PATHOLOGICAL SOCIETY
OF GREAT BRITAIN AND IRELAND

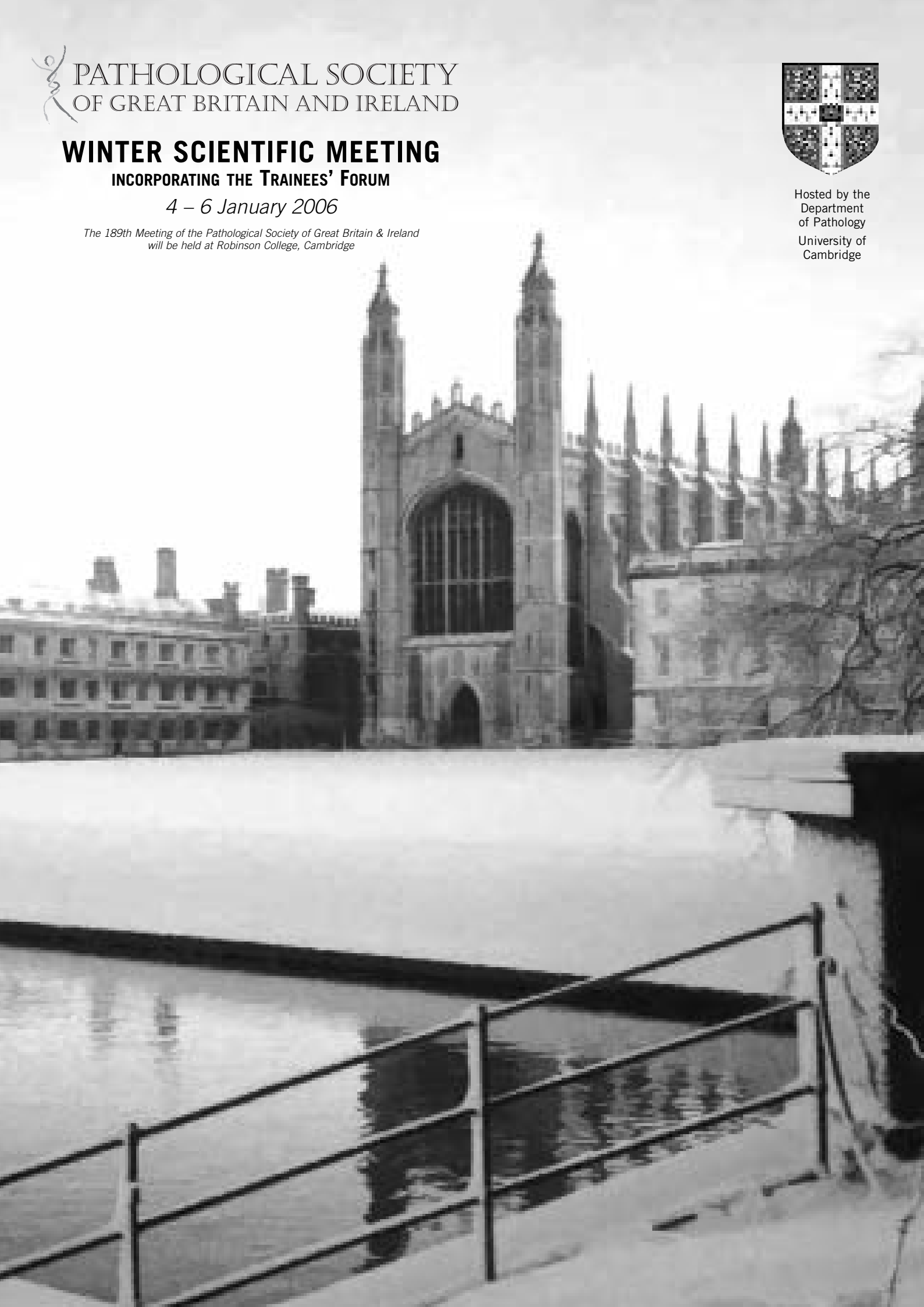
WINTER SCIENTIFIC MEETING

INCORPORATING THE TRAINEES' FORUM

4 – 6 January 2006

The 189th Meeting of the Pathological Society of Great Britain & Ireland will be held at Robinson College, Cambridge

Hosted by the Department of Pathology
University of Cambridge



CONTENTS

PROGRAMME ACKNOWLEDGEMENTS

Published by
The Pathological Society of Great Britain & Ireland

COVER PHOTOGRAPH
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Programme is typeset in Times and ITC Stone Sans

This programme was designed, produced and printed in England by
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PROGRAMME SYNPOSIS AND TIMETABLE

(Showing times, sessions and venues)

WEDNESDAY 4 JANUARY

09.00	**Registration** *(Auditorium Foyer)* **& Coffee** *(Balcony and Umney Foyer)*
09.30–17.00	Slide Seminar Competition – Case Viewing *(Garden Room)*
09.50–13.00	Trainees Forum *(Umney Lecture Theatre)*
11.00–11.30	Coffee *(Balcony and Umney Foyer)*
13.00–14.00	Lunch *(Garden Restaurant)* and Trade Exhibition *(Balcony, Umney Foyer and Junior Common Room)*
14.00–17.00	Symposium: *Developing Themes in Pathology (Auditorium Lecture Theatre)*
15.00–15.30	Tea *(Balcony and Umney Foyer)*
17.15–18.00	Royal College of Pathologist's Cameron Lecture, Dr K Polyak, Boston: *The role of the tumour microenvironment in breast cancer (Auditorium Lecture Theatre)*
18.30–20.00	Welcome Reception *(The Hall, King's College)*

THURSDAY 5 JANUARY

09.00–15.30	Slide Seminar Competition – Case Viewing *(Garden Room)*
09.15–09.30	Opening Address: Prof AH Wyllie, University of Cambridge *(Auditorium Lecture Theatre)*
09.30–13.00	Symposium: *Breast Cancer: theory into practice (Auditorium Lecture Theatre)*
11.00–11.30	Coffee *(Balcony and Umney Foyer)*
13.00–14.00	Lunch *(Garden Restaurant)* & Trade Exhibition *(Balcony, Umney Foyer and Junior Common Room)*
13.15–14.15	Academic Pathology Forum *(Auditorium Lecture Theatre)*
14.00–15.30	Poster Presentations & Rounds (All Categories) *(Balcony, Umney Foyer and Junior Common Room)*
15.00–16.00	Renal EQA Meeting *(Umney Lecture Theatre)*
15.30–16.00	Tea *(Balcony and Umney Foyer)*
16.00–17.00	Plenary Oral Communications *(Auditorium Lecture Theatre)*
17.15–18.00	Pathological Society's 2nd RB Goudie Lecture, Prof IR Hart, London *Tumour specific integrins in cancer invasion: functional effects and targeting possibilities (Auditorium Lecture Theatre)*
19.30	Society Dinner *(The Hall, Robinson College)*

FRIDAY 6 JANUARY

09.00–13.00	Oral Communications *(Auditorium and Umney Lecture Theatres)*
10.45–11.15	Coffee *(Balcony and Umney Foyer)*
13.00–14.00	Lunch *(Garden Restaurant)* and Trade Exhibition *(Balcony, Umney Foyer and Junior Common Room)*
14.00–17.00	Symposium: *Angiogenesis in Health and Disease (Auditorium Lecture Theatre)*
15.30–16.00	Tea *(Balcony and Umney Foyer)*

SCIENTIFIC SESSIONS INFORMATION

PLENARY ORAL SESSION *(Auditorium Lecture Theatre)*
The plenary oral session, in which the 4 highest-ranked submitted oral abstracts will be presented, will be held on **Thursday 5 January at 16.00–17.00 hrs**.

Prize: A prize for the best presentation, donated by the *Journal of Pathology* will be presented at the Society Dinner.

ORAL COMMUNICATIONS *(Auditorium and Umney Lecture Theatres)*
Oral communication sessions will be held on **Friday 6 January at 09.00–10.45hrs and 11.15–13.00 hrs**.

Note to presenters: Speakers are reminded that no communication may exceed the time allocated on the programme without the consent of the meeting, obtained through the Chairman.

POSTERS / VIEWING *(Balcony, Umney Foyer and Junior Common Room)*
Posters will be displayed on **Wednesday 4**, **Thursday 5** and **Friday 6 January**.
The dedicated poster viewing session will be on **Thursday 5 January at 14.00–15.30 hrs**.

*Ideally, posters should be **in place by 11.00 hrs on Wednesday 4 January** and **removed by 16.00 hrs on Friday 6 January**. At least one of the contributors must be in attendance during the viewing period, as indicated in the programme synopsis.*

Prizes: Prizes are awarded for the three best posters: The Sir Alastair Currie Prize, Second and Third prizes will be presented at the Society Dinner.

SYMPOSIA *(Auditorium Lecture Theatre)*
Three symposia will be held:

Wednesday 4 January at 14.00–17.00 hrs: *Developing Themes in Pathology*
Thursday 5 January at 09.30–13.00 hrs: *Breast Cancer: theory into practice*
Friday 6 January at 14.00–17.00 hrs: *Angiogenesis in Health and Disease*

SLIDE SEMINAR COMPETITION – *Breast Pathology (Garden Room)*
There will be a slide competition using digital slide images, which will be available for viewing on **Wednesday 4 January at 09.30–17.00 hrs** and on **Thursday 5 January at 09.00–15.30 hrs**.

Prize: A case of champagne will be awarded at the Society Dinner *(by tradition, distributed amongst those present!)*.

GUEST AND SOCIETY LECTURES *(Auditorium Lecture Theatre)*

Wednesday 4 January at 17.15–18.00 hrs
The Royal College of Pathologists' Cameron Lecture entitled: *The role of the tumour microenvironment in breast cancer,* will be given by Dr K Polyak, Dana-Farber Cancer Institute, Boston, USA.

