The Ninety-Seventh Annual General Meeting

The Ninety-Seventh Annual General Meeting was held in Winchester on Thursday 3 and Friday 4 April 2003. The attendance book was signed by ordinary members and senior members.

The President, Professor D. Barker, took the chair.

The Minutes of the last Annual General meeting, having been published in the QJM (September 2002), were taken as read, confirmed and signed. The following Officers and Executive Officers were elected:

Executive Committee
President: Professor D. Barker
President-elect: Professor G.H. Tomkin
Honorary Treasurer: Professor A.P. Weetman
Honorary Secretary: Professor J.M.C. Connell

Members for England and Wales
Professor C. Black
Dr C. Gelder
Professor J. Iredale

Members for Scotland
Professor R. Jung
Professor B. Walker

Members for Ireland
Professor A.B. Atkinson
Professor J. Donohoe

The following Honorary, Senior and Ordinary Members were elected:

Honorary Members
Professor C. Black
Professor P. Harper

Professor W.S. Hillis
Professor J.F. Martin
Professor O.F.W. James
Professor P.A. Poole-Wilson
Dr N.A.G. Mowat
Dr J. Reeve
Professor A.M.
Professor B.D. Williams

Ordinary Members

Adu, Dwomoa, MB, BChir, MD, FRCP, Department of Nephrology, Queen Elizabeth Hospital, Edgbaston, Birmingham, B15 2TH
Aziz, Qasim, MRCP, PhD, FRCP, Gastroenterology, Clinical Sciences Building, Hope Hospital, Salford, Manchester, M6 8HD
Barker, Johnathan, MSc(Hons), MB, BS, MRCP, FRCP, FRCPath, St John’s Institute of Dermatology, Guy’s King’s College and St Thomas’ School of Medicine, St Thomas’ Hospital, London, SE1 7EH
Brunskill, Nigel John, MBChB, MRCP, ECFMG, PhD, FRCPath, Department of Nephrology, Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW
Buckley, Christopher, BA, FMGEMS, MRCP, DPhil, CCST, Department of Rheumatology, The University of Birmingham, Edgbaston, Birmingham, B15 2TT
Byrne, Christopher David, MB BCh, MRCP, FRCPath, FRCPath, FRCPath, FRCPath, FRCPath, Medical Specialities, Level D, South Academic Block, Southampton General Hospital, Tremona Road, Southampton, SO16 7YD
Casadei, Barbara, MD cum Laude, MA, DPhil, FRCPath, Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford, OX3 9DU
Channon, Keith, BSc(Hons), MBChB, MRCP, FRCPath, FRCPath, FRCPath, FRCPath, Medical Specialities, Level D, South Academic Block, Southampton General Hospital, Tremona Road, Southampton, SO16 7YD
Custovic, Adnan, MSc, MD, PhD, North West Lung Centre, Wythenshawe Hospital, Manchester, M23 9LT
Firth, John, BA, BM, MRCP, FRCPath, Renal Dialysis Unit, Box 118, Addenbrooke’s Hospital, Cambridge, CB2 2QQ
Gabra, Hani, BSc Honours, MbChB, MSc, PhD, MRCP, FRCPath, Cancer Research UK, Edinburgh Oncology Unit, Western General Hospital, Edinburgh, EH4 2XR
Healy, Eugene, BA, MB, BCh, BAO(Hons), MRCP, PhD, Dermatopathology Unit, Level F, South Block, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD

QJM vol. 96 no. 11 © Association of Physicians 2003; all rights reserved.
The Honorary Secretary, Professor J.M.C. Connell, reported that a website for the Association had been commissioned. A prototype had been approved by the Executive Committee and would be launched over the next few months. Members would be contacted to be given details of appropriate passwords through which the website could be fully explored. It was anticipated that members should be able to download nomination forms and abstract forms from the Internet.

The Honorary Secretary then reported on the survey of members that had been carried out in 2002. He indicated that around 100 replies had been received. Overall, members were happy with the general style and content of the AGM. Members had expressed some concern about the limited numbers of ordinary members of the Association, bearing in mind the expansion of medical schools that had occurred over the last few years. It was felt that a number of appropriate candidates had been denied membership in the past on this basis, and that it would be reasonable to increase the number of ordinary members. The matter had been reviewed by the Executive Committee, and a formal proposal was put to the AGM that ordinary membership increase from the current level of 400 to a target of 500 over a period of five years. Progress in this regard, and the impact of the membership increase on the activity of the Association would be kept under review and, if necessary, modified. This proposal was approved by the AGM.

The Honorary Treasurer, Professor A.P. Weetman, reported that the accounts of the Association continued to be in good order. He presented the income and expenditure for the 12 months to 31 December 2002. Although he had predicted at the previous AGM that the income from Oxford University Press, arising from the publication of the QJM, might fall during 2002, in fact it had risen by over £7000 to £77 364. There was also an increase in income from subscriptions, as a result of the reconciliation of the membership list with the bank subscriptions, although he noted that some members continued to pay the wrong subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate.

The Honorary Secretary then reported on the survey of members that had been carried out in 2002. He indicated that around 100 replies had been received. Overall, members were happy with the general style and content of the AGM. Members had expressed some concern about the limited numbers of ordinary members of the Association, bearing in mind the expansion of medical schools that had occurred over the last few years. It was felt that a number of appropriate candidates had been denied membership in the past on this basis, and that it would be reasonable to increase the number of ordinary members. The matter had been reviewed by the Executive Committee, and a formal proposal was put to the AGM that ordinary membership increase from the current level of 400 to a target of 500 over a period of five years. Progress in this regard, and the impact of the membership increase on the activity of the Association would be kept under review and, if necessary, modified. This proposal was approved by the AGM.

The Honorary Treasurer, Professor A.P. Weetman, reported that the accounts of the Association continued to be in good order. He presented the income and expenditure for the 12 months to 31 December 2002. Although he had predicted at the previous AGM that the income from Oxford University Press, arising from the publication of the QJM, might fall during 2002, in fact it had risen by over £7000 to £77 364. There was also an increase in income from subscriptions, as a result of the reconciliation of the membership list with the bank subscriptions, although he noted that some members continued to pay the wrong subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate. A letter would be sent to all members this year to ask them to confirm their subscription rate.
administration of the Association remained much as before.

With regard to direct charitable expenditure, the Links with Developing Countries Scheme had proven less popular than previous years, with only seven submissions, four of which were chosen for funding. These were judged to be of high quality however, and in total £23,170 had been used for this scheme. The intercalated fees and undergraduate studentships continued to be very well received by Medical Schools. A new round of intercalated studentships was due to start, there being a four-yearly cycle to award studentships to every medical school in the UK and Ireland. Professor Weetman informed the AGM that with the creation of four new Medical Schools, this would increase the amount spent on intercalated fees to £40,000 a year as these new Schools were absorbed into the scheme. Maintaining the undergraduate studentships as before meant that £20,000 would be available in 2003 for the Links with Developing Countries Scheme. An invitation for submissions will be sent to members over the summer.

Investment losses had continued in 2002, reflecting the generally poor performance of the stock market during this period, although the losses were less than in 2001. Uncertainty with regard to investments was likely to persist during 2003, and it was also expected that the income from Oxford University Press would decline. Professor Weetman had also had discussions with Professor Tomlinson, President of the Association during 2002, and it had been agreed to set aside a sum of £20,000–25,000 over the next two years to allow the publication of a History of the Association, of £20,000–25,000 over the next two years to allow the publication of a History of the Association, to coincide with the 100th meeting in 2006. Professor Weetman therefore proposed that there should be a target of £300,000 at the end of 2003, and the charitable expenditure which had been proposed would most likely achieve that target.

