclerosis: Role of Heat Shock Proteins

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Current research is postulating infections or pathogen burden as a novel risk factor for the progression of atherosclerosis. While the mechanism of infection contributing to the pathogenesis is not clear, we hypothesise that heat shock protein (HSP) may serve as a link between infections and atherosclerosis (**Figure 1**). HSPs are a highly conserved family of proteins expressed in most cell types and have been shown to play a general role in protecting the cells in response to stress. The co-existence of chlamidial and human HSP60 in atherosclerotic lesions has been demonstrated . They have been found in soluble form in the general circulation of patients with atherosclerotic lesions. Both HSPs can stimulate cells expressing adhesion molecules and proinflammatory cytokines. Certain organisms are capable of synthesising HSPs, which have close structural homology with human HSPs. Because human HSPs have been detected on the surface of endothelial cells in the arterial wall, HSP60 could be a putative autoantigen involved in eliciting cell-mediated and humoral immune responses against the vessel wall causing vessel injury and leading to atherosclerosis. The aim of the article is to provide a synopsis on the involvement of infections in the pathogenesis of atherosclerosis with emphasis on the role of HSPs as potential mediators/ inducers of atherosclerosis.

Introduction

Atherosclerosis is a chronic, multi-factorial, degenerative disease characterised by continuous lipid deposition, fibrous cap formation and smooth muscle proliferation within the intima, which is regarded as an inflammatory disease[1;2]. Current research has demonstrated the expression of adhesion molecules on the endothelium including intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and E-selectin, which have a role in atherogenesis. Furthermore, detection of cytokines, activated T lymphocytes, macrophages and HLA class II antigen expression have revealed immune mechanisms in atherogenesis[3-6),(7]. Inflammatory cells constitute the majority of cells in early lesions (intimal xanthomas)[8].

There is growing evidence that microorganisms can play a role in the pathogenesis of atherosclerosis and coronary artery disease (CAD) and may be a primary risk factor in people who do not suffer from other established risk factors for CAD. Components of intracellular pathogens such as *C.pneumoniae* and cytomegalovirus (CMV) have been implicated, as have certain strains of *H.pylori*. It has been proposed that immune reactions (cell-mediated and humoral) to these organisms within the arterial wall results in endothelial damage via autoimmune reactions[6]. Microorganisms exhibit a wide variety of antigens one of which is HSP60. These proteins (also known as stress proteins) belong to a group of approximately two dozen proteins and cognates possessing high amino acid sequence homology between different species from prokaryotes to humans[9]. HSPs are highly expressed in cardiovascular tissues and induce inflammatory responses, possibly as autoantigens, in atherogenesis[10;11]. This review will provide an overview on the role of HSPs in infections and atherosclerosis as depicted in **Figure 1**.

Heat shock proteins and HSP expression

The HSP family of proteins are subdivided into groups based on their molecular weight (e.g. HSP60 is a 60kDa protein) and are produced by almost all cells and play an important role in the organism's general protective response to environmental and metabolic stresses. They exist in all major cellular compartments for example HSP10, HSP60 and HSP75 are mainly located in mitochondria, while others are located in different compartments throughout the cell[12]. They serve a variety of important physiological functions, primarily as a molecular chaperone[13-17]. HSPs also

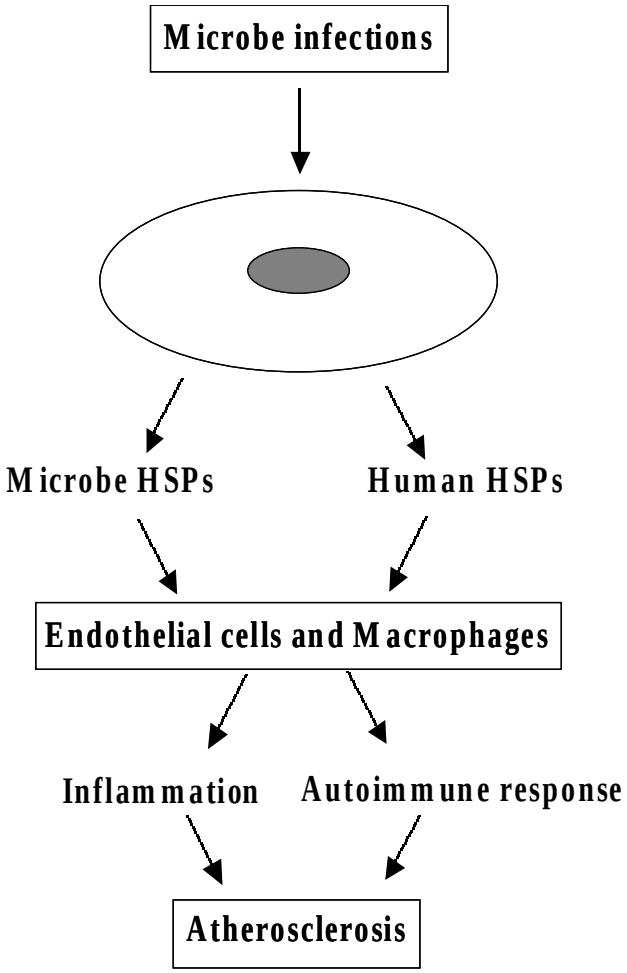

Figure 1. A schematic model showing how HSPs exert their role in the pathogenesis of atherosclerosis in response to infections.

appear to be important in preventing cellular damage during repair process following injury.

HSPs in the arterial wall have an essential protective role against stressors, including hypertension (biomechanical stress), oxidised LDL and cytokines (chemical stress) and heat shock (thermic stress). Both n vivo systems and in vitro experiments show that HSP expression can be induced by high temperature[18;19], exposure to oxygen radicals or cytokines, ischemia[20;21], surgery (trauma)[22], haemodynamic stress[23;24] or infections[25] in the vessel wall. HSPs are typically intracellular proteins, which, in response to stress are abundantly expressed, partially translocated to cell surface and present the immune system with antigens. Human HSP60 (huHSP60) can be found on the surface of stressed but not unstressed cells[26]. Increased expression of huHSP60 was observed in endothelial cells, macrophages[23], and vascular smooth muscle cells[18;19;27-29] .

Infection and HSP expression

The 60kDa HSP (HSP60) has been implicated in the immunological basis of atherosclerosis. This group of HSPs contains the human HSP60, *Chlamydia* HSP60, *E.coli* HSP60 and mycobacterial HSP65 (mHSP65). Bacteria produce HSPs as a means to evade intracellular killing by the human immune system[30;31]. Human cells produce HSPs to protect themselves from the toxic effects of the invading microorganism. HSPs have been demonstrated to be highly antigenic immunodominant molecules[10]. Wick et al put forward the autoimmune hypothesis of atherogenesis[6;11;26;32-34] and is supported by experiments which reveal the presence of auto-reactive T cells[23] and antibodies[27] to HSP60. Experiments show a strong involvement of HSP immunity in the development of CAD. Evidence for this came from an animal model in which arteriosclerotic lesions containing no lipid were induced by immunisation with recombinant mHSP65[35], a phenomenon which was reversed by immunosuppression[36]. There appears to be a dual role for HSP60 in immunity. Firstly, the immune response is directed against the bacterial form of HSP60 and confers protection against the pathogens involved. The greater the response to the bacterial specific HSP60 (as governed by serum antibody levels and T cells), the greater the level of protection . Secondly, there is a risk of autoimmunity if the immune response becomes directed against human HSP60.