Thursday 5 January at 17.15–18.00 hrs
The Pathological Society of Great Britain & Ireland's 2nd Goudie Lecture entitled: *Tumour specific integrins in cancer invasion: functional effects and targeting possibilities*, will be given by Prof IR Hart, Institute of Cancer Research, London.

TRADE EXHIBITION *(Balcony, Umney Foyer and Junior Common Room)*
Delegates are encouraged to visit the Trade Exhibition and are requested to support the companies represented there.

Quiz: Enter the exhibitors quiz and win a bottle of champagne. Quiz papers will be available on each stand.

CONTINUING PROFESSIONAL DEVELOPMENT (CPD)
This Meeting has been approved by the **Royal College of Pathologists** for the purposes of Continuing Professional Development. **Delegates who are eligible for CPD points should collect their certificates at the Registration Desk before leaving the Meeting.**
Credits can be accrued as follows – for each full day: 7 points,
for each half day: 3 points.

General Arrangements

REGISTRATION

Registration is only available via this website: **http://pathsoc.conference-services.net/directory.asp**

FEES

Fees include all refreshments and lunch.

- **Society Members:**

  Up to and including 21 November 2005
  £180 for the whole meeting, or £80 per day, or part day

  After 21 November 2005
  £240 for the whole meeting, or £100.00 per day or part day

- **Non-Members:**

  Up to and including 21 November 2005
  £240 for the whole meeting, or £100 per day, or part day

  After 21 November 2005
  £300 for the whole meeting, or £130.00 per day or part day

- **Concessions:**

  Qualifying Categories:
  - Honorary & Senior Members
  - PhD Students, Junior Technicians, Residents and Trainees, Biomedical Scientists and Undergraduates*

  * *To qualify for this reduced fee, delegates must submit an identification document signed by your Head of Training, including National Training Numbers where applicable. This requirement is waived for Trainees who are current Members of the Society.*
  Please send your identification document by post or via e-mail to: **julie@pathsoc.org.uk**

  £50 for the whole meeting
  £25 per day, or part day.

- **Society Dinner:**

  £50

ADVANCE REGISTRATION

Advance registration will close on **Monday 19 December**. Thereafter delegates may only register on-site in Cambridge.

CANCELLATIONS

Please note that we are unable to refund registration fees for cancellations **received after Monday 12 December**.

DELEGATE ENROLMENT

Enrolment at the Delegate Reception Desk will take place in the Auditorium Foyer at Robinson College as follows:

Wednesday 4 January from 09.00 hrs
Thursday 5 and Friday 6 January from 08.30 hrs

ENQUIRIES

Pathological Society of Great Britain & Ireland, 2 Carlton House Terrace, London, SW1Y 5AF
Tel: +44 (0)20 7976 1260 Fax: +44 (0)20 7976 1267 Email: admin@pathsoc.org.uk

MESSAGES

During the Meeting, messages for delegates may be left on tel: 01223 339131 situated in the Auditorium Conference Office.

There will also be a message board located beside the Registration Desk.

General Arrangements *continued*

PRESENTATION CHECKING AND PREVIEW
This will be available in the Garden Room.

ORAL PRESENTATIONS AND LECTURES
Format must be Microsoft Powerpoint, ideally versions should be:

- Mac (v2004 onwards), or
- PC (v2003 onwards).

Presentations should be submitted in advance of the meeting to arrive **no later than Friday 12 December**. They may be sent by the following methods:

- e-mailed as a compressed file to: **Caryn Wilkinson: cfw23@cam.ac.uk**
- sent on a CD by post to the following address:
  Caryn Wilkinson, P.A. to Prof Andrew Wyllie, Department of Pathology
  Tennis Court Road, Cambridge CB2 1QP (Tel: 01223 333692)

IMPORTANT: Please bring another copy of your presentation with you to the meeting.

SLIDE SEMINAR
PCs for Slide Seminar Viewing will be located in the Garden Room.

REFRESHMENTS
Coffee and tea will be served in The Balcony Area and Umney Foyer, lunch will be served in the Garden Restaurant.

BADGES
Delegates are requested to wear their badges at all times.

TRAVEL
Trains
A good train service exists from London (King's Cross or Liverpool Street) and the fastest trains (the *Cambridge Cruiser* from King's Cross) take only 52 minutes. Cross country rail services link Cambridge with the Midlands and the North. Robinson College can be reached from Cambridge Station by taxi (a journey of approximately 15 minutes). There are no buses direct from Cambridge Station to the College.

Buses and Coaches
There is a frequent express coach service between London and Cambridge and a coach service several times a day between Heathrow, Gatwick and Stansted airports and Cambridge. Details can be obtained from National Express, telephone 0870 580 8080. The College is a short taxi ride from Cambridge Bus Station in Drummer Street.

The number 8 bus route from Drummer Street stops at the Madingley Road end of Grange Road (approximately 10 minutes walk from Robinson College).

Parking
Free permit-parking will be available at the Wilberforce Road Athletics Ground (5–10 minutes' walk from the Robinson College). Please provide car registration details when registering if parking will be required.

By Air
Stansted Airport is approximately 40 minutes by road from Cambridge. Gatwick and Heathrow Airports are approximately 1.5–2 hours by road from the College. Buses from all these airports run regularly into the City Centre.

ACCOMMODATION
Accommodation has been reserved for delegates at Robinson College at the rate of £60/night for a single en-suite room, with breakfast.
Please contact Caryn Wilkinson, Department of Pathology, for a booking form: **cfw23@cam.ac.uk**

Alternative accommodation is listed overleaf.

General Arrangements *continued*

Alternative accommodation:

Garden House
Granta Place, Mill Lane, Cambridge CB2 1RT (Tel: 01223 259988) www.moathousehotels.co.uk

The Royal Cambridge Hotel
Trumpington Street, Cambridge CB2 1PY (Tel: 01223 351631, Fax: 01223 352972)
www.theroyalcambridgehotel.co.uk/leisure-breaks.htm

Arundel House Hotel
Chesterton Road, Cambridge CB4 3AN (Tel: 01223 367701, 01223 367721) www.arundelhousehotels.co.uk

Best Western Gonville Hotel
Gonville Place, Cambridge CB1 1LY (Tel: 01223 366611, 0800 528 1234, Fax: 01223 315470)
www.bestwestern.co.uk

Regent Hotel
41 Regent Street, Cambridge CB2 1AB (Tel: 01223 351470) www.regenthotel.co.uk/tourist.html

University Arms Hotel
17 Regent Street, Cambridge CB2 1AD (Tel: 01223 351241)
www.devereonline.co.uk/hotel_university

Travelodge
Cambridge Leisure Park, Cambridge CB1 7DY (Tel: 0870 191 1601) www.travelodge.co.uk/

Kirkwood Guest House
172 Chesterton Road, Cambridge CB4 1DA (Tel: 01223 306283)
http://cambridge.blackbirdtravel.co.uk/kirkwoodhouse.htm

SMOKING
Smoking is prohibited at all meetings and social events except in the designated areas.

DISCLAIMER
The Pathological Society of Great Britain & Ireland cannot be held responsible for any injury or loss sustained during the Meeting.

SOCIAL ACTIVITIES
Wednesday 4 January
Welcome Reception, The Hall, King's College, Cambridge.
Tickets are free – if you wish to attend please tick the relevant box when registering.

Thursday 5 January
Society Dinner, The Hall, Robinson College, Cambridge.
Tickets: £50. To reserve your ticket please ensure you tick the relevant box when registering.

LOCAL PLACES OF INTEREST
Please refer to the Internet for information: **www.cam.ac.uk/cambarea/tourist.html**

FUTURE MEETINGS

2006	4–7 July	Centenary Meeting, Manchester
2007	3–5 January	University College, London
	3–6 July	Glasgow Pathology 2007, 4th Joint Meeting of the Pathological Society and the British Division of the IAP
2008	9–11 January	Oxford
	1–4 July	Leeds
2009	7–9 January	London
	30 June–3 July	Cardiff Pathology 2009, 5th Joint Meeting of the Pathological Society and the British Division of the IAP

Detailed Programme – Wednesday 4 January 2006

Presenter = **{P}** Abstract numbers are shown in bold type and in square brackets eg **[S123]**

09.30–17.00 **Garden Room**
SLIDE SEMINAR COMPETITION – VIEWING

09.50–13.00 **Umney Lecture Theatre**
TRAINEES FORUM
Chair: Prof NA Wright, President, Pathological Society

09.50–10.00 *Welcome*, Prof NA Wright, President, Pathological Society

10.00–11.00 *Do's and don'ts in the use of digital images for presentation and publication*
Prof PW Hamilton, Queen's University, Belfast

11.00–11.30 COFFEE (Balcony and Umney Foyer)

11.30–12.00 *The application of tissue microarray techniques in research*
Dr SS Cross, Sheffield

12.00–12.30 *Research planning, pressures and funding – a personal view from a recent trainee*
Dr KA Oien, University of Glasgow

12.30–13.00 *Opportunities for trainees within the Pathological Society*
Prof DA Levison, University of Dundee, President-Elect, Pathological Society

13.00–14.00 LUNCH (Garden Restaurant) and
TRADE EXHIBITION (Balcony, Umney Foyer and Junior Common Room)

14.00–17.00 **Auditorium Lecture Theatre**
SYMPOSIUM: *Developing Themes in Pathology*
Chair: Prof PA Hall, Queen's University, Belfast

14.00–15.00 **[S1]** *Colorectal cancer: basic science and clinical applications*
Dr MJ Arends, University of Cambridge
Prof NA Shepherd, Gloucester Royal Hospital

15.00–15.30 TEA (Balcony and Umney Foyer)

15.30–16.15 *The Pathologist and Transgenic Models of Disease*
Prof S Fleming, University of Dundee