The members accepted the accounts and the proposals for expenditure.

Dr C.N. Martyn, the Editor of the QJM, was unable to be present, and his report was read by Professor Weetman. The rising trend in the number of unsolicited articles received by the QJM editorial office had continued, with the number of submissions in 2002 more than double what it had been in 2000. There had been an encouraging increase in use of the electronic QJM. Monitoring of the number of ‘hits’ on QJM web pages had shown a rise over the past year, and registrations by people wanting to receive the monthly electronic table of contents by e-mail were growing. The number of institutions with electronic access to the journal had also increased substantially. QJM’s impact factor had improved and was currently 2.6.

Unfortunately, library subscriptions continued to fall. Members of the Association however, should be aware that this was a trend affecting all established medical journals and that the loss of revenue was offset by consortia and aggregator sales. The financial state of the journal was sound, and its profitability last year greater than expected. It is intended that a proportion of the profits will be re-invested by promoting the journal in Australia, Japan and North America.

At the meeting of the Executive Committee of the Association last year, it was suggested that the QJM Editorial Board would benefit from new blood, and that board members need not necessarily be members of the Association.

Ten longstanding members of the board had generously agreed to stand down and six new members had been recruited, two from outside the UK. Editorial board members were now asked to serve for a period of three years. It is intended to recruit more overseas members to the board in 2003 to reflect the increasing number of submissions from Europe, North America and the Pacific Rim. The editor would be pleased to hear from members of the Association who are interested in joining the board.

After a long period of service as Senior Editor of the QJM, Professor David Warrell had resigned. The Association owed Professor Warrell a large debt of gratitude for his long-standing and steadfast support of the QJM. Rather than seeking a replacement for the post of Senior Editor, the Editorial Board had suggested that alternatives such as appointing an editor with responsibility for one section of the journal, or guest editors for a particular issue should be considered. The editor is negotiating ways to implement these suggestions.

Professor G. Tomkin, President-elect, invited the Association to its next meeting in Dublin on 25 and 26 March 2004.

Opening Reception and Annual Dinner
The welcome reception on Thursday evening was held in ‘The School’, Winchester College and was followed by a choral concert in the Winchester Cathedral. The musical performance by Southern Voices was much appreciated by all members. The Annual Dinner on the Friday evening was held in the Great Hall, Winchester. An excellent dinner was provided and the occasion was enjoyed by all.
The Role of Kruppel-Like Factor 6 (KLF6) in Colorectal Neoplasia.

We have recently described the ubiquitous transcription factor, KLF6, as a novel tumour suppressor gene inactivated in prostate cancers (Narla et al., Science 2001; 294:2563–6). In the present study we report that KLF6 is inactivated in over 50% (26/50) of both sporadic and inflammatory bowel disease (IBD)-related colorectal cancers (CRC) by a combination of loss of heterozygosity (LOH) and mutation of the second allele. Furthermore LOH was present in non-tumour IBD-affected colonic epithelium (7/8 cases) in patients with CRC and in 65% of colonic adenomas (17/26 < 1 cm, varying degrees of dysplasia) suggesting that this occurs as an early event in the pathogenesis of CRC. KLF6 is present at low levels in normal colonic epithelium, but abnormal cytoplasmic accumulation was detected in all 50 CRC cases. Cellular transfection of CRC-derived KLF6 tumour mutants led to cytoplasmic rather than nuclear accumulation, suggesting that intracellular mislocalization is directly related to mutations of KLF6. We have further explored the mechanisms by which KLF6 inactivation may contribute to carcinogenesis. Wild-type KLF6 significantly suppressed cell growth in both colonic fibroblasts (30%, p<0.001) and colorectal cancer cell lines (SW480, HCT15, HT29, HCT116). This was associated with a 2–3-fold increased expression of the cell cycle inhibitor p21/WAF and down-regulation of the proliferative epidermal growth factor receptor (EGF-R), thereby favouring growth inhibition. In addition, matrix metalloproteinase-2 (MMP-2) mRNA and protein was decreased, with a corresponding decrease in MMP-2 activity. In contrast, the CRC-derived mutant isoforms of KLF6 were pro-proliferative, failed to upregulate p21/WAF, and increased rather than suppressed the levels of the EGF-R and MMP-2. These CRC-derived KLF6-mutant-mediated effects therefore increase both the proliferative and invasive capacity of tumour cells. These data indicate that KLF6 inactivation plays a key role in the pathobiology of CRC.

3.25 p.m. (2)
J.R. Seckl, N.M. Morton (introduced), D.J. Wake, D.E. Livingstone, T.C. Sandeep, J. Paterson, R. Andrew, J.J. Mullins (all introduced) and B.R. Walker. Endocrinology Unit, Edinburgh University, Western General Hospital, Edinburgh. 11b-Hydroxysteroid dehydrogenase Type 1: a cause and therapeutic target for the metabolic syndrome.

The Metabolic Syndrome of visceral obesity, insulin resistance, hyperglycaemia, dyslipidaemia and hypertension closely resembles Cushing’s Syndrome, but in obesity, plasma cortisol levels are not elevated. Recent evidence suggests that an adipose-selective increase in 11b-hydroxysteroid dehydrogenase type 1 (11b-HSD1), which locally activates inert cortisone to cortisol, may underlie the Metabolic Syndrome by obesity in rodents and humans. In both obese humans (n=67) and rodents (Zucker rats, ob/ob mice) we found 2–3-fold increased 11b-HSD1 activity and mRNA levels in abdominal adipose tissue. To address causation we made transgenic mice with 2.5-fold overexpression of 11b-HSD1 only in adipose tissue using the aP2 promoter. These mice have elevated adipose (not plasma) corticosterone levels and show visceral obesity, hyperglycaemia, insulin resistance, dyslipidaemia and hypertension (+25 mmHg), the latter apparently driven by angiotensinogen over-production (4-fold) in adipose tissue. To explore the therapeutic potential of 11b-HSD1 inhibition we made 11b-HSD1 knock-out mice on obesity-prone (C57BL/6) and obesity-resistant (MF-1) genetic backgrounds. 11b-HSD-1–/– mice have 67% lower intra-adipose corticosterone levels, despite maintained plasma levels. Both strains of 11b-HSD-1–/– mice have reduced fat pad weights and with chronic high fat feeding, both exhibit reduced visceral fat accumulation, redistributing fat to ‘metabolically safer’ peripheral depots. C57BL/6 obesity-prone 11b-HSD-1–/– mice had 15% lower weight gain, despite eating 12% more calories than wild type. The favourably altered fat distribution was associated with improved glucose tolerance and insulin sensitivity, reduced free fatty acids and a ‘cardioprotective’ serum lipid profile (low LDL, high HDL). Isolated adipocytes from 11b-HSD-1–/– mice...
exhibited higher basal and insulin-stimulated glucose uptake indicating insulin sensitization. Intriguingly, wild-type mice and rats down-regulated 11β-HSD-1 in white fat in response to a high-fat diet. Moreover, obesity-resistant A/J mice had lower basal adipose 11β-HSD1 and down-regulated this more markedly (4-fold) on a high-fat diet than did obesity-prone C57BL/6J mice. These data show that adipose tissue 11β-HSD-1 deficiency contributes to a ‘protective’ metabolic phenotype. Down-regulation of adipose 11β-HSD-1 in response to dietary fat represents a novel adaptive mechanism, more pronounced in obesity-resistant animals, that counteracts central adiposity and its metabolic consequences.