Role of infections in atherosclerosis

The suggestion that antibiotic-sensitive processes may be involved in atherosclerosis[37;38] stemmed from recent reports which show a gradual decline in atherosclerosis-related mortality in the West[39], coinciding with the widespread use of antibiotics. Infectious microorganisms possessing proteins which are antigenically similar to our own are potential causative agents that may evoke an inflammatory response within the arterial wall ultimately leading to atherosclerosis as a consequence of the persistent activation of the vascular endothelium[25]. Viral[40] (such as CMV, HSV and Hep A) and bacterial[41] (such as *C.pneumoniae*, *E.coli* and *H.pylori*) infections are important in this hypothesis. Seroepidemiological studies have focused mainly on three pathogens, *Chlamydia pneumoniae, Helicobacter pylori* and

Cytomegalovirus, all of which are known to establish chronic life-long infections.

CMV

CMV is a virus of the herpes viridae family. It rarely causes clinical symptoms. As many as 50 to 100% of adults are seropositive for CMV[42-44]. Several studies have shown a link between CMV and atherosclerosis[45] while others have shown little or no association[46;47], though the virus itself may contribute to local inflammation. CMV seropositivity is associated with cardiac events in the presence of an inflammatory response[48]. Furthermore, many studies have reported the presence of CMV nucleic acids and antigens in human atheromatous plaques[49-52]. Although evidence does not point towards a direct involvement of CMV in atherogenesis, it has been proposed by Espinola-Klein et al[41] that bacterial pathogens enhance the progression of atherosclerosis but herpesviridae is responsible for plaque instability which, in turn, results in coronary and cerebrovascular events.

H.pylori

This gram negative bacteria typically infects human gastric epithelial cells and *H.pylori* has been demonstrated in atherosclerotic plaques[53]. *H.pylori* seropositivity was implicated as a risk factor in CHD from the first report in 1994[54] where Mendall et al showed a positive link between *H.pylori* seropositivity and CHD in adults. However a meta-analysis[55] of 18 studies failed to show any correlation of seropositivity against H.pylori with the presence or extent of CAD. This was supported by a recent murine model where the induction of atherogenesis by *H.pylori* was investigated in vivo[56]. The investigators concluded that *H.pylori* neither induces atherosclerosis nor alters its progression in hypercholesterolaemic mice prone to developing atherosclerosis. Currently the evidence supporting involvement of *H.pylori* in atherogenesis is inconclusive. Nevertheless, it may be important to differentiate between virulent and avirulent strains of *H.pylori* to determine its effects on atherogenesis. Mayr et al[57] conducted a population based study and investigated the effects of Cag A (cytotoxin-associated gene A) positive and Cag A negative strains of *H.pylori.* They concluded that there was an increased risk of atherosclerosis in individuals who were infected with Cag A positive strains of *H.pylori*. HSP60 is a component of *H.pylori*[58] and Yamaguchi et al[59] demonstrated an immune response to *H.pylori* involving HSP60 antigen, indicating a possible protective response against this microorganism. Alternatively, this protection may be an indirect mechanism that potentiates atherogenesis via molecular mimicry involving HSP60/65[60;61].

Chlamydia Pneumoniae

There is strong evidence for the involvement of *C.pneumoniae* in atherosclerosis. PCR, immunohistochemistry and electron microscopy have been used to study this hypothesis and many have shown the presence of *C.pneumoniae* in atherosclerotic plaques[62-67]. This obligate intracellular gram negative bacteria is a common respiratory pathogen that establishes chronic infection[68]. Up to 70% of adults were seropositive for this organism[69] in previously undertaken clinical trials[41]. The persistence of *C.pneumoniae* may be a stress response associated with prominent production of HSP60[70]. Saikku et al[71] were first to show a link between *C.pneumoniae* infection, coronary artery disease and atherosclerosis. Since then, many studies have shown an association of *C.pneumoniae* with atherosclerosis and at least 44 published reports have confirmed this[72] suggesting a possible relationship between seropositivity for *C.pneumoniae* and atherosclerosis. Simultaneous presence of human HSP60 antibodies and *C.pneumoniae* infection seems to increase risk for CAD[44].

In vitro experiments have shown that *C.pneumoniae* infects macrophages, the vascular endothelium and vascular smooth muscle. It is capable of replicating inside aortic endothelial cells[72;73], thus correlating highly with the distribution of HSP60 expression in the arterial wall. *C.pneumoniae* may have a tropism for macrophages which in turn accumulate in atherosclerotic plaques[5]. This is supported by studies of post-mortem specimens of vascular tissue which found a high correlation between the distribution of atherosclerosis and *C.pneumoniae*[74] and other organisms. Examination of normal, non-atherosclerotic vessels demonstrated the absence of these pathogens[75].

C. pneumoniae contributes to atherogenesis in a variety of ways. One mechanism is by its ability to promote macrophages to become lipid filled foam cells[76] due to lipopolysaccharide (LPS) in its cell wall, which has been shown to be an independent factor in the accumulation of LDL in macrophages[77]. *C.pneumoniae* can trigger antibody dependant cellular

cytotoxicity (ADCC) to the vascular endothelium as well as by innate immune mechanisms such as complement[78]. It has also been reported that Chlamydia specific HSP60 (a protein constituent of the bacteria) is involved in stimulating macrophages to secrete TNF-α and synthesise matrix metallo proteinases (MMPs). This causes plaques to be more prone to rupture and enhances the susceptibility of the vessel to occlusion via thromboembolism – a phenomenon that has also been shown for huHSP60[79]. Furthermore, HSP60 is involved in enhancing oxidative free radical formation within macrophages increasing the conversion of LDL to oxidised LDL (oxLDL)[80].

Causal relationship between infection and atherosclerosis.

Viruses are capable of inducing HSP expression in cardiovascular cells. Cardiocytes infected with viruses increase their HSP expression[81] where ultraviolet irradiation of the virus prevents HSP production as well as its replication in heart cells. Furthermore, HIV-infected lymphomas show increased synthesis of HSP70 [82]. Viruses such as CMV induce major histocompatability class I antigen expression in aortic smooth muscle cells[83] and transfection with the virus and *Chlamydia* also causes expression of genes for several cytokines[84]. In theory, viruses may provoke the disease but not persist in the plaque.

Bacterial infections can exacerbate the pre-existing plaque via inflammatory processes and T-cell activation which can lead to destabilisation of the fibrous cap[85]. *C.pneumoniae* produces large amounts of HSP60 during infection, which is thought to have a role in atherogenesis [79;85]. Bacterial and human HSP60 colocalise in atherosclerotic tissue [78] leading to increased expression of matrix degrading proteins (MMPs), tumour necrosis factor-alpha (TNF-alpha) and cytokines (IL-1,IL-2)[84;86]. The generation of these molecules can lead to damaging effects including free radical production, oxidation of LDL, chemotaxis and disturbances in haemostasis leading to thrombosis[87]. Indirect mechanisms may also have a role, whereby the infection instigates systemic changes to the immune response, affecting levels of cytokines, white blood cells and acute phase reactants which could have an effect on the development of atherosclerosis[88].