16.15–17.00 **[S2]** *New perspectives on neoplasia and the RNA world*
Prof PA Hall, Queen's University, Belfast

17.15–18.00 **Auditorium Lecture Theatre**
ROYAL COLLEGE OF PATHOLOGISTS CAMERON LECTURE
Chair: Prof AC Newland, President, Royal College of Pathologists

[S3] *The role of the tumour microenvironment in breast cancer*
Dr K Polyak, Dana-Farber Cancer Institute, Boston, USA

18.30–20.00 **The Hall, King's College, Cambridge**
Welcome Reception

Detailed Programme – Thursday 5 January 2006

Presenter = **{P}** Abstract numbers are shown in bold type and in square brackets eg **[S123]**

09.30–15.30 **Garden Room**
SLIDE SEMINAR COMPETITION – VIEWING

09.15–13.00 **Auditorium Lecture Theatre**

09.15–09.30 **OPENING ADDRESS**
Prof AH Wyllie, University of Cambridge

09.30–13.00 **SYMPOSIUM:** *Breast Cancer: theory into practice*
Chair: Dr S Pinder, Addenbrooke's Hospital, Cambridge

09.30–10.00 *Genetic susceptibility to breast cancer – recent results and future challenges*
Prof D Easton, Cancer Research UK Genetic Epidemiology Unit, Strangeways Research Laboratory, Cambridge

10.00–10.30 *Breast cancer pharmacogenomics and its clinical application*
Prof C Caldas, Cancer Genomics Programme, University of Cambridge

10.30–11.00 **[S4]** *Precursor lesions in the breast*
Dr S Pinder, Addenbrooke's Hospital, Cambridge

11.00–11.30 COFFEE (Balcony and Umney Foyer)

11.30–12.00 **[S5]** *Therapeutic exploitation of the DNA repair defects in BRCA mutant tumours*
Prof A Ashworth, Breakthrough Breast Cancer Research Centre, The Institute of Cancer Research, London

12.00–12.30 *BRCA1 a differential modulator of chemotherapy induced apoptosis*
Prof P Harkin, Queen's University, Belfast

12.30–13.00 *The progenitor cell concept of breast epithelium: a new basis of proliferative breast disease?*
Prof W Boecker, University of Münster, Germany

13.00–14.00 LUNCH (Garden Restaurant) and
TRADE EXHIBITION (Balcony, Umney Foyer and Junior Common Room)

13.15–14.15 **Auditorium Lecture Theatre**
ACADEMIC PATHOLOGY FORUM
Chair: Prof NA Wright, President, Pathological Society

Pathology in Crisis! A way forward?
Prof PA Hall, General Secretary, Pathological Society

The Research Assessment Exercise
Prof AH Wyllie, University of Cambridge *(Member of RAE, Main Panel A)*

Interactions with the Human Tissue Authority
Prof PN Furness, University of Leicester

14.00-15.30 **Balcony, Umney Foyer and Junior Common Room**
POSTER VIEWING
CATEGORIES
Autopsy & Forensic **[P1–P5]**
Breast **[P6–P15]**
Cardiovascular/Pulmonary **[P16–P18]**
Cellular/Molecular **[P19–P33]**
Education & Audit **[P34–P42]**
Endocrine **[P43–P44]**

14.00-15.30 **Balcony, Umney Foyer and Junior Common Room** *continued*

POSTER VIEWING

CATEGORIES

Experimental Tumour Pathology **[P46–P47]** *
Gastrointestinal **[P48–P60]**
Genitourinary/Renal **[P61–P65]**
Gynaecological **[P66–P68]**
Hepatobiliary/Pancreas **[P69]** *
Lymphoreticular **[P71–P73]**
Neonatal/Paediatric **[P74–P85]**
Neuropathology/Ophthalmic **[P86–P88]**
Osteoarticular/Soft Tissue **[P89]**
Skin **[P90–P91 & P93–P96]** *
Technical Advances [P97–P98]

* Note: Poster Numbers P45, P70 & P92 were withdrawn.

15.00–16.00 **Umney Lecture Theatre**

RENAL EQA GROUP MEETING

15.30–16.00 TEA (Balcony and Umney Foyer)

16.00–17.00 **Auditorium Lecture Theatre**

PLENARY ORAL SESSION

Chair: Prof M Pignatelli, University of Bristol and Bristol Royal Infirmary, and Prof A Wyllie, University of Cambridge

16.00 **[PL1]** *Reduced function of PDK1 protects from PTEN mutation induced malignancy*
{P} S Fleming, J Bayascos, D Alessi

16.15 **[PL2]** *Evidence of monoclonal origins in dysplasia in ulcerative colitis*
{P} SJ Leedham, LC Maia, O Sieber, SL Preston, SAC McDonald, IPM Tomlinson, NA Wright

16.30 **[PL3]** *Identification of a Key Step in Cervical Carcinogenesis: Selection of Integrated High Risk Human papillomavirus Correlates with Episome Loss and an Endogenous Antiviral Response*
{P} MR Pett, MT Herdman, RD Palmer, MK Shivji, GS Yeo, MA Stanley, N Coleman

16.45 **[PL4]** *Quantum Dot Based Multiplex Hybridisation for In-situ Gene Expression Profiling in Clinical Samples*
{P} E Tholouli, D Di Vizio, F O'Connell, D Twomey, K Ligon, R Levenson, JA Hoyland, JAL Yin, TR Golub, M Loda, RJ Byers

17.15–18.00 **Auditorium Lecture Theatre**

THE PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S 2nd GOUDIE LECTURE

Chair: Prof PA Hall, Queen's University, Belfast and Belfast City Hospital

[S6] *Tumour specific integrins in cancer invasion: functional effects and targeting possibilities*
Prof I Hart, Institute of Cancer Research, London

19.30 **The Hall, Robinson College**

SOCIETY DINNER

09.00–10.45 **Auditorium Lecture Theatre**
ORAL COMMUNICATIONS
Categories: Breast; Gynaecological; Neuropathology
Chairmen: Dr JJ Going, Glasgow and Dr JH Xuereb, Cambridge

09.00 **[O1]** *Chromosome Translocations on 8p in Breast Cancers*
{P} JCM Pole, SL Cooke, C Courtay-Cahen, PAW Edwards

09.15 **[O2]** *Basal phenotype provides the strongest prognostic factor in a subgroup of breast cancer*
{P} E Rakha, A Green, D Powe, I Ellis

09.30 **[O3]** *High Frequency of Co-existence of Columnar Cell Lesions, Lobular Neoplasia, and Low Grade DCIS with Invasive Tubular Carcinoma and Invasive Lobular Carcinoma*
{P} TMA Abdel-Fatah, DG Powe, Z Hodi, A Lee, IO Ellis

09.45 **[O4]** *Inflammation and prognosis in invasive carcinoma of the breast*
{P} AHS Lee, IO Ellis, M Mitchell, RW Blamey, CW Elston

10.00 **[O5]** *Survivin is an independent predictor of poor outcome in breast cancer*
AR Hinnis, **{P}** RA Walker

10.15 **[O6]** *Interferon-β Promotes Rapid Episomal Loss and the Emergence of Latent Integrants in Cervical Keratinocytes Infected with Human Papillomavirus Type 16*
{P} MT Herdman, MR Pett, I Roberts, WOF Alazawi, AE Teschendorff, XY Zhang, MA Stanley, N Coleman

10.30 **[O7]** *An Overlapping Homozygous Deletion At 1p36.22-23 In Glioblastomas Identified By Chromosome 1 Tile Path Array-CGH*
{P} K Ichimura, AP Vogazianou, L Liu, DM Pearson, C.F Langford, SG Gregory, VP Collins

10.45–11.15 COFFEE (Balcony and Umney Foyer)

11.15–13.00 **Auditorium Lecture Theatre**
ORAL COMMUNICATIONS
Categories: Gastrointestinal; Lymphoreticular
Chairmen: Prof M Novelli, UCL and Prof M-Q Du, Cambridge

11.15 **[O15]** *Disappearing lymph nodes. One explanation for the fall in number with increasing age*
{P} M Baxandall, F Lewis, G Casali, P Guillou, H Thorpe, J Walker, AMH Smith, RM Heath, JM Brown, P Quirke

11.30 **[O16]** *Monoclonal conversion in human gastric glands: insights into stem cell and clonal architecture*
{P} SAC McDonald, LG Greaves, SJ Leedham, SL Preston, RW Taylor, D Oukrif, M Deheragoda, MR Novelli, DM Turnbull, CY Lee, JAZ Jankowski, NA Wright

11.45 **[O17]** *Circumferential surgical margins in rectum and right colon in the MRC CLASICC trial. 3 year disease free survival and local recurrence*
{P} P Quirke, P Guillou, H Thorpe, J Copeland, D Jayne, AMH Smith, RM Heath, JM Brown, CLASICC investigators

11.15–13.00 **Auditorium Lecture Theatre**
ORAL COMMUNICATIONS *continued*
Categories: Gastrointestinal; Lymphoreticular

12.00 **[O18]** *Quantitative Proteomic Analysis Shows Downregulation of MAPK Pathway in Colon Cancer*
{P} C Gulmann, K Sheehan, G Eichler, E Kay, L Liotta, E Petricoin

12.15 **[O19]** *Sequence Analysis of the Immunoglobulin Heavy Chain Genes of Tumour Cells from Thyroid Follicular Lymphoma*
{P} AJ Goatly, R Hamoudi, T Diss, H Ye, A Dogan, P Isaacson, MQ Du, CM Bacon

12.30 **[O20]** *Chlamydia psittaci is Variably Associated with Ocular MALT Lymphoma in Different Geographical Regions*
{P} E Chanudet, Y Zhou, C Bacon, A Wotherspoon, H Muller-Hermelink, P Adam, Y Li, R Wei, X Gong, Q Wu, R Ranaldi, G Goteri, S Pileri, H Ye, H Liu, J Radford, MQ Du