4.15 p.m. (3)
M. Schmitt*, P. Gunaruwan, A. Broadley, J. Taylor, J.R. Cockcroft, M.P. Frenneaux (*introduced by M.P. Frenneaux). Department of Cardiology, Wales Heart Research Institute, University of Wales College of Medicine, Cardiff. **Atrial natriuretic peptide regulates human capacitance.**

Atrial natriuretic peptide (ANP) has well-documented effects on resistance arteries. Its effects on the venous system however remain controversial. For example ANP has no direct effects on dorsal hand veins or saphenous veins, but systemic infusion increases intestinal and decreases cardiac blood content. Furthermore, to date no studies have conclusively shown that basal ANP levels contribute to resting vascular tone in humans, a prerequisite for accepting that ANP is a physiologically important vasoactive peptide in health. Given that atrial stretch is the principal stimulus for ANP release, the apparent lack of a direct effect on venous tone seems counterintuitive. We hypothesized that ANP has direct venodilating effects on the small veins and venules which comprise the majority of the capacitance vasculature.

Combining equilibrium blood-pool-scintigraphy (EBPS) with a conventional occlusive technique (radionuclide plethysmography) we examined the effects of ANP and the ANP-receptor antagonist A71915 on forearm vascular volume in 14 healthy subjects. Creating pressure/volume relations (PVR) we determined changes in vascular volume (capacitance), compliance and tone. EBPS was then used to assess the effects of systemic administration of the ANP-receptor antagonist A71915 on regional intestinal vascular volume. Infusion of ANP increased forearm vascular volume in a dose-dependent manner (max 20%; \( p < 0.001 \)), exerting a maximum venodilating effect at plasma levels equivalent to those seen in heart failure. A71915 increased venous tone thereby decreasing vascular volume by 9.6 ± 1.1%; \( p < 0.001 \) (forearm) and 2.6 ± 0.5%; \( p = 0.01 \) (intestinal beds).

ANP regulates regional vascular volume and tone without affecting compliance. This effect was seen over a wide range of physiological and pathophysiological plasma levels.

4.40 p.m. (4)
M. Cobbold (introduced), J.M. Goldman (introduced), P. Mahendra (introduced), C. Craddock (introduced) and P.A.H. Moss (introduced by C. Savage). Cancer Research UK Institute for Cancer Studies, University of Birmingham, Birmingham. **Direct adoptive transfer of CMV-specific CD8+ T cells to transplant patients following isolation from the donor.**

Cytomegalovirus (CMV) remains a significant cause of morbidity and mortality following bone marrow transplantation (BMT). CMV reactivation occurs as a result of impaired virus-specific immunity and CD8+ T cells are believed to be the major effector mechanism for controlling viral replication. CMV-specific CD8+ T cells have previously been cultured from BMT donors and used in adoptive transfer to patients. This approach has been shown to reduce the incidence of viral reactivation but has not been widely adopted due to the technical demands and expense of long-term T-cell culture.

We have recently demonstrated that healthy CMV-seropositive donors have high numbers of CMV-specific T cells in their peripheral blood. We have used this finding to develop a rapid approach to the adoptive transfer of T cells. Cytomegalovirus-specific CD8+ T cells were isolated from seven transplant donors by staining peripheral blood lymphocytes with HLA-peptide tetramers followed by selection with magnetic beads. Cells were infused directly into transplant patients within 4 h of selection. The total cell dosage of infused cells ranged between 0.1 and 2 million, and CMV-specific T cells represented over 95% of all T cells. Cells were infused at the time of CMV reactivation and cytomegalovirus-specific CD8+ T cells became detectable in all patients within 10 days of infusion, reaching a peak of 22% of the total CD8 T-cell compartment. Functional immunity was detected in all patients and one patient with drug-resistant CMV antigenaemia became CMV-negative for the first time in 4 months.

This novel approach to adoptive transfer has considerable potential for antigen-specific T-cell therapy after allogeneic transplantation.

5.05 p.m. (5)
F.J. Charchar, M. Tomaszewski, B. Lacka*, M. Upton, G.C. Inglis, A. McConnachie, W. Wales Heart Research Institute, University of Wales College of Medicine, Cardiff. **Cancer Studies, University of Birmingham, Birmingham.**

4.01 p.m. (3)
M. Schmitt (introduced by M.P. Frenneaux). Department of Cardiology, Wales Heart Research Institute, University of Wales College of Medicine, Cardiff. **Atrial natriuretic peptide regulates human capacitance.**

Atrial natriuretic peptide (ANP) has well-documented effects on resistance arteries. Its effects on the venous system however remain controversial. For example ANP has no direct effects on dorsal hand veins or saphenous veins, but systemic infusion increases intestinal and decreases cardiac blood content. Furthermore, to date no studies have conclusively shown that basal ANP levels contribute to resting vascular tone in humans, a prerequisite for accepting that ANP is a physiologically important vasoactive peptide in health. Given that atrial stretch is the principal stimulus for ANP release, the apparent lack of a direct effect on venous tone seems counterintuitive. We hypothesized that ANP has direct venodilating effects on the small veins and venules which comprise the majority of the capacitance vasculature.

Combining equilibrium blood-pool-scintigraphy (EBPS) with a conventional occlusive technique (radionuclide plethysmography) we examined the effects of ANP and the ANP-receptor antagonist A71915 on forearm vascular volume in 14 healthy subjects. Creating pressure/volume relations (PVR) we determined changes in vascular volume (capacitance), compliance and tone. EBPS was then used to assess the effects of systemic administration of the ANP-receptor antagonist A71915 on regional intestinal vascular volume. Infusion of ANP increased forearm vascular volume in a dose-dependent manner (max 20%; \( p < 0.001 \)), exerting a maximum venodilating effect at plasma levels equivalent to those seen in heart failure. A71915 increased venous tone thereby decreasing vascular volume by 9.6 ± 1.1%; \( p < 0.001 \) (forearm) and 2.6 ± 0.5%; \( p = 0.01 \) (intestinal beds).

ANP regulates regional vascular volume and tone without affecting compliance. This effect was seen over a wide range of physiological and pathophysiological plasma levels.

4.40 p.m. (4)
M. Cobbold (introduced), J.M. Goldman (introduced), P. Mahendra (introduced), C. Craddock (introduced) and P.A.H. Moss (introduced by C. Savage). Cancer Research UK Institute for Cancer Studies, University of Birmingham, Birmingham. **Direct adoptive transfer of CMV-specific CD8+ T cells to transplant patients following isolation from the donor.**

Cytomegalovirus (CMV) remains a significant cause of morbidity and mortality following bone marrow transplantation (BMT). CMV reactivation occurs as a result of impaired virus-specific immunity and CD8+ T cells are believed to be the major effector mechanism for controlling viral replication. CMV-specific CD8+ T cells have previously been cultured from BMT donors and used in adoptive transfer to patients. This approach has been shown to reduce the incidence of viral reactivation but has not been widely adopted due to the technical demands and expense of long-term T-cell culture.

We have recently demonstrated that healthy CMV-seropositive donors have high numbers of CMV-specific T cells in their peripheral blood. We have used this finding to develop a rapid approach to the adoptive transfer of T cells. Cytomegalovirus-specific CD8+ T cells were isolated from seven transplant donors by staining peripheral blood lymphocytes with HLA-peptide tetramers followed by selection with magnetic beads. Cells were infused directly into transplant patients within 4 h of selection. The total cell dosage of infused cells ranged between 0.1 and 2 million, and CMV-specific T cells represented over 95% of all T cells. Cells were infused at the time of CMV reactivation and cytomegalovirus-specific CD8+ T cells became detectable in all patients within 10 days of infusion, reaching a peak of 22% of the total CD8 T-cell compartment. Functional immunity was detected in all patients and one patient with drug-resistant CMV antigenaemia became CMV-negative for the first time in 4 months.