Cumulative effects of several pathogens

Trials by Zhu et al[89;90] together with a clinical investigation by Espinola-Klein et al[41] support the notion that a significant association exists between the number of infectious organisms to which a person has been exposed and the extent of atherosclerosis. Epstein postulates 'pathogen burden' whereby multiple pathogens are involved in atherogenesis and the increased 'pathogen load' augments the risk for CAD[88] implying that the coexistence of organisms in the vessel wall have a synergistic effect in the induction of vessel injury. HSP60 antibodies may be directed against multiple pathogens including CMV, *H.pylori* and *C.pneumoniae*[91]. A population based study demonstrated that anti-mHSP65 correlates significantly with antibodies to *C.pneumoniae* and *H.pylori* which is highly suggestive of an autoimmune relationship between this antigenic molecule and atherosclerosis[47].

The association of heat shock protein antibodies with atherosclerosis.

The clinical significance of serum antibodies to HSP65 has been a topic of current research where raised serum antibodies to mycobacterial HSP65 has an association with atherosclerosis independent of other established risk factors[60;92;93]. Xu et al were first to demonstrate raised serum antibody titres against mycobacterial HSP65 in subjects (independent of established risk factors) aged 40-79 years with carotid atherosclerosis compared with those without lesions[92], results which remained consistent over a one year follow up period [93]. Zhu et al[91] demonstrated a significant, positive correlation between human HSP60 antibody titres and the severity of CAD. This has been supported by other studies[60;94-104] which have shown that high HSP antibody titres predict mortality[93]. A rise in coronary atherosclerosis was shown with *C.pneumoniae* infection and the presence of anti-HSP60 antibodies[44]. Seropositive patients have a significantly higher prevalence of coronary artery disease compared to seronegative subjects[44;91] .Human HSP60 IgA or Chlamydial HSP60 antibodies have been shown be to a significant risk factor for coronary events[95] which is present only when cross-reactivity to huHSP60 was established due to infection with *C.pneumoniae*. The role of infections in the production of anti-HSP antibodies is supported further by Mayr et al[47] who demonstrated the positive association of anti-mycobacterial HSP65 antibody titres with human IgA to *C.pneumoniae* and IgG to *H.pylori*. Therefore, elevated titres for human HSP60 antibody may be a risk factor for atherosclerosis and

could be a marker of the disease, especially when it co-localises with *C.pneumoniae* infection and inflammation.

Soluble HSP

Soluble forms of HSP60 and HSP70 have been detected in the circulation of healthy individuals[105;106]. Xu et al[107] were first to demonstrate in a population-based study that atherosclerosis was associated with raised levels of soluble HSP60 independent of age, sex and other risk factors. Pockley et al[108] [106]confirmed that soluble HSP60 levels together with anti-mycobacterial HSP65 titres were increased in patients with borderline hypertension which was associated with intima-media thickness and early atherosclerosis. Current evidence suggests that sHSPs have a role in the induction/progression of both hypertension and atherosclerosis.

The source of the soluble HSP is currently unknown and the mechanisms of their release have not been identified. There are a number of theoretical possibilities. First, the presence of the infectious organism within the host cells could lead to increased synthesis of HSP as an immune defence mechanism by the host cell to protect itself from the toxic effects of the bacteria. The effects of these "extracellular" proteins exert on the body may include a cytokine-like activity. Another possibility could be that infections such as *C.pneumoniae*, which eventually lyse the infected cell as part of their replication cycle, cause the release of these typically intracellular proteins[109]. Support for this hypothesis is that sHSP60 levels are significantly correlated with anti-Chlamydial antibodies[107] and both Chlamydial and human HSP60s exist at high levels in human atherosclerotic lesions[79]. Second, the elevation of soluble HSP could be an effect of the general inflammatory processes that are occurring within the vascular wall during coronary artery disease. Third, sHSP60 may be released from necrotic cells in the plaque as studies have shown the presence of cell death within atherosclerotic lesions[110;111]. Fourth, cell-surface HSPs may be released into the circulation from apoptotic cells via the formation of microparticles[112-115], which have been detected in the circulation of patients suffering from acute coronary syndromes and in non-ischaemic patients[112]. The involvement of serum soluble HSP in the development of coronary heart disease and their relationship to anti-HSP antibodies and infections is clearly complex and further research needs to be conducted within this area.

Proinflammatory activities of soluble HSPs

It is thought that autologous sHSPs may signal to the innate immune system[116] through a similar system as for microbial pathogens consequently resulting in inflammatory responses in the vessel wall. The first evidence for this was provided by Kol et al[79] where it was shown that Chlamydial HSP60 and human HSP60 are capable of activating macrophages to produce TNF-alpha and matrix metalloproteinase-9. Following this, it was also demonstrated that HSP60 (Chlamydial or human) can activate human endothelial cells, smooth muscle cells and macrophages[29]. Up-regulated expression of adhesion molecules (ICAM-1, VCAM-1 and E-selectin) can also be induced by HSP60. Studies have also shown HSP can serve as a cytokine[117] and stimulate innate immune system to express TNF-alpha, IL-1 and IL-6 as well as acting directly as a danger signal[118] to the innate immune system. Therefore, Chlamydial and human HSP60s can directly and indirectly affect the vascular wall and encourage atherogenesis.

Summary

A large number of studies have investigated the role of infections in the pathogenesis of atherosclerosis, in particular pathogen burden. Due to the conserved nature of HSPs, the high sequence homology (over 70% at amino acid level)[119] between bacterial and human HSPs, it is plausible that molecular mimicry has a role in the mechanism of the disease whereby infection converts host HSP60 into an autoantigen leading to vessel wall damage. Autoimmune reactions to HSPs may contribute, at least in part, to atherogenesis. The phenomenon has been demonstrated in several experiments[19;28;35;78;120] where human anti-HSP65 antibodies react with human HSP60 present in endothelial cells, macrophages and smooth muscle cells of atherosclerotic plaques and lead to cell lysis through antibody dependant cellular cytotoxicity (ADCC) as well as complement mediated cytotoxicity. Furthermore, identification of HSP cross-reactive T-lymphocytes within atherosclerotic tissue indicates that cell-mediated responses are also involved. Since atherosclerosis is multi-factorial and although traditional risk factors account for the disease in a significant number of patients, infection with proatherogenic organisms may be important in individuals lacking these risk factors as well as acting synergistically with established risk factors. As the organisms implicated in the disease are sensitive to a variety of antibiotics, it is thought antibiotic

therapy may be useful in the primary or secondary prevention of atherogenesis[121] in a select group of patients in whom infection is the major underlying cause.

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The BSCR Bulletin is now featured on the BSCR website, in pdf format. All issues since July 2001 are available.