12.45 **[O21]** *Immunophenotyping and Clonality Analysis in the Diagnosis of Refractory Coeliac Disease*
H Liu, **{P}** R Brais, K Payne, Y Huang, H Ye, C Bacon, J Woodward, M-Q Du

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09.00–10.45 **Umney Lecture Theatre**
ORAL COMMUNICATIONS
Categories: Technical Advances; Cellular/Molecular; Experimental Tumour Pathology; Neonatal/Paediatric
Chairmen: Prof VP Collins, Cambridge and Dr F Jessop, Cambridge

09.00 **[O8]** *Application of array CGH on archival formalin fixed paraffin embedded tissues*
{P} NA Johnson, R Hamoudi, K Ichimura, L Liu, D Pearson, P Collins, M-Q Du

09.15 **[O9]** *Characterisation of CpG Island Methylation in a Colorectal Cancer Cell Line by a Novel Array-based Method*
{P} AEK Ibrahim, N Thorne, K Baird, N Barbosa-Morais, VP Collins, AH Wyllie, JD Brenton

09.30 **[O10]** *Glycosylation and golgi apparatus structural integrity are essential in targeting glut1 to membranes of colorectal cancer cells*
{P} S Bakhiet, M Izzuan, M Tosetto, H Mulcahy, D O'Donoghue, K Sheahan, JO'Sullivan

09.45 **[O11]** *The VDR Promoter Polymorphism A-1012G affects T-cell Response in Malignant Melanoma and Psoriasis Through GATA-3 Signalling*
{P} JA Halsall, JE Osborne, PE Hutchinson, JH Pringle

10.00 **[O12]** *Comparison of Wnt5a Expression With Alterations of p16 and B-raf In Cutaneous Melanoma Progression*
{P} PD Da Forno, G Saldanha, A Fletcher, L Potter, JH Pringle

10.15 **[O13]** *Angiogenesis and Lymphangiogenesis in Testicular Germ Cell Tumours (TGCT)*
{P} P Kumar, C Nickols, M Naase, SI Baithun, RTD Oliver, VH Nargund

10.30 **[O14]** *Global Gene Expression Analysis of Paediatric Malignant Germ Cell Tumours Reveals Common Patterns of Transcription and Expression Signatures of Different Histological Types*
{P} RD Palmer, NA Foster, I Roberts, D Schneider, JC Nicholson, N Coleman

10.45–11.15 COFFEE (BALCONY AND UMNEY FOYER)

11.15–13.00 **Umney Lecture Theatre**
ORAL COMMUNICATIONS
Categories: Genitourinary/Renal; Cardiovascular/Pulmonary; Skin; Autopsy & Forensic; Education & Audit
Chairmen: Prof P Domizio, London and Dr M Griffiths, Cambridge

11.15 **[O22]** *Human macrophages kill human mesangial cells by Fas-L-mediated apoptosis when triggered by antibody via CD16*
{P} J J Boyle

11.30 **[O23]** *Renal regeneration following acute tubular necrosis utilises cells of bone marrow origin, but is unaffected by EPO*
{P} TH Yen, MR Alison, HT Cook, NA Wright, R Poulsom

11.45 **[O24]** *Complement C1q plays a bidirectional role in early atherosclerotic lesions in LDL receptor knock-out mice*
V Bhatia, **{P}** JJ Boyle, CE Roberts, Y Sadler, JL Witztum, GM Benson, M Botto, DO Haskard

12.00 **[O25]** *Immunohistochemical expression of $VEGF_{xxx}b$ predicts metastasis in primary melanoma*
{P} RO Pritchard Jones, DBA Dunn, Y Qui, H Rigby, A Orlando, SJ Harper, DO Bates

12.15 **[O26]** *Prognostic scoring in patients with melanoma after adjuvant Isolated Limb Perfusion (ilp)*
{P} JS Nagabhushan, WJ Angerson, DB Kingsmore, DS Byrne, AJ McKay

12.30 **[O27]** *Communication of Autopsy Findings: The Role of a Pathology Follow-Up Clinic After Autopsy*
{P} MR Cranley, WR Roche

12.45 **[O28]** *Diagnostic Accuracy of Internet-based Virtual Microscopy – A randomised controlled trial*
{P} PN Furness

13.00–14.00 LUNCH (GARDEN RESTAURANT) and
TRADE EXHIBITION (BALCONY, UMNEY FOYER AND JUNIOR COMMON ROOM)

14.00–17.00 **Auditorium Lecture Theatre**
SYMPOSIUM: *Angiogenesis in Health & Disease*
Chair: Prof AH Wyllie, University of Cambridge

14.00–14.30 **[S7]** *Investigation of signalling pathways in human endothelial cells using Bayesian Gene Regulatory Networks*
Dr CG Print, Auckland University, New Zealand

14.00–17.00 **Auditorium Lecture Theatre** *continued*
SYMPOSIUM: *Angiogenesis in Health & Disease*

14.30–15.00 *Signalling Angiogenesis*
Dr N Brindle, University of Leicester

15.00–15.30 *The role of Integrins in Angiogenesis*
Dr K Hodivala-Dilke, Barts & the London School of Medicine & Dentistry

15.30–16.00 TEA (BALCONY AND UMNEY FOYER)

16.00–17.00 **Plenary Lecture:**
Chair: Dr D S Charnock-Jones, Cambridge

[S8] *Role of vascular receptor tyrosine kinases during angiogenesis, tumour progression and metastasis*
Prof H Augustin, Angiogenesis Research Centre, Freiburg, Germany

17.00 FINISH

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Abstracts

Plenary

PL1

Reduced function of PDK1 protects from PTEN mutation induced malignancy

{P} S Fleming, J Bayascos, D Alessi
University of Dundee, Dundee, United Kingdom

The regulatory phosphatase PTEN is the second most frequently mutated gene in human cancer, the gene encodes a phosphatase which controls the level of activity of the PI 3 kinase pathway. This is a key signal transduction pathway linking ligand binding to receptors such as the insulin receptor through the protein kinases S6 kinase and PKB to gene expression and cell and tissue growth and survival. Loss of function mutations affecting PTEN lead to dysregulation and overactivity of the Pl 3 kinase pathway and an increased risk of tumour formation. PTEN mutations are found in human tumours of breast, colon, endometrium, prostate and brain. PDK1 is a recently discovered member of this signalling pathway which phosphorylates both PKB and S6 kinase. We have tested the hypothesis that reduced activity of PDK1 will reduce the frequency of tumours induced by PTEN mutation. PTEN -/+ mice, which have a high frequency of tumours, were crossed with a transgenic mouse which has reduced levels of PDK1 expression (PDK1 fl/-). These mice have a *flox* site introduced in intron 1 which leads to expression of only 10% of wild type levels of the kinase. Control mice (PDK1 fl/+) had wild type levels of PDK1. 28/39 mice with normal levels (PDK1 fl/+; PTEN +/-) of PDK1 developed tumours. By contrast only 5/23 mice with reduced PDK1 levels (PDK1 fl/-; PTEN +/-) developed tumours. The tumours encountered included carcinomas of breast (5), endometrium (8), prostate (7) but also lymphomas (21) and phaeochromocytoma (15). This provides genetic evidence that reducing PDK1 activity may protect from the development of PTEN mutation induced malignancy.

PL2

EVIDENCE OF MONOCLONAL ORIGINS IN DYSPLASIA IN ULCERATIVE COLITIS

{P} SJ Leedham, LC Maia, O Sieber, SL Preston, SAC McDonald, IPM Tomlinson, NA Wright
Cancer Research UK, London, United Kingdom

Aim: Ulcerative Colitis (UC) is a chronic inflammatory condition that increases the risk of developing colorectal cancer. Loss of heterozygosity (LOH) of important tumour suppressor genes such as Adenomatous polyposis coli (APC), deleted in colon cancer (DCC) and SMAD4, can occur in UC associated dysplastic tissue. LOH analysis can be used as a simple and reliable marker of clonality. The aim of this study was to use LOH at the above 3 loci for the assessment of clonality within dysplastic and inflamed tissue in UC to test the hypothesis that dysplastic lesions arise from a single mutated clone. **Methods:** Paraffin embedded tissue was obtained from St Marks Hospital. Tissue was categorised histologically into normal, acutely or chronically inflamed or dysplastic, based on H&E slides. Laser capture microdissection was used to isolate individual crypts. DNA was extracted and amplified for microsatellite markers close to the loci of APC (5q21.1), DCC (18q21) and SMAD4 (18q21.1). Abnormal tissue allelic areas were compared with normal tissue allelic areas as a ratio. **Results:** LOH for microsatellite markers was found in chronic inflammation in 1 patient at a low frequency (1 marker, 50% of crypts). LOH of the same microsatellite marker was seen in low grade dysplasia at a low frequency (44%) but at a very high frequency across multiple high grade dysplastic patches in different patients (up to 100%). LOH of multiple markers was seen in some patients. **Conclusions:** Lower LOH frequency in inflamed and low grade dysplasia compared to high grade dysplasia suggests which marker is lost first, and the earliest lost marker can be used a clonal marker. 'Across the patch' loss of the same allele in high grade dysplasia suggests monoclonal derivation. Increased crypt fission is likely to be responsible mutation spread.