This novel approach to adoptive transfer has considerable potential for antigen-specific T-cell therapy after allogeneic transplantation.
N.H. Anderson, E. Sukowska-Szczechowska*, W. Grzeszczak* G.C.M. Watt (all introduced), J.M.C. Connell, A.F. Dominiczak. University of Glasgow, Glasgow, and *Silesian School of Medicine, Poland.

The Y chromosome—the link between cardiovascular risk and sex?

Males are at higher risk of cardiovascular disease compared with females. Most of the male-determining Y chromosome does not recombine with the X chromosome, therefore we can use one marker to determine the presence of genes that can contribute to a phenotype. To examine if there was an association between cardiovascular phenotypes and the Y chromosome we phenotyped (for blood pressure and lipids) and genotyped (for a polymorphic HindIII biallelic marker) 3 European cohorts: 155 middle-aged Polish males, 762 middle-aged Scottish males and 1257 young Polish males. We also tested for possible interaction between the Y chromosome and a mutation in the steroidogenic factor binding site of the aldosterone synthase gene within the Scottish population. There was no significant difference in age or body mass index between the two genotypes in the study groups. Men with the HindIII(+)* genotype had significantly higher systolic and diastolic pressures than those with the HindIII(−)* genotype in both the Polish and Scottish studies. This difference between the two genotypes was 5.3 mmHg (p = 0.0014) and 3.1 mmHg (p = 0.0005) for systolic blood pressure adjusted for age, BMI and smoking in the Polish and Scottish study, respectively and 2.6 mmHg (p = 0.0045) and 1.4 mmHg (p = 0.0084) for diastolic blood pressure in the Polish and the Scottish study, respectively. On binary logistic regression analysis, males with the HindIII(+/−)/TT SF1 genotype combination had an odds ratio for elevated blood pressure of 3.92 (95% CI 1.21–12.68, p = 0.023). We also found an association between the HindIII(−)* genotype, and total and LDL cholesterol levels in the young males. Our results indicate that the Y chromosome harbours a locus that contributes to blood pressure and cholesterol variation in hypertensive and normotensive men. This Y chromosome locus appears to interact with the autosomal aldosterone synthase gene to increase the odds of an individual developing higher blood pressure.

Friday 4 April 2003

9.00 a.m. (6)

S.F. Stewart, E. Albano*, A.K. Daly (all introduced), O.F.W. James, D.E. Jones, C.P. Day. Centre for Liver Research, University of Newcastle upon Tyne, UK and *University of East Piedmont, Novara, Italy. Susceptibility to alcoholic liver disease has an immunogenetic basis.

The reasons why less than 10% of heavy drinkers develop advanced alcoholic liver disease (ALD) remain unclear. We have previously shown that sera from some heavy drinkers contain allo-antibodies directed at protein adducts arising as a result of ethanol metabolism and oxidative stress, and auto-antibodies directed at native non-adducted proteins. In light of this we hypothesized that susceptibility to ALD may have an immune basis. First we examined autoantibody titres to the ethanol-inducible enzyme CYP2E1 in sera from 127 drinkers with and without ALD. We observed titres > 95th percentile of the controls in 40% of drinkers with ALD, but in only 11% of drinkers without disease (5.5[1.65–20.1], p < 0.002). We then examined in vitro T-cell responses to ethanol-derived adducts. While no responses were observed in heavy drinkers without disease, 39% of ALD patients had positive responses (p = 0.007). To determine whether susceptibility to ALD may have an immunogenetic basis, in > 400 heavy drinkers we looked for, and found, an association between advanced ALD and the A→G exon 1 polymorphism in CTLA-4, associated with various autoimmune diseases (2.2[1.4–3.3], p < 0.0005). Finally, to test the hypothesis that this polymorphism predisposes heavy drinkers to immune-mediated disease mechanisms, we compared anti-CYP2E1 titres in ALD patients according to CTLA-4 genotype. 51% of patients with the G allele had positive titres compared with 21% of patients homozygous for the A allele (3.8[1.3–10.3], p = 0.011). Similarly, 25% of patients with the G allele had extensive lymphocyte infiltration and associated apoptosis on their liver biopsies compared with only 3% of AA homozygotes (13[1.7–276], p = 0.03). These data suggest that susceptibility to ALD may be due, in part, to genetically determined differences in the immune response to allo-antigens arising during ethanol metabolism and an associated breakdown in self tolerance. This information has important implications for the development of individually tailored treatment strategies.

9.25 a.m. (7)

P.J. Barnes, K. Ito (introduced), B. Cosio (introduced), I.M. Adcock (introduced). National Heart & Lung Institute, Imperial College Faculty of Medicine, London. Oxidative stress inhibits histone deacetylases: a mechanism of steroid resistance in COPD.

While corticosteroids are highly effective as anti-inflammatory treatments in asthma, they provide
little clinical benefit in chronic obstructive pulmonary disease (COPD) and do not suppress the chronic inflammatory process. We have demonstrated that alveolar macrophages from normal smokers and to a greater extent from patients with COPD have increased basal expression of inflammatory genes, such as TNF-α, IL-8 and MMP-9 in vitro. There is also an amplified response to cigarette smoke-conditioned medium (CSM), but little or no suppression even by high concentrations of corticosteroids, compared to normal macrophages. CSM activates proinflammatory transcription factors, such as NF-κB, which results in acetylation of core histones, particularly histone-4, leading to increased transcription of multiple inflammatory genes. Corticosteroids normally suppress inflammation by recruiting histone deacetylases (HDAC) to the active transcriptional complex. However, in alveolar macrophages from smokers and COPD patients there is a marked reduction in HDAC activity, and this is correlated with both the increased expression of inflammatory proteins and reduced responsiveness to corticosteroids. We have shown a striking reduction in HDAC activity and expression in peripheral lung of patients with COPD compared to normal subjects, with selective reduction of HDAC2 and HDAC5. Inhibition of HDAC2 expression using interference RNA reduces steroid responsiveness. There is nitration of tyrosine residues on HDAC2, which correlates with reduced HDAC activity and a rightward shift in the dose-response to corticosteroids. This is restored by the antioxidants N-acetyl cysteine and ebselen. In an epithelial cell line (A549) we have demonstrated that H₂O₂ selectively reduces HDAC2 by 72% and HDAC5 by 38%, with little or no effect on other HDACs. This suggests that oxidative and nitrosative stress in COPD patients impairs HDAC activity, which both amplifies inflammatory gene expression and impairs responsiveness to corticosteroids. More effective antioxidants, inhibitors of inducible nitric oxide synthase or theophylline (which directly activates HDACs), may therefore be predicted to restore steroid responsiveness in COPD.

9.50 a.m. (8)
D.E. Newby (introduced), D.J. Webb, K.A.A. Fox, N.A. Boon. Departments of Cardiology and Clinical Pharmacology, University of Edinburgh, Royal Infirmary, Edinburgh. Clots, Kinins and Coronaries: beneficial effects of ACE inhibition on endogenous fibrinolysis.