Also, for up to date information on forthcoming meetings, workshops and symposia, please remember to check the BSCR Website:

www.kcl.ac.uk/bscr

Secretary's Column

All too soon, the summer vacation seems a distant memory as the activity of the new academic year impinges ever more. The business of the BSCR too started early in September with the AGM held at the University of Bristol on the 6th. There was a good attendance of members and others captured at the end of the first session of the excellent meeting on 'Biology and protection of the developing heart' organized by Dr Saadeh Suleiman and Mr Massimo Caputo. At the AGM, the Chairman reported on previous also highly successful meetings which took place during 2001/2, in Oxford and Reading, and gave notice of future main meetings to be held in Glasgow and Edinburgh. This highlights how the BSCR is reaching many places, thankfully served well by EasyJet. A total of 15 travel bursaries were awarded during 2001/2, continuing to provide encouragement to postgraduate students to present their work at the main meetings. There have been no workshops held since September 2001, so this was encouraged with a promise of a financial safety net from BSCR funds. A BSCR symposium on 'MRI in Heart Failure' was held at the 2002 BCS meeting in Harrogate and one is scheduled for the Glasgow meeting. Finally, the backing from Aventis was highlighted as a significant contribution to the strength of the Society as it enters another year of commitment to supporting high quality research meetings. This was taken up in the Treasurer's report, which showed the total reserves to be in good shape, largely as a result of the core sponsorship. Also, the contributions made by meeting organizers who raised funding from the major charities and commercial companies were acknowledged. The Secretary's report concerned mostly a consideration of the current committee membership and the proposals to fill vacancies which would arise at the end of 2002 when a number of members finish their terms of office. Firstly there is Professor Metin Avkiran, who has performed magnificent work for the BSCR over the last three years as Chairman, especially by raising significant external sponsorship, and fostering links with the BCS. On behalf of the BSCR committee and membership, Metin was thanked for bringing such fine qualities of leadership to the position. Mindful of the need for a new Chairman to take up the post in January 2003, this was discussed at the meeting of the committee held last April, and the election of Professor Mike Marber was supported unanimously by other members. This was approved by the Society membership present at the AGM. We are all looking forward to working with Mike and

wish him every success in this capacity. Three ordinary members of the committee will also retire, namely Dr Adrian Brady, Dr Sarah George and Dr Lip Bun Tan, and they were thanked for their work in support of the BSCR. So with four vacant positions to be filled, a postal ballot of the membership was held in August. Those elected were Dr Keith Channon (Oxford), Professor David Eisner (Manchester), Professor Nilesh Samani (Leicester), Dr Peter Weinberg (Reading), and approval was obtained from the membership at the AGM. The composition of the committee from January 2003 shows a reasonable balance of clinical (4) and non-clinical (9) scientists and for the next two years, the position should be stable. At the end of 2004, however, six members will finish their terms of office. If you have a desire to serve the Society in this capacity, keep it in mind that there will be an opportunity to do so from January 2005.

BSCR main meetings in 2003 will be concentrated north of the border. The Spring meeting is being organized by Dr Andy Baker and Dr Sarah George on the subject of 'Molecular therapy for cardiovascular disease' and will take place in Glasgow on 27-28 March. The sessions, accommodation and BSCR dinner will all be held at the Kelvin Conference Centre, which should provide excellent opportunities for focused discussion. Details are given on the back cover, and registration and abstract forms are included as inserts. The Autumn meeting is scheduled for the beginning of September at the University of Edinburgh. This is being organized by Dr Gillian Gray and colleagues, who plan to include a meeting of the Scottish Cardiovascular Forum, such that the total programme will cover two full days. At the next BCS meeting in May 2003, the BSCR Symposium will be organized by Dr Andrew Grace from the University of Cambridge and Papworth Hospital on the theme of 'Genetics and mechanisms of cardiac arrhythmias'.

Lastly, recent copies of the BSCR Quarterly Bulletin may now be viewed / downloaded (PDF format) from the BSCR Website www.kcl.ac.uk/bscr. This will not replace the paper copy, which I am sure is received gratefully for addition to your stack of coffee time reading.

Dr Barbara McDermott

ATTENTION

IMPORTANT NOTICE FOR BSCR MEMBERS

We are currently updating our membership database and hope to make future use of e-mail alerts for BSCR-related announcements and discussion with members.

To ensure that we have your correct details, please e-mail Tony Cavalheiro (antonio.cavalheiro@kcl.ac.uk), <subject: bscr e-mail database>, giving the following information:

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Any information given will remain confidential and will be used only by the BSCR

BSCR Spring Meeting 2003

MOLECULAR THERAPY FOR CARDIOVASCULAR DISEASE

Preliminary Programme

Dates: 27th and 28th March, 2003

Venue: Kelvin Conference Centre, University of Glasgow

Organisers: Andrew Baker (Glasgow) and Sarah George (Bristol)

PLEASE NOTE

Places at this meeting are strictly limited, due to venue capacity.

Please register early to ensure your place.

Day 1

1.00 Registration and Lunch

2.00 Welcome Andrew H Baker

2.00 **Session 1: Current Concepts in Gene Delivery Technology**

Efficiency of non-viral vectors	Steve Hart (*London*)
Novel gene delivery techniques	EWFW Alton (*London*)
Ultrasound-mediated gene delivery	Chris Newman (*Sheffield*)
AAV and long-term therapy	Hildegard Buening(*Munich*)
Antisense therapeutics	Cathy Holt (*Manchester*)

4.00 Coffee/Tea

4.30 **British Cardiac Society Lecture 'Adenoviruses and Atherosclerosis: The Potential'**

Lawrence Chan, Baylor Medical College, Texas, USA

5.30 **Poster Session**

7.30 **Scottish Dinner in Dining Room at Kelvin Conference Center**

Day 2

9.00 **Session 2: New Technology and Modified Vectors**

Modified Ad vectors	Keith Channon (*Oxford*)
Phage display technology	Erik Biessen (Leiden)
Targeting for transplanation	Andrew George (*London*)
Targeted gene delivery	Len Seymour (*Birmingham*)
Genetic modification of viral capsids	Stuart Nicklin (*Glasgow*)

11.00 Coffee

11.15 **Session 3: Disease Targets for Molecular Therapy I**

Plaque stability	Martin Bennett (Cambridge)
Atherosclerosis and plaque rupture	Sarah George (Bristol)
Restenosis following angioplasty	H. von der Leyen (*Germany*)
Vein graft failure	Andrew Newby (*Bristol*)

1.15 Lunch

2.15 **6 Selected Abstracts**

3.15 Coffee

3.30 **Session 4: Disease Targets II**

Essential hypertension	Anna Dominiczak (*Glasgow*)
Lipid lowering by gene transfer	George Dickson (*London*)

4.30 **National Heart Research Fund Lecture:**

Gene Therapy for Pulmonary Disease	Paul Reynolds (*Australia*)

Book reviewer required

The following book has been received for the Book Review feature in *The* **Bulletin**. If you would like to review this title, please contact the Editors as soon as possible.

• From the *Developments in Cardiovascular Medicine* series: *"Exercise Testing, New Concepts for the New Century"*, edited by Myrvin H Ellestad and Ezra A Amsterdam (Kluwer Academic Publishers) ISBN 0-7923-7378-2, September 2001

The reviewer may keep the book after submitting the review.

BSCR 2001 Autumn Meeting (postponed)
and
SIXTH INTERNATIONAL SYMPOSIUM ON MAGNETIC RESONANCE IN CARDIOVASCULAR RESEARCH

22nd & 23rd March 2002, University of Oxford

report by Andrew Murray, Department of Biochemistry, University of Oxford

With a great deal of anticipation, and much relief on the part of the organizers, this popular meeting finally got underway in the impressive setting of the University Museum of Natural History on the 22nd March 2002. Organized this year by Dr. Kieran Clarke and Dr. Stefan Neubauer, the meeting aimed to bring together researchers with a broad interest in the potential that magnetic resonance could offer to cardiovascular research. In uniting the innovations of physicists and engineers in developing techniques with the wish-lists of cardiologists, geneticists, molecular biologists and physiologists hoping to gain from their endeavors, a unique combination of a large meeting with an intimate atmosphere was created. With no shortage of questions and comments at the close of presentations, an eclectic poster presentation and several civil yet highly competitive debates, the meeting, at times, resembled a large workshop. Those of us who are relative outsiders in the field could not fail to be impressed by the great enthusiasm and friendship expressed by speakers and delegates alike.