PL3

Identification Of A Key Step In Cervical Carcinogenesis: Selection Of Integrated High Risk Human papillomavirus Correlates With Episome Loss And An Endogenous Antiviral Response

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Integration of high-risk human papillomavirus (HR-HPV) into the host genome is an important event in cervical neoplastic progression. The oncogenes E6/E7 are overexpressed from the integrant, provided there is loss of the viral transcriptional repressor E2. We hypothesised that loss of residual E2-encoding episomes from cells in which integration had occurred would be required for such cells to acquire a growth advantage. Using the unique W12 model of cervical carcinogenesis we show that spontaneous selection of integrated HPV16 during long-term keratinocyte culture is associated with rapid episome loss from cells containing the integrant being selected. Episome loss leads to reducing levels of E2 and proportionate deregulation of the homologous promoter of the integrant. Microarray analysis showed that episome loss is closely associated with activation of antiviral response genes. Such genes are inducible by type I interferon and in a related study (see Herdman-MT abstract) we showed that exogenous interferon-beta causes very rapid episome loss from W12 and the emergence of latent integrants. We conclude that induction of episome loss through activation of antiviral response genes is a key event in spontaneous selection of cells containing integrated HR-HPV. Cervical carcinogenesis requires not only HR-HPV integration but also loss of regulatory episomes.

PL4

Quantum Dot Based Multiplex Hybridisation for In-situ Gene Expression Profiling in Clinical Samples

{P} E Tholouli[1], D Di Vizio[2], F O'Connell[2], D Twomey[3], K Ligon[2], R Levenson[4], JA Hoyland[5], JAL Yin[1], TR Golub[3], M Loda[2], RJ Byers[5]
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Background: Gene expression profiling has identified many potentially useful prognostic gene signatures but there has been limited application to formalin-fixed, paraffin-embedded diagnostic biopsy specimens. We performed multiplexed in-situ hybridisation (ISH) using quantum dot (QD)-labelled oligonucleotide probes to visualise known expression signatures to biopsy specimens. Signals were detected and deconvoluted by spectral imaging. Design: Streptavidin coated QDs were coupled to oligonucleotide probes and used in manual and automated ISH. Signal stability and ability to detect mRNA in archived tissue were assessed. As proof of concept, tissue specific oligonucleotide probes were utilised to identify tumour types by spectral imaging analysis and quantitation of specific probes / beta actin ratios. Finally, duplex ISH and triplex signal deconvolution was performed on singlr slides. Results: Fluorescent signal was preserved over 18 months from the initial hybridisation experiment while gene expression was detected in 30 year old prostatic cores. Tissue-specific probes (e.g. CDX2 and MITF) blindly identified the appropriate tumour tissues. Duplex ISH on trephine sections in FL using MPO and bcl-2 probes demonstrated accurate signal detection as confirmed by single gene ISH as well as conventional methods such as immunohistochemistry (IHC). Finally, triplex ISH and duplex ISH combined with single IHC were successfully deconvoluted by spectral imaging. Conclusions: We have demonstrated that QD-labelled oligonucleotides can be successfully utilised by multiplex ISH in routinely processed clinical tissue. This will facilitate translational application of microarray identified gene signatures in the clinical setting with multiplexed probe detection.

Abstracts

Posters

P1

TB-Related Sudden Death Due to Myocarditis Complicating Miliary TB. The Importance of Histopathology in Coroner's Autopsy Work

{P} OJ Biedrzycki, SI Baithun
The Royal London Hospital, London, United Kingdom

TB-related sudden death (TBRSD) is rarely reported in the literature, and in the majority of cases is due to bronchopneumonia and haemoptysis. Cardiac complications of tuberculosis causing sudden death can take many forms, and are rarer still, with only a handful of cases reported. We describe a case of a previously fit and healthy 20 year old Asian female who, after returning from a holiday in India, collapsed whilst getting off a bus. At post-mortem the only macroscopic finding of note was a localised area of fibrosis on the anterior wall of the left ventricle. Microscopic examination of this area showed Langhans giant cells, non-caseating epithelioid granulomas and acid fast bacilli were demonstrated on Ziehl-Nielsen staining. In addition the lungs, liver and kidneys contained multiple non-caseating granulomas. The case serves to highlight the protean nature in the presentation of this disease and the importance of post-mortem histology in routine coroner's autopsy work.

P2

Post Insertion Migration of a Robinson Drain With Erosion of the Tip into the Liver and Biliary Tree Causing Fatal Biliary Peritonitis

{P} OJ Biedrzycki[1], G Lauffer[2], SI Baithun[1]
[1]. The Royal London Hospital, London, United Kingdom, [2]. Barking, Havering and Redbridge Hospitals, Goodmayes, Essex, United Kingdom

Iatrogenic injury due to incorrectly sited drains and tubes is a rare but recognised complication, and can occur at many different sites. Migration of correctly sites drains and tubes is rarer still. Only a handful of cases involving long standing ventriculo-peritoneal and lumbo-peritoneal shunts migrating and causing perforation of the bowel exist, often complicated by central nervous system sepsis. We present a previously unreported complication of a right sided Robinson drain, inserted under direct vision during a subtotal gastrectomy for carcinoma, in a frail 78 year old female. Twenty four days post operatively, after a period of predictably slow but steady recovery, bile stained fluid was noted in the drain. At this point a second, left sided Robinson drain was inserted. Unfortunately the patient rapidly deteriorated and died. Autopsy revealed multi-organ failure due to peritonitis. Both drains were noted to be correctly and firmly sutured to the skin. The tip of the right sided Robinson drain was found to have migrated, eroding into the liver parenchyma and biliary tract resulting in biliary peritonitis. The left sided Robinson drain was correctly sited in the peritoneal cavity. We present the post mortem findings and a review of the literature.

P3

The Slow Death of the Clinical (Consented) Post-mortem

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Introduction: The clinical (consented) post-mortem examination (PM) is important in the development of the modern medicine. During recent years there has been a marked decline in the number of adult clinical PMs. We describe the consented PM rate for patients dying in the Trust and explore the clinicians' opinions about this final medical investigation.
Methods: We examined the hospital mortuary records for the period of 1 January 1996 to 31 December 2003. The clinical PM rate for adults was obtained. We also determined the clinical PM rate for stillbirths and perinates during the period of 1 January 2000 to 31 December 2003. 107 relevant consultants were sent a questionnaire asking about their attitudes to consented PMs.
Results: The number of adult clinical PMs fell from 167 (1997) to 34 (2003), a reduction of nearly 80%, the PM rate declining from 8.4% to 1.4%. That on stillbirths and perinates fell from 69% in 2000 to 50-54% during 2001-2003. Ninety-three (87%) consultants responded to the questionnaire.
Clinical PMs were valued as a means of establishing the cause of death (76/86; 88.4%) and revealing unexpected diagnoses (82/86; 95.3%), and also in the training of medical students (84/88; 95.5%) and junior doctors (78/87; 89.7%). However, 21% of responders reported difficulty in asking the family for a PM. Twenty-three consultants said that family distress would inhibit their asking. The complexity of the process and paperwork and the time involved were also cited as reasons for not requesting clinical PMs. The Trust has recently employed a Pathology Liaison Nurse to undertake this responsibility and to ensure the quality of consent for clinical PMs.

P4

A Post Mortem Case Of Interstitial Pneumonia, Endomyocardial Fibrosis And Fibrillary Glomerulonephritis; One Possible Unifying Theory.

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A man, aged 72, presented with breathlessness, pulmonary haemorrhage, impaired ventricular function, haematuria and worsening renal function. There was radiological evidence of interstitial lung disease. Echocardiograms and a ventricular biopsy revealed endomyocardial fibrosis which fluctuated over time. A renal biopsy revealed fibrillary glomerulonephritis, diagnosed on electron microscopy.
Apart from a positive pANCA, all other immunological investigations were negative.
His condition improved on treatment with methotrexate and steroids. He experienced two relapses over seven years.
His respiratory and left ventricular function deteriorated rapidly during his second relapse and he died from respiratory failure secondary to acute interstitial pneumonia.
Post mortem histology findings included acute changes of diffuse alveolar damage with a background of non-specific interstitial pneumonia. The heart showed endomyocardial fibrosis with overlying thrombosis.
One possible unifying mechanism may be immune deposit formation leading to vascular damage. This could account for the fibrillary deposits in the kidneys. Although no histological evidence of vasculitis was found, the patient had been on immunosuppression. The haemosiderin deposition in the lungs is indirect evidence of vascular damage. Cryoglobulin production is a possible mechanism to explain involvement of all three organ systems.

P5

Giant atherosclerotic aneurysm of the middle cerebral artery

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A 70-year-old woman, who was an ex-smoker and known to be hypertensive, was admitted to hospital complaining of slurred speech and weakness of her right side. CT scan revealed several aneurysms of the cerebral arteries, including a giant aneurysm of the left middle cerebral artery, and evidence of related cerebral infarction.

Post mortem examination showed extensive acute subarachnoid haemorrahge over the left cerebral hemisphere, at the base of the brain and within the left lateral and fourth ventricles. The cerebral arteries showed multiple abnormalities, with widespread severe advanced atherosclerosis. The basilar, both vertebral and both internal carotid arteries were diffusely dilated and tortuous. There was a 7 mm-diameter aneurysm of the left anterior cerebral artery. The left middle cerebral artery showed a giant aneurysm, measuring 3.6 cm. Histopathological examination confirmed its atherosclerotic origin and excluded other conditions. Other systemic arteries also showed severe advanced atherosclerosis.

The pathogenesis of spontaneous fusiform aneurysms of the middle cerebral arteries is uncertain. Arterial dissection and weaknesses of the internal elastic lamina have both been suggested and may apply to most patients, who tend to be relatively young. Atherosclerotic aneurysms of the middle cerebral arteries appear to be rarer and usually occur in elderly patients with generalized advanced atherosclerosis. The basilar trunk and supraclinoid parts of the internal carotid arteries are commoner sites for such aneurysms. The structure of intracranial arteries may favour the development of aneurysms. The poorly developed external elastic lamina and adventitia, and gaps in the media may all be factors. The patient's age at the diagnosis and diameter of the aneurysm are predictors for a rupture. Smoking is also a risk factor for rupture and predisposes individuals to multiple aneurysms, as in this case.