The fibrinolytic factor, tissue plasminogen activator (t-PA), is a serine protease that regulates the degradation of intravascular fibrin and is released from the endothelium through the rapid translocation of a dynamic intracellular storage pool. Using selective local intra-arterial infusions, we have been able to develop and characterize a novel model of assessing the acute release of endogenous t-PA in the peripheral and coronary circulations of man. This has enabled us to demonstrate, for the first time, that the coronary atheromatous plaque burden (as determined by three dimensional reconstructions of intracoronary ultrasound images) inversely correlates with acute local t-PA release from the heart (r = −0.61, p = 0.003).

Large-scale clinical trials in patients with heart failure or ischaemic heart disease indicate a major reduction in re-infarction rates with ACE inhibitor therapy. Bradykinin, a potent stimulus for endothelial t-PA release, is generated during the contact phase of blood coagulation triggered by atherosclerotic plaque rupture. We therefore investigated the influence of ACE inhibition on the contribution of bradykinin to vascular tone and t-PA release. Using highly selective antagonists, we have shown that bradykinin contributes to the vasodilatation associated with chronic ACE inhibitor therapy in patients with heart failure (p = 0.01). Additionally, ACE inhibitor therapy augments bradykinin-induced vasodilatation and t-PA release, especially in patients with heart failure and ischaemic heart disease (up to 10-fold increase; p < 0.001). Indeed, maximal plasma t-PA activity approached 100 IU/ml with a forearm protein release of ~4.5 μg/min (p < 0.001). At this level, local t-PA activity approaches that seen during systemic thrombolytic therapy for myocardial infarction. Thus, the potentiation of bradykinin-mediated vasodilatation and t-PA release may contribute to the primary anti-ischaemic benefits of chronic ACE inhibitor therapy.

Coronary atherosclerosis impairs local vascular t-PA release in man. ACE inhibitor therapy markedly potentiates bradykinin-mediated vasodilatation and t-PA release, and may explain its anti-ischaemic benefits.

10.15 a.m. (9)
J.P. Legg (introduced), S.L. Johnston, J.A. Warner (introduced), J.O. Warner. Allergy and Inflammation Sciences Division (Child Health), University of Southampton, Southampton. Deficient type 1 immunity in bronchiolitis and role of antenatal sensitization to RSV.
Respiratory syncytial virus bronchiolitis is a major cause of childhood morbidity and mortality and is associated with the later development of wheezing/asthma. Most infants are infected with respiratory syncytial virus in the first year of life, but a minority develop bronchiolitis for reasons unknown. We prospectively studied the immune responses of 88 infants who developed mild upper respiratory tract infection alone or acute bronchiolitis during their first natural respiratory syncytial virus infection. Infants with bronchiolitis had impaired type 1 cytokine production, increased type 2/type 1 cytokine ratios in nasal fluid and peripheral blood, impaired IL-18 production and impaired virus clearance compared with infants with upper respiratory infection. These results indicate that augmenting type 1 responses might be beneficial in infants at risk of developing respiratory syncytial virus bronchiolitis and subsequent asthma.

Bronchiolitis has a peak age incidence of 2–4 months and augmenting type 1 responses this early in life is problematic. Therefore, in the knowledge that antenatal sensitization to soluble protein antigens occurs from 22 weeks gestation, we also investigated whether antenatal sensitization to respiratory syncytial virus could occur, and whether this would augment type 1 or type 2 immunity. We observed respiratory syncytial virus-specific proliferative responses in one-third of cord blood samples taken from infants whose mothers had been potentially exposed to respiratory syncytial virus from 22 weeks gestation. Respiratory syncytial virus-induced proliferative responses were associated with induction of type 1 but not type 2 cytokines.

These data confirm that sensitization to respiratory syncytial virus can occur antenatally if the mother is exposed at the appropriate stage of gestation and that this exposure is associated with augmentation of protective type 1 immunity. These data combined suggest maternal immunization after 22 weeks gestation as a novel strategy for augmenting respiratory syncytial virus-specific type 1 immunity.

11.10 a.m. (10)

D. Wynick, P. Li (introduced). URCN, Bristol University, Bristol. **An activating mutation in the pituitary galanin receptor may be responsible for a sub-set of human prolactinomas.**

The neuropeptide galanin is predominantly expressed by the prolactin-secreting cells (lactotrophs) in the rodent anterior pituitary. Prolactin and galanin co-localize in the same secretory granule, the expression of both proteins is extremely sensitive to the oestrogen status of the animal. We have previously shown that knock-out of galanin reduces pituitary prolactin message levels and protein content of adult female mutant mice by 30–40% compared with wild-type controls. There is an almost complete abrogation of the proliferative response of the lactotroph to high doses of oestrogen, with a failure to up-regulate prolactin release, STAT5 expression or to increase pituitary cell numbers. In contrast, constitutive and sustained over-expression of pituitary galanin in transgenic mice increases prolactin expression and induces hyperplasia of the gland followed by adenoma formation. These studies provide good evidence for a causal role for galanin as a growth factor to the lactotroph. A novel galanin receptor sub-type, designated GALR2, has been identified in the pituitary. We now report the screening of a bank of human pituitary tumours for mutations in the GALR2 using conformation-sensitive gel electrophoresis. A single base-pair mutation has been identified in two unrelated individuals that is tumour specific. The mutation occurs in the cytoplasmic C-terminal tail of the gene and appears to be specific to prolactinomas. We have established stable cell lines expressing either the mutant or wild-type receptor. The mutation induces a supra-normal dose-dependent stimulation of PKC and ERK activity for any given concentration of ligand but does not constitutively activate the receptor in the absence of ligand. Using an adenoviral expression system we have demonstrated that the mutation stimulates proliferation in an endocrine clonal cell line (SCLC) in an ERK-dependent manner. These studies represent the first candidate gene to be associated with the commonest human pituitary tumour type, the prolactinoma.

11.35 a.m. (11)

P. Flood-Page¹ (introduced), A. Menzies-Gow¹ (introduced), A. Wangoo¹ (introduced), N.C. Barnes², J. Barkans¹ (introduced), S. Phipps¹ (introduced), D.S. Robinson¹ (introduced), A.B. Kay¹. ¹Department of Allergy and Clinical Immunology, Faculty of Medicine, Imperial College London, National Heart and Lung Institute, London; ²Department of Respiratory Medicine, Barts and the Royal London Hospitals Trust, London. **Intravenous administration of an anti-IL-5 monoclonal antibody to mild atopic asthmatics reduces the expression of tenascin, procollagen 111 and lumican in the bronchial mucosal reticular basement membrane: evidence for a role for eosinophils in airways remodelling.**

The deposition of extracellular matrix proteins in the bronchial reticular basement membrane (RBM) is characteristic of airway remodelling in chronic
asthma. Eosinophils have been previously implicated in wound healing and remodelling events associated with allergic inflammation. We have studied the effect of eosinophil reduction by an anti-IL-5 monoclonal antibody on the expression of three extracellular matrix proteins—tenascin, lumican and procollagen III. Twenty-four mild atopic asthmatics were randomized to receive three infusions of mepolizumab (a humanized, monoclonal antibody directed against IL-5) or placebo in a double-blind parallel group design over an eight-week period. Bronchoscopy with bronchial mucosal biopsy and bronchoalveolar lavage was performed before and after treatment. The thickness and density of tenascin, lumican and procollagen III immunoreactivity in the RBM were quantified using confocal microscopy. At baseline, the thickness of extracellular matrix protein deposition was increased in the RBM of asthmatics compared with non-asthmatics (tenascin, p = 0.004, lumican, p < 0.0001, and procollagen III, p < 0.0001) and in asthmatics, tenascin thickness correlated with eosinophil numbers (r = 0.617, p = 0.0007). Treatment with mepolizumab significantly reduced the expression of tenascin (p = 0.004), lumican (p = 0.008) and procollagen III (p = 0.007) in the RBM as well as the numbers of eosinophils (p = 0.009) and the concentration of TGF-b1 in bronchoalveolar lavage fluid (p = 0.042). We conclude that eosinophils may contribute to tissue remodelling processes in asthma by regulating deposition of extracellular matrix proteins in the bronchial mucosal basement membrane.