The meeting was opened by Dr. Clarke, who took the opportunity to welcome the audience to Oxford, and to thank everyone for their support after postponement of the meeting from its original date, in the wake of the September 11th attacks on New York. The opening lecture, delivered by Prof. Sir George Radda (Oxford), set the scene for the next two days, covering the human genome, heart research and magnetic resonance, along with the current interests of the Medical Research Council.

The first session, chaired by Prof. Radda and Dr. Monique Bernard (Marseille), dealt with the role of creatine kinase and the phosphocreatine shuttle; asking if the creatine kinase knockout mouse can provide an answer. Prof. Joanne Ingwall (Boston) gave an overview of creatine kinase isoforms in the intact heart, before Prof. Theo Wallimann (Zurich) discussed a rationale for creatine action in the context of compartmentation, structure and function. Dr. Matthias Spindler (Würzburg) and Dr. Renée Ventura-Clapier (Chatenay-Malabry) introduced the creatine kinase knockout mouse, respectively covering the response of the model to acute and chronic myocardial stress; and ultrastructural and functional adaptations in cardiac and skeletal muscle. The session was closed by Prof. Arend Heerschap (Nijmegen) who presented work on gene deletion and MRS in skeletal muscle and brain.

A second session, chaired by Dr. Raad Mohiaddin (London) and Prof. Sir Charles George (London), tackled the broad field of human genetics and magnetic resonance. Prof. Hugh Watkins (Oxford) spoke out for his field in telling those present what the human geneticist wants to know from cardiac magnetic resonance, and in doing so, introducing a visionary lecture from Prof. Charles Springer (Upton) who predicted a Golden Age of magnetic resonance imaging contrast reagents for detecting

gene expression. Dr. Saul Myerson (London/Oxford) spoke about ventricular mass and the ACE gene, and Dr. Matthias Friedrich (Berlin) opened a discussion on the phenotyping of cardiomyopathies with MRI. The session was concluded with the debate: "Magnetic resonance imaging of tissue function in clinical cardiology: Tool or toy?" Dr. Frank Rademakers (Leuven) presented an argument supporting the usefulness of the technique, whilst Prof. Udo Sechtem (Stuttgart) suggested that MRI was severely limited in clinical studies. This debate brought several interesting and pertinent comments from the audience.

The final session of the day, chaired by Prof. Peter Styles (Oxford) and Prof. Patrick Cozzone (Marseille), concentrated on the future of studies on genetically engineered mice using MRI. Dr. Ulrich Decking (Dusseldorf) set the scene by describing what the physiologist requires from cardiac mouse MRI. A lecture, delivered by Prof. Robert Weiss (Baltimore) outlined the means by which cardiac energetics and function are assessed in mice, non-invasively, using MRS and MRI. The final talk of the day, presented by Dr Frank Wiesmann (Würzburg), gave the audience an insight into new MRI techniques for the characterization of mouse cardiovascular phenotype. The scientific discussion continued during a champagne reception in the impressive setting of the museum balcony.

The first session on Saturday morning, chaired by Prof. Georg Ertl (Würzburg) and Dr. Bheeshma Rajagopalan (Oxford) examined the current situation in clinical cardiac magnetic resonance spectroscopy. Dr. Gerald Pohost (Birmingham, Alabama) summarised the current state and future directions of human cardiac magnetic resonance spectroscopy, and Dr. Frank Kober (Marseille) presented the value of ^{31}P-magnetic resonance spectroscopy in patients with myocardial infarction. Dr. Meinrad Beer (Würzburg) provided insights into the functional and metabolic changes after aortic valve replacement as assessed by ^{31}P-MRS and MRI. Dr. Hildo Lamb (Leiden) discussed the functional and metabolic evaluation of the diabetic heart using MRI and ^{31}P-MRS. The benefits of ^{31}P-MRS in clinical practice were further exemplified by Dr. Wulf-Ingo Jung (Buehl) who discussed the genetic aspects of human hypertrophic cardiomyopathy and Friedreich's ataxia. Dr. Paul Bottomley (Baltimore) presented his "final frontier" for quantitative ^{31}P-MRS in the form of his exciting work on creatine kinase reaction kinetics in patients. The session was concluded by a closely fought debate in which Dr. Stefan Neubauer argued that cardiac MRS and non-proton MRI will become accepted techniques in clinical practice, a controversy upon which Prof. Marcus Schwaiger (Munich) disagreed.

The late morning session, chaired by Prof. Michael Horn (Goteborg) and Dr. Paul Matthews (Oxford) stepped back from clinical practice to examine experimental MRS and MRI. Dr. Robert Balaban (Bethesda) took a break from interrogating the other speakers with searching questions to take the stand himself. His physiological insights into the cardiovascular system provided by MR studies proved to be fascinating. Similarly Prof. Jürgen Schrader's (Dusseldorf) work on the cardiac phenotype of the myoglobin knockout mouse gave food for thought. Prof. Cees van Echteld (Utrecht) then presented his new tools to assess myocardial viability in the form of ^{23}Na magnetic resonance spectroscopy. The exciting possibilities presented by these novel techniques were accompanied by those of Dr. Pamela Garlick (London) who presented her work on simultaneous positron emission tomography and NMR studies of isolated perfused hearts, and of Dr. Anne-Marie Seymour (Hull), whose work on metabolism in heart disease utilized the difficult technique of ^{13}C MRS.

After a much deserved lunch and a great deal of anticipation, an extended afternoon session, chaired initially by Dr. Adrian Banning (Oxford) and Prof. Peter Morris (Nottingham), and later by Prof. Udo Sechtem (Stuttgart) and Dr. David Greaves (Oxford) began. The subject was magnetic resonance and blood vessels, and the first speaker, Dr. Keith Channon (Oxford) opened with a broad request, letting the speakers know what the vascular biologist wants to know from MR. First Dr. Robin Choudhury (New York/Oxford) presented work on the

detection of the atherosclerotic plaque using MR, and then, in the absence of his colleague Dr. Wolfgang Schaper, Dr. Shawn Wagner (Bad Nauheim) presented MRI time-of-flight blood flow assessments in femoral occluded mouse lower limbs. Dr. Paul Hockings (Welwyn) gave a clear account of 3D MRI of atherosclerosis in LDLR (-/-) mice. Yet another hotly contested debate preceded a tea break and poster display, the controversy: "Will magnetic resonance perfusion imaging replace nuclear perfusion imaging?" Prof. Michael Jerosch-Herold (Minneapolis) argued for the motion, whilst Prof. Paolo Camici (London) argued against.

The final group of talks was opened by Dr. Markus von Kienlin (Basel) who presented his work on the assessment of animal models for peripheral artery occlusive disease. The measurement of blood flow and its interactions by MRI was the subject of Dr. David Firmin's (London) presentation, whilst Dr. Thomas Voigtländer (Mainz) gave an account of flow measurement in coronary arteries and in coronary grafts. The final talk of the day came from Prof. Jürgen Hennig (Freiburg), who gave an update on magnetic resonance coronary angiography. The scientific section of the meeting was closed with a final controversy: "Can clinical magnetic resonance angiography compete with x-ray angiography?" Dr. Christine Lorenz (Erlangen) presented the case for clinical MR angiography, whilst Prof. Axel Haase (Würzburg) put forward the case against the technique.