P6

Myoepithelial cells in cancer-containing breasts are different

CM Rodrigues, **{P}** RA Walker
University of Leicester, Leicester, United Kingdom

We have previously identified differences in growth regulation of non-involved tissue from cancer-containing breasts (NTCCB) in comparison to breast from age-matched women without breast cancer. Myoepithelial cells are recognised as having a tumour suppressor function. The aim of this study was to determine whether expression of growth-regulatory factors in myoepithelial cells differed between NTCCB and controls.

Tissue from 58 NTCCB and 61 age-matched controls were examined using immunohistochemistry for oestrogen receptor (ER) β, epidermal growth factor receptor (EGFR), fibroblast growth factor 2 (FGF-2), p63 and 14-3-3σ. Only myoepithelial cell reactivity was evaluated.

The median index score for ERβ was lower in ≥50yr old cases (NTCCB) than controls (p=0.03), with a trend for the median index for EGFR to be lower overall in NTCCB. The median index for FGF-2 was higher in NTCCB (p=0.02) with a highly significant difference for ≤ 39yr old group (p=0.002). There were no differences overall for p63 but there was a variation with age in the controls but not in NTCCB. The median index for 14-3-3σ was higher in NTCCB for ≤ 39yrs (p=0.045) and ≥50yrs (p=0.05).

There are significant differences in the nature of myoepithelial cells from cancer-containing breasts and breasts without cancer, particularly for FGF-2, indicating their importance in predisposition to breast cancer development.

P7

Comparison of Hormone Receptor Status in Breast Cancer Diagnostic and Excision Specimens

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Background: The oestrogen receptor (ER) and sometimes progesterone receptor (PR) status of breast carcinomas is routinely determined by immunohistochemistry on initial diagnostic specimens and used as a guide to subsequent therapy. These results were compared with the hormone receptor status of subsequent excision specimens to determine whether they accurately predict receptor status of the tumour in the definitive excision.
Method: ER and PR status were determined on both diagnostic (FNA microbiopsy or core biopsy) and excision (wide local excision or mastectomy) breast cancer specimens on 87 randomly selected patients over a 13-month period. Slides from the same patient were scored in the same sitting by a single pathologist using a semi-quantitative quickscore method. Where a significant discrepancy was identified, immunohistochemistry was repeated and the slides re-scored.
Results: On initial scoring, significant differences were found in 6/87 cases (6.9%). The discrepancies between initial diagnostic and final excision specimens was found to persist when immunohistochemistry was repeated in 5 of these cases (5/87 or 5.7%) cases. In the remaining case, there was insufficient material to repeat the assay.
Conclusion: Discrepancies in receptor status may be present between initial diagnostic specimens and subsequent excision specimens. Possible reasons for this are discussed and include tumour heterogeneity and sampling error and differing responses of different specimen types to fixation, processing or antigen retrieval.

P8

Is Sentinel Lymph Node Biopsy Warranted In Cases Of DCIS Diagnosed By Needle Core Biopsy?

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St. Vincent's University Hospital, Dublin, Ireland

Background: Sentinel lymph node biopsy (SNB) is widely used as an alternative to formal axillary dissection in the staging of invasive breast cancer. The role of SNB is controversial in the setting of ductal carcinoma in situ (DCIS)
Aim: To analyse 60 consecutive cases diagnosed as DCIS on needle core biopsy (NCB) who went on to have SNB performed at the time of surgical excision.
Results: Of 60 patients diagnosed with DCIS on NCB, 22 (37%) went on to show invasive carcinoma on excision. 4 patients had a positive SNB. Three of these had invasive carcinoma on excision and only one showed pure DCIS (intermediate grade). A further 4 patients had isolated tumour cells diagnosed by immunohistochemistry. These were classified as negative in accordance with the TNM classification of malignant tumours (6^{th} edition).
Conclusion: Lymph node metastases are rare in patients with pure DCIS. However, the tendency of NCB to underestimate invasive disease makes SNB at the time of surgical excision appropriate in this group.

P9

Cell Cycle Alterations And Their Relationship To Proliferation In Apocrine Metaplasia Of The Breast

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G1/S transition defects have been a proposed requirement for tumour development. Apocrine metaplasia (APM) in the breast has been held as a sign of benignity. Yet, a number of studies have reported the presence of molecular abnormalities in some forms of APM suggesting a possible oncogenic potential for some of these lesions. We currently investigate some of the cell cycle proteins that have been reported to be deregulated in breast cancer. The results were related to the Ki-67 index. Using immuohistochemistry, the expression of cyclin D1, cyclin A, p27, p21, p16, pRb and Ki-67 was examined in 93 cases of (APM). The cases were divided into non-papillary (NAPM) (30 cases) and papillary metaplasia (PAPM) (63 cases). Papillary metaplasia was further subdivided into simple papillary (SPAPM) (29 cases), complex papillary (28 cases) and highly complex papillary (6 cases). For statistical analysis, the last two groups were merged together (CPAPM). The results showed that increased histological complexity was associated with significant increase of proliferative capacity and alterations of the cell cycle control. The median Ki-67 index was 1.5% in SPAPM and 4.8% in the CPAPM. Also, alterations of the cell cycle regulators were significantly higher in the CPAPM than in the SPAPM. NAPM was generally similar to normal breast epithelium. Apocrine cells were negative for p16 while pRb was expressed in all cases. These findings suggest that in complex forms of APM, there is a considerable degree of cellular unrest. This may contribute to increased susceptibility to carcinogenesis.

P10

Cell Turnover In The Various Forms Of Apocrine Metaplasia Of The Breast

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Apocrine Metaplasia (APM) is a common finding in the breast of post-menopausal women. To examine the patterns of cell turnover in APM, the status of apoptosis was studied. Also, the expression of (hTERT) protein was determined. Using immunohistochemistry, the expression of the apoptotic markers Bak, Mcl-1, Bcl-x and Bcl-x_L were studied in 45 cases of APM (13 cases of Non-papillary APM, 21 cases of Simple papillary APM and 12 cases of complex papillary APM. The expression of hTERT and the proliferation marker Ki-67 were also determined. The TdT-mediated dUTP Nick-End Labeling (TUNEL) technique was employed to study the apoptotic status in 21 cases (5 cases NAPM and 16 cases of papillary APM including simple and complex forms). The results showed that all cases were positive for the expression of Bak, Mcl-1, Bcl-x and Bcl-x_L. Punctate nuclear staining of hTERT was not related to the degree of proliferation. The TUNEL results showed an Apoptotic Index (AI) of 0.4% and 0.2% in the papillary and non-papillary groups of APM, respectively. There was no statistical significance between the AI of these two groups and that of the normal breast epithelium (0.3%). The ki-67 index in the non-papillary group was 0.7% while in the papillary group a value of 4.1% was recorded.

The current results show that apoptosis is not a common event in APM irrespective of the degree of proliferation. Yet, apoptotic pathways are highly complex and hence more studies are needed to investigate other apoptotic pathways.

P11

Cell Cycle Alterations And Their Relationship To Proliferation In Apocrine Adenosis of The Breast

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Apocrine adenosis (AA) is generally considered a benign disease of the breast. However, recent studies have suggested a precancerous potential to some of these lesions. We investigated the status of some cell cycle proteins previously reported to be deregulated in breast cancer. The results were related to the Ki-67 index. The cases were categorised into AA without atypia (NAA) and atypical AA (AAA) based on the presence or absence of atypia. Using immuohistochemistry, the expression of cyclin D1, cyclin A, p27, p21, p16, pRb and Ki-67 was determined in 45 cases (29 NAA and 16AAA) The results showed that Cyclin D-1, p21 and cyclin A were over-expressed in 58.6%, 51.7% and 31.8%, of the NAA cases respectively. While 81.3%, 62.5% and 41.7% of the AAA cases showed overexpression of Cyclin D-1, p21, and cyclin A respectively. The over-expression was significantly associated with increased proliferation. All cases were found to be negative for p16 while pRb was expressed in all cases. The results showed that the proliferation in AA (4.5%) was significantly higher than that of normal breast epithelium (1%). There was no statistical significance between the degree of proliferation in the NAA (3.7%) and AAA (4.8%) groups.
The study indicates that NAA and AAA appear to be biologically similar. A subset of AA defined by increased proliferation and significant alterations of the cell cycle may be susceptible to oncogenesis.

P12

Cell Turnover In Apocrine Adenosis Of The Breast

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To investigate cell turnover in apocrine adenosis (AA), immunohistochemistry was employed to study the expression of the apoptotic markers Bak , Mcl-1, Bcl-x and Bcl-x_L in 34 cases of AA [23cases of non atypical AA (NAA) and 11 cases of atypical AA (AAA)]. The expression of hTERT and the proliferation marker Ki-67 were also determined. The TdT-mediated dUTP Nick-End Labeling (TUNEL) technique was employed to study the apoptotic status in 22 cases of AA (15 cases of NAA and 7 cases of AAA). The results showed that all 34 cases studied by immunohistochemistry were positive for the expression of Bak, Mcl-1, Bcl-x and Bcl-x_L showing a pattern of staining similar to that seen in the normal breast epithelium. There was no relation between hTERT positivity and the degree of proliferation. The TUNEL results revealed an apoptotic index (AI) of 0.4% and 0.3% in NAA and AAA respectively. There was no statistical significance between the AI of these two groups and that of the normal breast epithelium (0.3%). The ki-67 index was 5.2% and 6.6% in the NAA and AAA respectively.
The current results show that apoptosis is not a common event in AA even in the presence of increased proliferation which may render some of these lesions more susceptible to oncogenic changes. Further studies are needed to study other apoptotic pathways that may be involved in apocrine adenosis.