12 noon (12)
F.E. Karet1, M.A.J. Devonald2, G. Ihrke1 (introduced by D.A. Lomas). Departments of 1Medical Genetics and 2Clinical Biochemistry, University of Cambridge, Cambridge, Institute for Medical Research, Addenbrooke’s Hospital, Cambridge. Non-polarized targeting of AE1 causes autosomal dominant distal renal tubular acidosis.

Autosomal dominant distal renal tubular acidosis (ddRTA) is caused by mutations in SLC4A1, encoding the Cl-/HCO3- exchanger AE1 found at the basolateral surface of α-intercalated cells (α-IC) in the distal nephron. Most reported mutations involve a missense alteration of R589. We have reported a complex mutation that instead truncates AE1 by 11 residues at the C-terminus. As data suggest that ddRTA is not explained simply by haploinsufficiency, we investigated whether mis-targeting of AE1 could explain the disease. We examined distribution of epitope-tagged AE1 (AE1wt) and a similar construct introducing the truncation (AE1Tr), in two polarized renal epithelial cell lines (MDCK and IMCD). AE1wt localized exclusively to the basolateral plasma membrane domain. In contrast, AE1Tr appeared at both basolateral and apical cell surfaces, with a minor fraction seen intracellularly. We used CD8, an apical reporter protein, to assess the basolateral targeting effect of the isolated C-terminus of AE1. A chimera containing mutant AE1 tail in place of the C-terminus of CD8 (CD8-AE1Tr) remained at the apical surface, whereas wild-type tail (CD8-AE1wt) was able to redirect a proportion of the protein to the basolateral surface, supporting the presence of a basolateral targeting motif within the C-terminal 11 amino acids. This sequence includes YDEV, which we predicted to be a sorting motif of the YXXØ type. Substitution of Y904 with A recapitulated the non-polarized distribution of AE1Tr, confirming this residue to be critical. Finally we determined that targeting of AE1 is independent of the AP-1B adaptor protein by expression studies in LLC-PK1 cells. Our data implicate aberrant targeting of AE1 to the apical surface as the primary cause of α-IC dysfunction in this form of ddRTA at least, and is the first example of a primary renal transporter disorder of epithelial polarity.

12.25 p.m. (13)
R.L. Batterham, S.R. Bloom. Imperial College Faculty of Medicine at Hammersmith Campus, London. The gut hormone peptide YY3-36 regulates food intake in humans.

Obesity is a major cause of morbidity and mortality. Understanding the mechanisms controlling food intake may help elucidate the pathogenesis of obesity and identify new treatments. The hypothalamic arcuate nucleus is a key brain area regulating appetite. Activation of arcuate neuropeptide Y (NPY) neurons increases food intake while activation of pro-opiomelanocortin (POMC) neurons decreases food intake. These neuronal subsets respond to circulating hormones that reflect body energy status such as leptin. In contrast, the identity of peripheral factors signalling food ingestion to these circuits remains unclear. The Y2-receptor is an inhibitory auto-receptor expressed on arcuate NPY neurons. Peptide YY3–36 (PYY3–36), a Y2-receptor agonist, is released from the gut postprandially in proportion to calories ingested. Thus PYY3–36 is a candidate signal from the gut to the appetite circuits in the brain. We examined the effects of PYY3–36 on feeding behaviour. In rodents, peripheral administration of PYY3–36 inhibited food intake and decreased body-weight. However, Y2-receptor knockout mice were resistant to the anorectic effect of PYY3–36, suggesting that PYY3–36 acts via this receptor. PYY3–36 administration increased arcuate POMC neuronal activation as determined...
by c-fos expression. Electrophysiological studies revealed that PYY$_{3-36}$ inhibited NPY neurons and activated POMC neurons. To investigate the role of PYY$_{3-36}$ in humans we infused saline or PYY$_{3-36}$ to 12 normal-weight volunteers in a randomized crossover double-blind study. PYY$_{3-36}$ infusion decreased appetite and total 24-h food intake by 33 ± 7.4%. To assess the potential role of PYY$_{3-36}$ as an obesity treatment, we studied 12 obese subjects. PYY$_{3-36}$ infusion reduced appetite and food intake (24-h caloric intake; saline = 3341 ± 401 kcal vs. PYY$_{3-36}$ = 2534 ± 195 kcal, p < 0.01). These findings suggest that PYY$_{3-36}$ acts via the arcuate Y2-receptor to regulate food intake and may be a potential obesity treatment.

3.00 p.m. (14)
D.C. Crowther, K. Kinghorn, D. Belorgey, L. Serpell, L. Sharp, L. Sharp, D. Gubb$^*$ (all introduced) and D.A. Lomas. Department of Medicine, University of Cambridge, Cambridge Institute for Medical Research and $^*$Department of Genetics, University of Cambridge, Cambridge. Neuroserpin binds to the A$\beta_{1-42}$ peptide in Alzheimer’s plaques and modulates neurotoxicity.

We have described a novel inclusion body dementia, FENIB, that results from point mutations in the neuroserpin gene (Nature 1999; 401:376–379). More recently we have shown that wild-type neuroserpin is co-localized to the neuritic plaques in the brains of patients with Alzheimer’s disease. We have now shown that there is a specific interaction between neuroserpin and the A$\beta_{1-42}$ Alzheimer’s peptide in vitro and in vivo. Recombinant wild-type neuroserpin binds to A$\beta_{1-42}$ to form a complex with a 1:1 stoichiometry that is inactive as a proteinase inhibitor and stable in 8M urea. Moreover neuroserpin accelerates the oligomerization of A$\beta_{1-42}$ as assessed by fluorescence assays using the fluorophore thioflavin T and electron microscopy. The importance of this interaction between neuroserpin and A$\beta_{1-42}$ is underscored by its effect in a standard cell culture model of A$\beta_{1-42}$ neurotoxicity. PC12 cells were titrated with A$\beta_{1-42}$ to give 50% cell viability at 36 hours. Wild-type neuroserpin alone was not toxic. However the combination of wild-type neuroserpin with A$\beta_{1-42}$ markedly reduced neurotoxicity. Similar data have also been obtained using primary rat neurones. The effect is not seen if the A$\beta_{1-42}$ peptide is incubated with another members of the serpin superfamily (z$_1$-antitrypsin) or if neuroserpin was inactivated by polymerization. The neuroserpin-A$\beta_{1-42}$ interaction was proven at the level of the organism by developing a Drosophila model of Alzheimer’s disease. Co-expression of neuroserpin with the A$\beta_{1-42}$ rescued the Alzheimer’s phenotype. Taken together, our data show that neuroserpin binds to A$\beta_{1-42}$ favouring the rapid conversion of toxic oligomers of A$\beta_{1-42}$ to fibrils and thereby reducing neuronal damage in Alzheimer’s disease.

3.25 p.m. (15)
J.C. Alcolado, P. Lang, M. Evans, R. Gill-Randall (all introduced by M.F. Scanlon). Departments of Medicine and Cardiology, University of Wales College of Medicine, Cardiff. Endothelial dysfunction in adult offspring reared in a diabetic uterus: an embryo transfer experiment.