Dr. Stefan Neubauer gave sincere thanks to all the speakers and especially to everyone in the Oxford team who had helped to make the event possible. Thankfully his farewell proved to be only temporary. Mentally drained, but extremely satisfied, the majority of speakers and delegates gathered two hours later at Christ Church for the conference banquet. Readers with young relatives may be interested to know that much of the college, including the Great Hall, had recently been used as the set for Hogwart's School of Witchcraft and Wizardry in the film Harry Potter and the Philosopher's Stone. This evening, however, the atmosphere was slightly less supernatural yet the conversation just as stimulating, as Dr. Kieran Clarke commenced the dinner with the Latin college grace. Later in the evening, Dr. Stefan Neubauer, welcomed the guests to his college and introduced the after-dinner speaker, Prof. Sir George Radda, who delivered a fascinating commentary on the recent progress and imminent directions of medical research in Europe and beyond. After the final toasts from European and US representatives (Prof. Jürgen Schrader and Prof. Charlie Springer, respectively) the meeting was drawn to a close.

The meeting received generous financial support from the BSCR and the European Commission, as well as grants from the Wellcome Trust, the British Heart Foundation and the University of Oxford Wellcome Trust Cardiovascular Research Initiative. In addition, a number of companies (AstraZeneca, Bayer, IGE Medical Systems, Merck, Novartis, Amersham Health, Pharmacia, Philips Medical Systems, Roche, Sanofi-synthelabo, Siemens Medical Solutions and Takeda) formed a trade exhibition and provided the extra support needed to allow the meeting to go ahead. The opportunity to rub shoulders with celebrated MR scientists, the MR pioneers, and to hear firsthand about such a wealth of groundbreaking research was appreciated by many of the attendees, not least by those of us who are relatively new to the field.

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
16(1)	***January 2003***	*December 1st*
16(2)	***April 2003***	*March 1st*
16(3)	***July 2003***	*June 1st*
16 (4)	***October 2003***	*September 1st*

Cardiovascular Related Meetings

Scientific Sessions of the American Heart Association. November 17-20, 2002. Chicago, Illinois, USA. 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: scientificconferences@amhrt.org

Keystone Symposium: Molecular Pathology of Cardiac Arrhythmias. January 14 - 19, 2003. Santa Fe, New Mexico. Organizers: Dan M. Roden and Andrew R. Marks. Early Registration Deadline: November 14, 2002. For further information: e-mail: info@keystonesymposia.org/; tel: +1 800-253-0684; http://www.symposia.com/

XXIII Congress of the European Society of Cardiology, together with Heart Failure 2003 (ESC). 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

XXV Annual Meeting of the ISHR North American Section. June 28-July1, 2003. Mystic, Connecticut, USA. 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: gcordis@neuron.uchc.edu; http://ishr2003.uchc.edu

Congress of the European Society of Cardiology. Vienna, Austria; 30 August-3 September. For further information, please contact: 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. E-mail: webmaster@escardio.org.

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, 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 HEART FOUNDATION GRANTS

Chairs and Programme Grants Committee, May 2002

Programme Grants

Prof K M Channon, John Radcliffe Hospital, Oxford. "Endothelial nitric oxide synthase regulation in vascular disease" 5 years. £836,166

Prof M J Brown, Addenbrooke's Hospital, Cambridge. "Candidate gene analysis of highly selected patients with spironolactone sensitive low-renin hypertension" 5 years. £797,972

Prof D Lane et al, Hammersmith Hospital, London. "von Willebrand factor cleaving" 3 years. £286,513

Dr A P Davenport, Addenbrooke's Hospital, Cambridge. "Endothelins in cardiovascular disease: role of multiple synthetic pathways, functional interactions with vasoactive transmitters and non-invasive imaging of receptor sub-types using positron emission tomography" 2 years (reinstating years 4 & 5). £174,945

Special Projects

Prof A Camm, St George's Hospital, London. "The drug-induced arrhythmia risk evaluation (DARE)" 5 years. £1,557,589

Fellowships Committee, July 2002
DEFERRED APPLICATIONS AWARDED

Intermediate Research Fellowships

Dr M.T. Kearney, Kings College, London. "Mechanisms of impaired NO bioactivity in obesity: studies in murine models of increased adiposity" (3 years) £244,612

Dr K. Bowers, Addenbrooke's Hospital, Cambridge. "Characterisation of intracellular sodium/ proton exchangers of the NHE family" (3 years). £112,033

Junior Research Fellowship

Mr J.R. Emberson, Royal Free Hospital London. "Re-assessing the role of major coronary risk factors: implications of measurement imprecision" (2 years). £66,421

PhD Studentships

Unnamed and Prof L. Poston, Kings College London. "In utero programming of offspring cardiovascular dysfunction by raised maternal dietary fat intake"(3 years). £70,295

Mr J.L. Williams, University of Birmingham. "The differential control of in vivo angiogenesis" (3 years). £65,157

Ms D. Lo, St George's Hospital Medical School, London. "The role of plokaglobin in the molecular mechanism of arythmogenic right ventricular cardiomyopathy in Naxos disease" (3 years). £70,580

PhD Studentship (Clinical)

Dr N.D. Forester, University of Leeds. "Role of gamma-delta T cells in inflammation in abdominal aortic aneurysms" (2 years). £96,356

Travelling Fellowship

Dr D.A. Giussani, University of Cambridge. "Fetal origins of cardiovascular disease in adulthood: contribution of high altitude hypoxia" (6 months) To: Universidad Mayor de San Andres, Bolivia. £8,670

NEW APPLICATIONS

Intermediate Research Fellowships

Dr S.A. Nicklin, Western Infirmary, Glasgow. "Regulated expression of putative therapeutic genes in a model of human essential hypertension" (3 years). £119,561

Dr S. Wijetunge, St Mary's Hospital, London. "Mechanisms of pressure-induced activation of calcium channels (Cav1.2) in arterial smooth muscle" (3 years). £151,205

Dr D.A. Slatter, University of Cambridge. "Structural study of collagens interactions with integrins and glycoprotein VI in atherosclerosis via synthesis of model collagen heterotrimeric peptides" (3 years). £129,734

Junior Research Fellowships

Ms L. Edwards, University of Birmingham. "Sensory-motor function in hypertension" (2 years). £58,351

Mr R. Merrifield, Imperial College. "Rapid imaging of stress induced haemodynamic changes with cardiovascular magnetic resonance" (2 years). £70,748

Dr L.J. Bowman, University of Oxford. "Development, conduct and analysis of large-scale randomised trials of cardiovascular disease prevention" (2 years). £85,450

PhD Studentships

Unnamed and Dr S. Watson, University of Birmingham. "Regulation and role of phospholipase D in platelet activation" (3 years). £65,502

Ms G. Tolhurst, University of Cambridge. "Activation mechanisms and molecular identity of cation influx channels in the platelet megakaryocyte" (3 years).