P13

A Fluorescence In Situ Hybridysation (FISH) Study Of Cyclin D-1 Gene Amplification In Apocrine Metaplasia And Apocrine Adenosis Of The Breast

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Cyclin D-1 protein over-expression and/or gene amplification have been shown to be frequent events in subsets of breast carcinomas. Cyclin D-1 is generally considered as a weak oncogene and its over-expression has been shown to occur in early benign breast lesions. However, several studies have reported that the protein over-expression is not always associated with concomitant gene amplification and vice versa. In a previous series, we have shown that cyclin D-1 was over-expressed in subsets of apocrine metaplasia (APM) and apocrine adenosis (AA) of the breast and that such over-expression was associated with significant increase in the proliferative capacity of these lesions. To examine the mechanisms involved in cyclin D-1 over-expression in apocrine lesions, a total of 41 cases were analysed by FISH. The cases were divided as: 18 cases of APM and 23 cases of AA. All cases analysed were previously analysed by immunohistochemistry and all showed over-expression of cyclin D-1 protein. A dual cyclin D-1 (spectrum orange)/chromosome 11 centromere (spectrum green) probe was used. The results showed that none of the cases studied had gene amplification. These results suggest that other post-transcriptional mechanisms might be responsible for cyclin D-1 protein over-expression in apocrine lesions. Further studies are needed to understand the mechanisms involved in cyclinD-1 abnormal expression in apocrine lesions.

P14

Myoid Hamartoma of the Breast – A report of two cases

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Hamartoma is an abnormal mixture of tissue elements or an abnormal proportion of a single element normally present at that organ site. Myoid hamartoma is a rare variant of breast hamartoma with smooth muscle component. The origin of smooth muscle component in hamartoma is uncertain. We report two cases of myoid hamartomas of the breast and review of the literature. We also discuss that smooth muscle component may have arisen from either myoepithelial cells or myofibroblasts.

P15

Aberrant Staining in Paget's Disease of the Nipple

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We would like to report a case of 50year old lady who had a background history of a lobular carcinoma in 2002. She presented this year with irregularity of her nipple, which was biopsied as there was a concern that it might be Paget's Disease. The H&E stains of the biopsy showed an abnormal intraepithelial proliferation consistent with Paget's disease, but immunohistochemistry was performed to exclude a malignant melanoma. Immunohistochemical studies showed the intraepithelial cells to be positive for AE1AE3, CK7 and EMA, but the abnormal cells were also positive for S100 protein, HMB45 and Melan A. The case was referred to another institution for an external opinion, where immunostains for HMB45 and tyrosinase were performed and were also found to be positive.
The slides and blocks of the original breast carcinoma were retrieved and a lobular carcinoma was confirmed. Immunostains for cytokeratins were positive. Immunostains for HMB45 and Melan A were also performed and were found to be positive. Staining for S100 protein showed cytoplasmic staining. However, the possibility of the staining being due to endogenous biotin was raised and so the immunostains were repeated using an endogenous biotin block. The repeat staining was negative. This case highlights the importance of reviewing immunohistochemical techniques when inappropriate immunostaining is obtained. An endogenous biotin block is now being done routinely at our institution.

P16

IgM immunostaining is selectively increased in ruptured human atherosclerotic plaques

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Introduction: Atherosclerosis is now viewed as a systemic vascular inflammatory disease. Many forms of vascular inflammation are immune-complex in aetiology. There is some evidence that autoimmunity may play a role in modulating atherosclerosis. Patients with multiple forms of autoimmunity are increased risk of atherosclerosis. We wondered whether immune complex deposition may contribute to atherosclerosis. **Objective:** To carry out a simple study with potential to disprove the hypothesis that atherosclerosis is the commonest form of immune-complex vasculitis **Methods and results:** Ruptured and unruptured atherosclerotic coronary segments from 1992-1995 were studied anonymised with consent, LREC, COREC, Trust approval, NHS research governance registration. Plaques were immunostained for IgM, IgG, C3 and C9 by methods routine for vasculitis, and staining intensity evaluated by 2 observers by a 10-point visual analog scale. Scores were (mean ± SEM): Ruptured plaques: IgM 7.15±0.55, IgG 1.00±0.26; control plaques: IgM 1.94±0.52, IgG 1.00±0.19. For all pairwise comparisons using Dunn's test, IgM scoring was higher in ruptured plaques, but all other intensities were equivalent. Then, ruptured plaques were double-stained for IgM and for either CD68 or C9. IgM colocalised with CD68 (macrophages) but not with C3 or C9. **Discussion:** Immunohistochemical staining for IgM (but not IgG) is more intense in ruptured plaques compared to unruptured. This is opposite to the pattern usual for immune-complex vasculitis (IgG>IgM). The mechanism is beyond the scope of the present study. Of note, many autoantibodies against oxidised LDL are IgM. **Summary:** IgM immunohistochemical staining is more intense in ruptured plaques compared to unruptured.

P17

The Use Of WT1 Immunohistochemistry In The Differential Diagnosis Of Adenocarcinoma In Pleural Fluid

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The identification of the site of origin of adenocarcinoma in pleural fluid is a common diagnostic problem, often requiring the use of immunohistochemistry (IHC). Given the variability of antigen expression between tumours and technical difficulties using IHC on cytology preparations, a range of markers is often required to make the differential diagnosis. In this study, we describe the use of WT1 IHC as an adjunct to differentiating between lung, breast and ovary primary sites of adenocarcinoma. The use of WT1 IHC on pleural fluids has not previously been described. IHC for WT1 was performed on 20 known cases of lung, breast and ovarian adenocarcinoma and 20 previously diagnosed pleural fluids. Strong WT1 staining was seen in 95% of ovarian, compared to patchy staining in 75% of breast and weak staining in only 5% of lung adenocarcinomas studied. Of the pleural fluids, those diagnosed as lung primary (n=10) were consistently negative for WT1, other diagnoses showed variable staining patterns. Our results suggest that WT1 may be used as part of a panel of markers, including BerEP4, ER, CA-125 and TTF1 in the differential diagnosis of adenocarcinoma in pleural fluids. The staining of other cell populations by WT1 and its implications are also discussed.

P18

Is there a Pathological Basis for Diastolic Heart Failure?

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Traditionally heart failure has been viewed as a disorder of ventricular function produced by ischaemic heart disease, valvular disorders or hypertension. Although survival is improved with modern therapy heart failure remains a disorder with a poor long term outcome and a substantial risk of sudden death. Echocardiography is the most reliable method of confirming the diagnosis. Cardiologists now recognise that a proportion of patients with typical signs and symptoms of heart failure appear to have preserved ventricular function with a normal or near normal ejection fraction ($\geq 50\%$). This is generally termed diastolic heart failure. In this audit we have studied the macroscopic changes at post mortem in patients who died suddenly of cardiac disease. Our intention was to identify patients who might have fulfilled criteria for the clinical diagnosis of diastolic heart failure.

We studied over 100 patients who died suddenly. Features of established heart failure such as oedema and hepatic congestion were recorded and graded and wherever possible the cause of cardiac failure was identified. Mitral valve circumference, left ventricular thickness and the distance from the valve ring to apex were recorded. We attempted to classify the shape of the left ventricular cavity using descriptions that included globular, normal, conical and pencil shaped.

Over a six month period we identified only 6 patients who may have fulfilled the criteria for a clinical diagnosis of diastolic heart failure. All appeared to have died of cardiac disease but had no clear evidence of ischaemic or valvular disease. In each case the ventricular cavity appeared to be reduced in size.

While we accept that diastolic failure is a significant clinical problem it is not a common entity at post mortem. We suspect that patients who are initially identified with this pattern of failure progress to a more typical pathological form of disease by the time of their death.

P19

Role of PKC Zeta Alternative Splicing and Prostate Cancer

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Introduction: PKC isoforms are important regulators of many homeostatic signalling mechanisms and may be responsible for co-ordinating subtle changes that determine cellular phenotype.
Expression of PKC zeta isoforms has been implicated in the metastatic behaviour of human epithelial malignancies including prostate cancer
Methods: Immunohistochemistry: performed on a number of malignant and normal prostate tissues to compare expression.
Western blotting: performed on prostate cancer cell lines PNT2 (benign), PC3 (malignant) and DU145 (metastatic) and a non-prostatic positive control cell line (HeLa).
Genome walking and splice variant analysis: mRNA was extracted from 5 prostate cell lines PNT2, LNCaP, Du145, PC3 and PC3-M. cDNA was synthesised by reverse transcription. Genome walking analysis was performed from the 3' poly A tail to the 5' end using sequence specific primers.
Results: Immunohistochemistry and western blot data show that expression of PKC ζ protein increases with progression of prostate cancer. Splice variant analysis presents a pattern of expression of variants within the 5 cell lines and matched tissue samples. Features include an exonised intron and point mutations. A region of the gene encodes a short sequences of RNA which may act as regulators of PKC zeta expression through an miRNA–type mechanism
Conclusions: Changes in expression patterns of PKC zeta variants are associated with different behavioural phenotypes of neoplastic prostatic epithelial cells. The data support the hypothesis and define the variable exonic regions of the gene involved in these distinct phenotypes.

P20

The Atlas of Protein Expression: High Throughput Mapping in Health and Disease at the Cellular Level

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The aim of the Atlas of Protein Expression Project (http://www.sanger.ac.uk/Teams/Team86/) is to build a comprehensive image and data set describing protein expression at cellular level using immunohistochemistry. This process is undertaken in high throughput with an initial objective of providing information on 500 to 1000 proteins per year. Antibodies are selected on protein fragments using phage display technology. A primary antibody screen is undertaken using a single composite slide containing frozen murine tissues. On this there are 92 TMA cores representing 24 normal adult tissues and a sagittal section of adult brain and E14.5 embryo. Other TMA and section panels are available covering frozen human tissues and murine and human formalin fixed paraffin embedded tissue. Up to 60 slides can be automatically immunostained in a day using an alkaline phosphatase detection procedure. These are then scanned, to provide a complete image record, analysed for staining intensity and exported to an Oracle database. From this annotation is undertaken using a series of drop down menus that are governed by ontology tables.
The 'Atlas' database will be available for viewing in 2006 and this, together with a mechanism to distribute antibody clones for immunostaining, will provide the interface with the scientific community.