Although genetic factors are undoubtedly involved in the inheritance of Type 2 diabetes, other mechanisms play a role. These include the effects of impaired intrauterine nutrition (the thrifty phenotype hypothesis) and exposure of the developing embryo to hyperglycaemia (the fuel-mediated teratogenesis hypothesis). In order to investigate these influences we have developed an embryo transfer model of diabetes. Briefly, day-old Wistar rat embryos, at low genetic risk of diabetes, are transferred into either the uterus of a Wistar rat (W/W control group) or the uterus of a diabetic Goto Kakizaki rat (W/GK group). The resultant offspring are genetically similar but differ as to whether they have developed in a euglycaemic or hyperglycaemic environment.

The aim of the present study was to investigate the endothelial function of adult offspring using isolated preparations of endothelium–intact aorta. Tissues were prepared for isometric tension recording and incubated at 37°C for 3 hours in the absence or presence of either folic acid (FA 50 µM) or sepiapterin (SEP, the precursor of BH4, 10 µM). All rings were constricted with phenylephrine (PE, 1 µM) before exposure to acetylcholine (ACh, 1 nM–10 µM). After washing rings were reconstricted with PE followed by exposure to the endothelium-independent vasodilator sodium nitroprusside (SNP, 1 nM–10 µM) and the maximum relaxation (R$_{max}$) responses compared using ANOVA.

In W/GK rats, endothelium-dependent relaxation to ACh (R$_{max}$ 72.8 ± 2.6%) was significantly (p < 0.01) impaired when compared to W/W rats (R$_{max}$ 95.5 ± 1.2%). Incubation of tissues for W/GK rats with FA or SEP significantly (p < 0.01) reversed the inhibition of endothelium-dependent relaxation (R$_{max}$ 88.7 ± 2.4 and 87.4 ± 1.6% respectively). No differences in R$_{max}$ values were observed between any of the groups with SNP.

These data demonstrate endothelial dysfunction in adult Wistar rats that have developed in a diabetic (GK uterus). Furthermore, FA and BH4
reversed the endothelial dysfunction, probably due to augmented NO production. These results may have important implications for the increasing number of children born to mothers with gestational diabetes.

3.50 p.m. (16)
E.M. Gurnell¹, P.J. Hunt², S.E. Curran¹, C.L. Conway², F.A. Huppert¹, J. Herbert⁴ (all introduced), V.K.K. Chatterjee¹. Departments of ¹Medicine, ²Psychiatry, ⁴Anatomy, University of Cambridge, ³Department of Endocrinology, Christchurch Hospital, New Zealand. DHEA replacement in Addison’s disease

Dehydroepiandrosterone (DHEA), is the major circulating adrenal steroid and a substrate for sex hormone biosynthesis in peripheral tissues. In Addison’s disease, glucocorticoid and mineralocorticoid deficiencies require lifelong hormone replacement, but the associated near-total failure of DHEA synthesis is not corrected. In a double-blind trial, we randomized 106 (44 males, 62 females) patients with Addison’s disease to receive either 50 mg of DHEA or placebo orally for 12 months, with measurement of biochemical and psychological parameters, together with bone mineral density (BMD) and body composition. Circulating DHEAS and androstenedione rose significantly in both sexes, but testosterone increased to low normal levels only in females. At baseline, subscales of well-being (SF-36, GHQ-30 questionnaires) were significantly worse in patients versus control populations (p<0.001), improving at 3 and 6 months (p=0.03) following treatment, with marked deterioration (p=0.03 to <0.001) following washout of DHEA at the end of the study. After DHEA, both physical (p=0.04) and mental (p=0.03) fatigue were lessened significantly. DHEA enhanced total body (p=0.03) and truncal (p=0.02) lean mass with no change in fat mass; BMD increased at the femoral neck (p=0.05) but not other sites. Supraphysiological DHEAS levels were achieved in older females who experienced some androgenic side-effects (spots, greasy skin, axillary hair growth). Our results show that DHEA replacement corrects this hormone deficiency in Addison’s disease with improvement in fatigue, well-being, body composition and bone mineral density. Beneficial psychological effects in males, without changes in sex steroid levels, suggest that DHEA may also act directly as a neurosteroid. If further studies, with adjustment of dosage, establish its long-term benefit and safety, the addition of DHEA to conventional steroid hormone replacement therapy in Addison’s disease may be indicated.

4.45 p.m. (17)
S.C. Ferguson¹, A. Blane², J. Wardlaw², P. Perros¹, R.J. McCrimmon¹, I.J. Deary², (all introduced). B.M. Frier. ¹Department of Diabetes, Royal Infirmary of Edinburgh, ²Department of Clinical Neurosciences, University of Edinburgh and ³Department of Psychology, University of Edinburgh. The onset age of type 1 diabetes influences intellectual ability and brain structure in adulthood.

The onset of type 1 diabetes (T1DM) during childhood may compromise intellectual development, and ability; children who develop T1DM aged <7 years have comparatively poorer cognitive ability in adulthood. Whether this relates to psychosocial and education factors or an organic cause related to diabetes and its complications remains unresolved. If differences in cognitive ability could be demonstrated between two well-defined patient groups, defined as early onset (<7 years) or later onset (>7 years) T1DM, it was proposed that neuroimaging may help elucidate the pathogenesis of any cognitive difference.

The effects of diabetes onset age on cognitive ability (psychometric test battery) and brain structure (magnetic resonance imaging) were examined in a cross-sectional evaluation of 71 young adults who had long-duration T1DM, diagnosed during childhood or adolescence. Severe hypoglycaemia exposure, retinopathy status and diabetes duration were also examined as possible correlates of cognitive and brain structure differences. Multivariate general linear modelling and logistic regression were used to determine whether significant differences existed between groups of interest. No participants had previous neuropsychological pathology.

The onset age of T1DM independently predicted cognitive performance (F = 3.0, p = 0.03) and brain volumes (F = 4.0, p = 0.04). Current intellectual ability (WAIS-R performance IQ, p=0.03) and information processing ability (Choice reaction time, p=0.006) were comparatively poorer in those with early onset T1DM. Furthermore, lateral ventricular volumes were greater (p=0.002) and ventricular atrophy was more prevalent (60% vs. 20%, odds ratio 4.6, p=0.01) when compared to those with later onset T1DM.

The onset of T1DM in early childhood was independently associated with the presence of mild central brain atrophy and modest differences in intellectual ability in adulthood. An organic, rather than psychosocial pathogenesis is implied by these observations which suggest that the onset of T1DM in early childhood may affect neurodevelopment adversely.
Demonstrations

1. Evidence for effects by alpha-melanocyte stimulating hormone on ultraviolet radiation-induced apoptosis. Healy E. Allergy & Inflammation Sciences, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

2. Carbamazepine-specific T cells are detected in drug-allergic patients after metabolic bioactivation by peripheral blood mononuclear cells. Acharya N, Smith A, Strickland I, Hawkins Z, Friedmann PS. Allergy & Inflammation Sciences, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

3. Alpha-melanocyte stimulating hormone suppresses antigen-driven lymphocyte proliferation in vitro, which is unrelated to MC1R genotype. Cooper A, Robinson SJ, Jackson C, Al-Bader T, Friedmann PS, Healy E. Allergy & Inflammation Sciences, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

4. Investigation of percutaneous absorption of anti-viral agents using microdialysis. Morgan CJ, Renwick AG, Friedmann PS. Allergy & Inflammation Sciences, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

5. Dermal levels of penciclovir following oral administration of famciclovir measured by microdialysis. Morgan CJ, Renwick AG, Friedmann PS. Allergy & Inflammation Sciences, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

6. Vascular function of non-lesional skin in psoriasis. Platt SD, Friedmann PS, Clough G. Allergy & Inflammation Sciences, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

7. Polymorphisms of the growth hormone gene are associated with adult bone mass and infant growth. Dennison E, Day I, Voropanov A, Syddall H, Cooper C. MRC Environmental Epidemiology Unit & Dept Rheumatology, Southampton General Hospital.