£76,920

Unnamed and Prof N. M. Hooper, University of Leeds. "Molecular characterisation of the aminopeptidase P gene promoter" (3 years). £65,752

Unnamed and Dr A. Tinker, University College London. "The distribution and function of the ATP-sensitive potassium channel subunit Kir6.1 in cardiac and skeletal miscle cell lines" (3 years). £79,505

Mr K. Sadek, University College London. "Effects of stable prostayclin analogues on human pulmonary smooth muscle and endothelial cell growth: an investigation into cellular mechanisms" (3 years). £75,773

Miss K. Taylor, University of Wales College of Medicine, Cardiff. "Role of C reactive protein and complement in cardiovascular disease. Mechanisms and therapeutic implications" (3 years). £65,763

Mr T.C. Clarke, University of Wales College of Medicine, Cardiff. "Gap junction assembly and intercellular communication in cardiac myocytes exposed to hypoxia" (3 years). £65,327

Unnamed and Dr S. Ponnamalam, University of Leeds. "Regulation of receptor-mediated endoctosis by ubiquitinaation in endothelial cells" (3 years)N/A. £65,772

Mr I.N. McSherry, University of Bath. "Role of Ca2+ signalling pathways in controlling vascular tone in resistance arteries" (3 years). £66,792

Miss H.N. Pemberton, University of Birmingham. "A study into the roles of protein kinase C and nitric oxide in vascular endothelial growth factor mediated angiogenesis" (3 years) £66,102

Miss M. Pitsiouni, King's College, London. "Transcriptional regulation of the NADPH oxidase subunit gp91phox in endothelial cells" (2 years). £49,514

PhD Studentships (Clinical)

Dr J. Buckley, University College London. "Does actin cytoskeletal distruption account for Katp channel dysfunction and vascular hyporeactivity in sepsis?" (3 years). £148,575

Dr M. Dissanayake, Leeds General Infirmary. "Identification of factor XIII A-subunit residues involved in B- subunit binding" (3 years). £129,613

Dr L. Mayahi, University College London. "Endothelial and sympathetic function in inherited and acquired tetrahydrobiopterin deficiency" (3 years). £138,957

Dr K. Hasan, Royal Brompton Hospital, London. "Role of cyclo-oxygenase-1 and cyclo-oxygenase-2 in atherosclerosis" (3 years). £148,990

PROJECT GRANTS COMMITTEE, JULY 2002

DEFERRED APPLICATIONS AWARDED

Dr E. White et al., University of Leeds. "Gene expression, regional hypertrophy and changes in mechanical and electrical activity of the myocardium in response to voluntary exercise training" (3 years). £161,741

Dr R.J. Schilling & Dr A.W. Nathan, St Bartholomew's Hospital, London. "A multicentre randomised controlled trial comparing catheter ablation against direct current cardioversion for the treatment of coarse atrial fibrillation" (2 years). £199,458

Dr D.O. Bates & Dr J.C. Hancox, University of Bristol. "The role of TRP channels in VEGF-mediated calcium influx" (3 years). £124,575

Professor N.J. Severs, Royal Brompton Hospital, London. "Transfected cell models to investigate connexin co-expression in the cardiovascular system" (3 years). £196,053

Dr J.W. Honour et al., University College London. "Birth weight relationships with abdominal obesity, blood pressure and insulin sensitivity: are they mediated by adrenal steroids?" (8 months). £45,116

Professor D.S. Latchman, Institute of Child Health (UCL). "Role of the transcriptional co-factors CBP and p300 in cardiac hypertrophy" (3 years). £95,651

Professor W.A. Large, St George's Hospital Med Sch, London. "Physiological regulation of Ca2+ store-operated ion channels in vascular smooth muscle" (3 years). £165,534

Professor Q. Xu & Dr Y. Hu, St George's Hospital Med Sch, London. "The role of poly(ADP-ribose) polymerase (PARP) in vein bypass graft arteriosclerosis" (3 years). £92,230

Dr G.A. Ng & Professor J.H. Coote, University of Leicester. "The role of the autonomic nervous system and nitric oxide in determining the susceptibility of ventricular myocardium to lethal arrhythmias" (3 years). £134,673

Dr J.M. Gibbins, University of Reading. "Generation and use of knockout mice to investigate the role of integrin-linked kinase (ILK) in platelets" (3 years). £135,742

Dr S.P. Burns et al., St Bartholomew's Hospital, London. "Mechanisms of fetal programming of hypertension" (3 years). £134,992

New Applications

Dr A.J. Jovanovic, Ninewells Hospital Med Sch, Dundee. "Sarcolemmal KATP channel protein complex: structure

and regulation" (3 years). £129,381

Dr D.E. Newby et al, Royal Infirmary, Edinburgh. "Role of the B1 kinin receptor in the regulation of vascular function in patients with ischaemic heart disease. Effect of angiotensin converting enzyme inhibition" (2 years). £114,955

Dr H. Zhang et al., Addenbrooke's Hospital, Cambridge "Is enterovirus infection involved in Sudden Arrhythmic Death Syndrome (SADS)?" (3 years). £181,230

Dr E. Davies et al., Western Infirmary, Glasgow. "Identification and analysis of mutations in steroidogenic genes and their functional implications for human cardiovascular homeostasis" (2 years). £65,281

Dr B.M. Matata et al., Glenfield Hospital, Leicester. "The role of TNF-alpha gene promoter polymorphism on cardiopulmonary bypass induced-oxidative stress and perioperative complications in patients undergoing cardiac surgery" (3 years). £70,457

Professor S.M. Gardiner et al., Queen's Medical Centre, Nottingham. "Haemodynamic effects of human urotensin II - multiple receptors and mediators?" (2 years). £83,313

Dr P.R.M. Siljander et al., University of Cambridge. "Procoagulant activity in platelets: parallels with apoptosis and role of receptors and signals distinct from those for platelet aggregation" (3 years). £150,855

Dr M. Bond & Professor A.C. Newby, Bristol Royal Infirmary. "Regulation of vascular smooth muscle cell proliferation by the extracellular matrix" (3 years). £37,450

Professor E.R. Maher & Dr F. Latif, University of Birmingham. "Molecular pathology of phaeochromocytoma" (3 years). £130,574

Dr J.M. Garland et al., University of Manchester. "Molecular regulation of angiogenesis: elucidation of a novel signaling mechanism by CD105/endoglin in vascular cells and its impact on the bioengineering of vascular grafts" (3 years). £136,553

Dr J. Deuchars et al., University of Leeds. "Expression and sub-cellular compartmentalisation of voltage gated potassium channels in cardiac vagal preganglionic neurones" (1 year). £49,709

Dr E.J. Griffiths & Dr G.A. Rutter, University of Bristol. "Mitochondrial calcium: role in energy production and intracellular calcium homeostasis in cardiomyocytes under physiological and pathological conditions" (3 years). £145,977

Dr I.B. Wilkinson et al., Addenbrooke's Hospital, Cambridge. "Endothelin-1 and the regulation of arterial stiffness" (2 years). £46,908

Professor A.M. Shah et al., King's College School of Med & Dent. "Endothelial modulation of myocardial contractile function in the normal and diseased human heart" (2 years). £108,972

Professor M.S. Marber et al., St Thomas' Hospital, London. "An exploration of the paradoxical relationship between p38 mitogen-activated protein kinase and HSP25/27" (3 years). £130,752

Professor N.M. Hooper et al., University of Leeds. "Evaluation of genetic influences on the bradykinin-degrading enzyme aminopeptidase P" (3 years). £144,125

Dr P.A. Kingston et al., University of Manchester. "Gene therapy for in-stant (Re)stenosis: a study of the effects of adenovirus-mediated antagonism of transforming growth factor-beta after coronary stenting" (2 years). £96,280

Professor G. Hart & Dr M. Hussain, University of Liverpool. "Control of calcium current inactivation during the action potential in cardiac hypertrophy" (1 year). £48,588

Professor C.N. Hales et al., Addenbrooke's Hospital, Cambridge. "Programming of appetite by nutrition during early life" (3 years). £138,990

Professor A.S. Ahmed et al., University of Birmingham. "The regulatory role of vascular endothelial growth factor receptor-1 and nitric oxide in angiogenesis" (3 years). £124,373

Professor P S Mortimer et al., St George's Hospital Med Sch, London. "Defining the lymphatic and venous phenotype in human hereditary lymphoedema" (3 years). £163,549

Professor A.M. Shah & Dr J. Li, King's College School of Med & Dent. "Regulation of superoxide production by the endothelial cell NADPH oxidase complex: role of the p47phox subunit" (3 years). £123,736

Dr D.E. Newby et al., Royal Infirmary, Edinburgh. "Inflammation and the local vascular regulation of glucocorticoid metabolism: effect on endothelial and fibrinolytic function" (3 years). £193,045

Professor M.J. Lewis et al., University of Wales College of Med. "Improvement of endothelial function in ischaemic heart disease by high dose folic acid: an effect independent of homocysteine- lowering?" (1 year). £36,003

Dr J.A. Higgins, University of Sheffield. "Investigation of the mechanisms regulating absorption of cholesterol in the small intestine: the role of dietary lipids" (3 years). £178,468

Professor J.R. Pepper et al., Royal Brompton &

Harefield Hospital. "Randomised controlled trial of programme to reduce risk factors in patients waiting for coronary artery bypass surgery" (3 years). £129,224

Dr A.J. Jovanovic & Dr D.R. Alessi, Ninewells Hospital Med Sch, Dundee. "The role of the 3-phosphoinositide-dependent kinase-1 (PDK1) in mediating cardioprotective signalling" (3 years). £131,114

Dr S. Jeffery et al., St George's Hospital Med Sch, London. "Mutation analysis in Noonan syndrome and the search for a second locus" (2 years). £104,528

Dr S. Plein et al., Leeds General Infirmary. "Follow up of myocardial function and perfusion in patients with heart failure but no angina - a substudy of the HEART UK-trial" (2 years). £125,371

Dr M.Y. Alexander et al., University of Manchester. "Molecular analysis of a novel gene and its involvement in vascular calcification" (2 years). £92,446

Professor M.L. Rose, Harefield Hospital. "Inhibition of migration of alloreactive CD4+ T cells across endothelial cells; a novel avenue for immunosupressive therapy" (2 years). £86,882

Dr E. Kiss-Toth, Northern General Hospital Sheffield. "The biological role of human tribbles proteins in vascular cells in health and disease" (3 years). £122,246

Professor H.S. Markus et al., St George's Hospital Med Sch. "An automated embolic signal detection system for ambulatory transcranial doppler recordings" (2 years). £69,910

Dr R.A.S. Ariens et al., Leeds General Infirmary. "Role of factor XIII dependent cross-linking in fibrin clot structure and function: site-directed mutagenesis of cross-linking sites" (3 years). £133,629

Cardiovascular Related Wellcome Trust Grants

May 2002 to July 2002

Srif

Prof Chris Haslett, Dept of Medical and Radiological Sci, Respiratory Medicine Unit, University of Edinburgh Research Institute for Medical Cell Biology at the new Royal Infirmary of Edinburgh: establishment of linked basic and clinical research facilities for reproductive biology, inflammation research and cardiovascular biology. 24 months £11,200,000

Project Grant

Dr David R McCance, Metabolic Unit, , Royal Victoria Hospital, Belfast, Northern Ireland. A Randomised Controlled Trial of Vitamins C and E to Prevent Pre-Eclampsia in Type 1 Diabetic Pregnancy: Acronym DAPIT (Diabetes and Pre-Eclampsia Intervention Trial). 54 months £865,155

Wellcome Programme Grants

Dr Martin Bobak, Dept of Epidemiology & Public Health, University College London. Determinants of cardiovascular diseases in Eastern Europe: a multi-centre cohort study. 60 months £1,117,563

Prof Anna F Dominiczak, Dept of Medicine & Therapeutics, Western Infirmary, University of Glasgow. Cardiovascular Functional Genomics: translating experimental work to human disease. 60 months £5,353,678

University Awards

Dr Mary J Morrell, Sleep and Ventilation Unit, Royal Brompton Hospital, National Heart and Lung Institute London . Arousal from sleep: mechanisms and cardiovascular consequences. 60 months £371,060

BSCR Spring Meeting 2003

Molecular Therapy for Cardiovascular Disease

Dates: 27th and 28th March 2003

Venue: The Kelvin Conference Centre, University of Glasgow

Organisers: Andrew Baker and Sarah George

Overall aims:

1. Discuss the advantages and disadvantages of current gene therapy vector
2. Examine the potential of modifying current strategies
3. Examine present and potential use of gene therapy for cardiovascular disease.

Invited Speakers include: Steve Hart (*London*), EWFW Alton (*London*), Chris Newman (*Sheffield*), Hildegard Buening (*Munich*), Cathy Holt (*Manchester*), Lawrence Chan (*USA*), Keith Channon (*Oxford*), Erik Biessen (*Leiden*), Andrew George (*London)*, Len Seymour (*Birmingham*), Stuart Nicklin (*Glasgow*), Martin Bennett (*Cambridge*), H. von der Leyen (*Germany*), Andrew Newby (*Bristol*), Sarah George (*Bristol*), Anna Dominiczak (*Glasgow*), George Dickson (*London*), Paul Reynolds (*Australia*).

Communications: Part of this meeting will be devoted to the presentation of selected abstracts and posters. **Abstract deadline February 14th, 2003**.

Registration: Free to BSCR members, £40 for non-members. Please register early as places are limited

Travel & Accommodation: The conference centre is located on the Garscube site in North Glasgow, just 5 miles from the city centre and 12 miles from Glasgow International Airport. Accommodation is available on site. Bed & breakfast and conference dinner will cost £60.

For further information contact: Dr Andrew H Baker, Division of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary, Glasgow, G11 6NT, Tel: 0141 211 2100 or 2116, Fax: 0141 211 1763 Email: ab11f@clinmed.gla.ac.uk or Sarah George, Bristol Heart Institute, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW. Tel: 0117 928 3154 or 3582;

Fax: 0117 928 3581; Email: s.j.george@bristol.ac.uk

Deadline for registration is February 14th, 2003.

Bursaries: The Society will consider awarding travel grants of up to £150 to *bona fide* PhD students. Application forms are available from: Dr Barbara McDermott, Secretary of the BSCR, Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. Tel: 02890-272242/33577o; Fax: 02890-438346; E-mail: b.mcdermott@qub.ac.uk

Membership: Membership forms can be downloaded from the BSCR website: www.kcl.ac.uk/depsta/biomedical/bscr/membership.htm or by contacting Dr Barbara McDermott at the address above.