8. Is human aging related to early growth? Aihie-Sayer A, Rauf A, Evans JR, Wormald RPL, Barker DJP, Cooper C. MRC Environmental Epidemiology Unit & Dept Rheumatology, Southampton General Hospital.

9. Haplotypic associations of the growth hormone gene cluster with early growth and later life insulin resistance. Day I, Gaunt T, Rodrigues S. Genetics Group, Foetal Origins Of Adult Disease Division Division, School of Medicine, University of Southampton.

10. Identification of novel tumour antigens in human lung cancer. Darby AJ, Johnson P, Elliott T. Cancer Research UK Oncology Unit, University of Southampton.

11. DNA vaccine therapy for lymphoma. Ottensmeier C, Stevenson F. Cancer Sciences Division, School of Medicine, University of Southampton.

12. Malnutrition on hospital wards—achieving change. Stratton R, King C, Elia M, Jackson AA, Stroud M. Institute of human nutrition, University of Southampton, Southampton General Hospital.

13. Causal attributions for somatic sensations in patients with chronic fatigue syndrome and their partners. Butler JA, Chalder T, Wessely S. University Department of Psychiatry, Southampton; Institute of Psychiatry, London.

14. Potentially modifiable correlates of non-adherence with immunosuppressants following renal transplantation. Butler JA, Peveler RC, Roderick PK, Horne R, Mason JC. Mental Health Group & Healthcare Research Unit, University of Southampton; Healthcare Research, University of Brighton; Wessex Renal Unit, Portsmouth.

15. Patients with vascular dementia differ from patients with Alzheimer’s disease with respect to population characteristics and pattern of cognitive decline. Wilkinson DG, Pratt RD. Memory Assessment and Research Centre, Moorgreen Hospital, Southampton, UK; Division of Clinical Neurosciences University of Southampton, & Eisai Inc., Teaneck, New Jersey, United States.

16. Systemic infection, interleukin-1b and cognitive decline in Alzheimer’s disease. Holmes C, EI-Okl M, Williams AL, Cunningham C, Wilcockson D, Perry VH. Memory Assessment and Research Centre, Division of Clinical Neurosciences. University of Southampton.
17. A failure in SMAD signalling contributes to sustained NF-kB activation in chronic inflammatory bowel disease. Monteleone G, Mann J, Monteleone I, Vavassori P, Bremner R, Fantini M, Tersigni R, Alessandroni L, Mann D, Pallone F, MacDonald TT. Cattedra di Gastroenterologia, Universita Tor Vergata, Rome Italy & Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

18. Activated STAT4 and a functional role for IL-12 in human Peyer’s patches. Monteleone G, Holloway J, Salvati VM, Pender SLF, Fairclough PD, Croft N, MacDonald TT. Infection, Inflammation & Repair Division, School of Medicine, University of Southampton, Dept of Pediatrics, University Federico II, Naples Italy & Dept of Adult and Paediatric Gastroenterology, St Bartholomew’s & the Royal London School of Medicine, London.

19. NFkB and hepatic fibrosis: Novel regulatory mechanisms and therapeutic advances. Mann D. Tissue remodelling & repair group, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

20. Matrix metalloproteinase-2 promotes hepatic stellate cell apoptosis via degradation of collagen-I and N-Cadherin: Implications for spontaneous resolution of liver fibrosis. Murphy FR, Zhou X, Hussain H, Collins JE, Nagase H, Brew K, Krane S, Arthur MJP, Mann D, Benyon RC, Iredale JP. Tissue remodelling & repair group, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

21. Killer cell immunoglobulin-like receptor (KIR) mRNA expression in natural killer cells. Khakoo S. Tissue remodelling & repair group, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

22. Modulation of hepatic stellate cell proliferation and activation by extracellular matrix and integrins—a pertinent regulatory mechanism in liver fibrogenesis. Zhou X, Gaca M, Iredale JP, Benyon RC. Tissue remodelling & repair group, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

23. Pro-inflammatory cytokines and coronary heart disease. Sheron N. Tissue remodelling & repair group, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

24. Dendritic cell phenotype and function in chronic hepatitis C infection. Rosenberg W. Tissue remodelling & repair group, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

25. Models of mucous hypersecretion in airway disease. Puddicombe S, Steel M, Djukanovic R, Holgate ST, Davies DE. Respiratory Cell & Molecular Biology, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

26. TNF alpha as an important therapeutic target in asthma. Babu S, Yang Y, Davies DE, Puddicombe S, Chauhan A, Howarth PH, Holgate ST. Respiratory Cell & Molecular Biology, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

27. Anti-IgE: a novel treatment for asthma. Djukanovic R, Holgate ST, Howarth PH, Wilson SJ. Respiratory Cell & Molecular Biology, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

28. Role of pharmacogenetics in determining leukotriene receptor antagonist responsiveness in asthma. Holloway J, Howarth PH, Holgate ST, Sampson AP. Respiratory Cell & Molecular Biology, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

29. Airways remodelling in asthma. Howarth PH, Lau L, Redington A, Shute J, McConnell W, Beckett P. Respiratory Cell & Molecular Biology, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

30. Mechanisms for the adverse health effects of particulate pollution. Parnia S, Puddicombe SM, Berubé K, Richter A, Holgate ST, Frew AJ, Davies DE. Respiratory Cell & Molecular Biology, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

31. Sublingual grass pollen immunotherapy for hay fever: a two year double-blind, placebo-controlled study. Smith HE, White PJ, Poole J, Frew AJ. Wessex Primary Care Research Network & Respiratory Cell & Molecular Biology, Infection, Inflammation & Repair Division, School of Medicine, University of Southampton.

32. Interaction between air pollution and respiratory virus infection in childhood.
33. **Early life predictors of atopy and childhood asthma.** Expression of PPAR alpha correlates with expression of PPAR alpha response genes in fat metabolism in vivo in human skeletal muscle. Zhang J, Phillips DIW, Wang C, Byrne CD. Endocrinology & Metabolism Unit, Foetal Origins Of Adult Disease Division, School of Medicine, University of Southampton.

34. **Should waist circumference be used as the measure of obesity to identify men at risk of the metabolic syndrome?** Holt H. Endocrinology & Metabolism Unit, Foetal Origins Of Adult Disease Division, School of Medicine, University of Southampton.

35. **Electrical muscle stimulation acutely increases energy expenditure but does not reduce features of the metabolic syndrome in women with type 2 diabetes.** Poole R. Endocrinology & Metabolism Unit, Foetal Origins Of Adult Disease Division, School of Medicine, University of Southampton.

36. **Oestrogen replacement in postmenopausal women with type 2 diabetes promotes resistance to the anticoagulant activated protein C.** Englyst N, Masding M, Stears A, Sandeman DD, Byrne CD. Endocrinology & Metabolism Unit, Institute of Human Nutrition, and Diabetes & Endocrinology, Southampton University Hospitals Trust.