P21

Targeting The Telomeres By Small Molecules Approach: Perspectives For Leukaemia Treatment.

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Maintenance of the telomere length is a major determinant of replicative lifespan in human cells and thus of the immortalized state. This correlation made the telomere/telomerase complex an attractive target for development of new cancer therapeutics. BIBR1532 is a non-nucleosidic small molecule inhibitor, which is highly selective for the inhibition of telomerase resulting in telomere dysfunction and delayed growth arrest in tumour cells. In this study we have shown that using this class of telomerase inhibitor at higher concentration has a direct cytotoxic effect on malignant cells from leukaemia patients and several leukaemia cell lines. Importantly there was no effect on the in-vitro proliferative capacity of the normal $CD34^+$ haematopoietic stem cells, obtained from cord blood and leukapharesis samples. Furthermore, using quantitative FISH analysis we demonstrated early loss of individual telomeres in malignant cells, which was associated with loss of hTERT/TRF2 proteins and activation of apoptosis. We conclude that BIBR1532 at higher concentrations exerts a direct cytotoxic effect on malignant haematopoietic cells, which appears to be initiated by loss of individual telomeres and that telomere damaging agents might represent an interesting avenue for novel cancer therapies.

P22

High Resolution Array-Comparative Genomic Hybridisation Profiling of Human Oligodendroglial Tumours

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Oligodendrogliomas account for 5-19% of all primary brain tumours. Deletions of chromosomal arms 1p and 19q are extremely frequent (~70%), correlating with enhanced chemoradiosensitivity and survival. However, the putative major tumour suppressor genes at 1p/19q and at other recurrently aberrated loci still remain unidentified.

We profiled genome-wide DNA copy-number alterations in 55 WHO-classified oligodendrogliomas [33 grade II (OII), 22 anaplastic grade III (AOIII)] using array-CGH (3040 BAC/PAC/Cosmid clones at 1Mb intervals) coupled with microsatellite analyses of 1p/19q and other loci.

We observed LOH of 1p (71%) and 19q (72%) in all tumours. Malignant progression related losses of 9p21 (CDKN2A/2B locus, OII=12%, AOIII= 45.5%), and 10q (OII=8.8%, AOIII=9%) were also seen. Other non-random recurrent chromosomal aberrations were identified, including loss of regions on 4 (21.8%), 13q (16.5%), 14q (26%), 15q (18.7%), 18q (16.5%), and gain of regions on 11q (19%) and 17q (14%). Overall, the number of aberrations increased with grade. Notably, known and novel amplifications including CDK4, CDK6, MYC, MET and homozygous deletions e.g. CDKN2A/2B, CDKN2C and PTEN were found.

These results provide insights into the genetic mechanisms driving oligodendroglial tumorigenesis, and identify novel molecular targets/pathways of possible prognostic significance and/or therapeutic intervention.

P23

Characterisation of SEPT9_v1 protein expression in human epithelial cells

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The expression of SEPT9, one of 13 known human septins, is perturbed in human neoplasia. While mutations have not been found, alterations in the level of SEPT9 transcripts are seen. In particular, changes in the levels of SEPT9_v1, v4 and v4* transcripts have been observed. Furthermore, we have shown that SEPT9_v4 can promote altered motility, perturb polarity and promote resistance to microtubule acting drugs. Our attention has therefore turned to the properties of SEPT9_v1 and we have constructed a model system that mimics the over-expression of this transcript in epithelial neoplasia. To this end we have over-expressed SEPT9_v1 in MCF7 cells both transiently and stably. We have also expressed point mutants that represent both gain of function (G308V) and dominant negative (loss of function; S312N) forms. Immunofluorescence showed both cytoplasmic and nuclear localization for wild-type SEPT9_v1 ranging from filamentous to particulate in nature, similar to that seen with endogenous SEPT9_v1 protein. In contrast neither mutant was associated with filaments. Biochemical fractionation studies showed that both endogenous SEPT9_v1 and epitope-tagged wild-type SEPT9_v1 was present in cytosol, membrane, cytoskeleton and nuclear fractions. The latter observation is supported the presence of a bipartite-NLS in the N-terminus of SEPT9-v1. In contrast, epitope tagged mutant SEPT9_v1 (G308V and S312N) protein was not detected in nuclear fractions. Expression of SEPT9_v1 S312N induced prominent microtubule containing neurite–like extensions, not seen in the wild type or G308V expressing cells. We observe that the expression of SEPT9_v1 alters the adhesive properties of epithelial cells paralleling these morphological changes. Moreover the growth of SEPT9_v1 S312N expressing cells differs from that of other cells with a propensity to form multilayered colonies. These studies provide possible insights into the role of deregulated SEPT9_v1 expression in neoplasia

P24

Characterisation of the functional domains of SEPT9

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Altered expression of SEPT9 is a common occurrence in neoplasia and recent data indicates that over-expression of SEPT9_v4 promotes cell motility, perturbs polarity and can induce resistance to microtubule interacting drugs. We wish to understand the domains of SEPT9 that can confer such properties and determine the functional elements that contribute to SEPT9 interactions both with itself and other proteins. In addition to all wild type forms of SEPT9 (v1,v2,v3,v4 & v5), we have generated a series of nested deletion mutants as epitope tagged constructs, including the N terminal variants (v1 residue 1- 164; v2 residue 1-157; v3 residue 1-146); the unique region of SEPT9_v1 (residue 1-25); the common region of the N terminal forms (v1 residue 26-164); the N terminus of SEPT9_v4 (v4 residue 1-87); the GTP binding moiety, with (v5 residue 1-220) and without the polybasic region (v5 residue 51-220); the GTP binding region plus the septin unique region (v5 residue 50-335) and the septin unique region (v5 residue 221-335). We have employed these constructs to examine homotypic and heterotypic interactions of the various domains in cell based assays by immunoprecipitation as well as confirming interactions using purified proteins. We observe evidence for homotypic interaction of SEPT9_v1 and this appears to be mediated by sequences in both the GTP binding domain as well as via sequences in the N terminus. SEPT9_v2 and v3 are almost identical to SEPT9_v1, yet do not appear to show an interaction with SEPT9_v1 mediated by the N terminal moieties. Other immunoprecipitation experiments show that SEPT9_v5 can participate in homotypic interactions. In other experiments we are investigating the localisation of the various transgene encoded proteins and examining their functional consequences. Based upon this we can propose a model of how SEPT9 complexes can be formed. These data provide insight into how such complexes may be deranged in disease and how Cdc42 can interact with specific domains of SEPT9.

P25

Microsatellite genotype assay for specimen mix-up detection

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Specimen mix-ups occur within histopathology. DNA fingerprinting should be able to identify the origin of tissue. In this study we have audited the effectiveness of a routine service for this test over a 6 year period. Since 1999 we have investigated 48 cases by using multiple microsatellite markers to identify the tissue and amelogenin to identify sex. We have used paraffin embedded blocks, paraffin sections, mouthwashes and EDTA blood samples as a source of material for identification. Cases have been received from all over the U.K.

Results:

48/48 (100%) successfully genotyped.

27/48 (56%) cases showed no evidence to suggest the tissue originated from different patients.

21/48 (44%) cases showed at least one marker differing between two individuals suggesting that the mixed up tissue originated from different patients.

Conclusion: genotyping histological material appears to be a reliable method of identifying mixed up specimens within the laboratory. One half of cases confirm a mix up of material.

P26

Genome-wide High Resolution Array CGH of Medulloblastomas and Supratentorial Primitive Neuroectodermal Tumours

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Medulloblastomas (MBs) and supratentorial primitive neuroectodermal tumours (stPNETs) are embryonal intracranial tumours predominantly occurring in childhood. Consistent large-scale chromosomal abnormalities have previously been reported in these tumours. We have used high-resolution whole-genome array CGH to identify novel small regions of genomic copy number alterations, homozygous loss and high-level amplification.

All samples examined had copy number changes. Gain was consistently seen in MBs on 17q (59%), 7q(44%), 1q (32%), 9p (27%), 18q (24%), 5p (21%) and 12q, 19p and 19q (18%); losses were seen on 17p (35%), 11p and 16q (29%), 3p, 8p and 10p (27%), 10q (23%) and 20q (21%). In each case a minimally affected region was identified. StPNETs showed a different spectrum of copy number alterations. For example, gain of 17q was not seen in stPNETs but loss of 13q34 was common (57%).

A subset of tumours had high-level amplifications, some involving known oncogenes, including MYCN, PDGFRA and KIT. High-level amplification was more frequent in stPNETs than MBs (Fisher's p-value = 0.02782).

In conclusion, we have identified novel small regions of genomic copy number change and several novel amplicons and we have found significant differences in the genomic changes affecting these morphologically similar tumours.

P27

Haem Oxygenase-1 Mediates the Anti-inflammatory Actions of 2'-Hydroxychalcone in RAW 264.7 Murine Macrophages

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Haem oxygenase-1 (HO-1) is a cytoprotective inducible stress protein that plays a crucial role in the control of inflammation. HO-1 down regulates the pro-inflammatory cytokines and mediates the increase of anti-inflammatory mediators. Plant-derived polyphenolic compounds are also known for their anti-inflammatory activity as they possess the intrinsic ability to up-regulate cytoprotective and detoxifying enzymes. In this study, we investigated the anti-inflammatory action of 2'-hydroxychalcone (2-HC) in lipopolysaccharide (LPS)-activated RAW 264.7 murine macrophages and examined a possible mechanistic link with HO-1 induction. We found that 2-HC potently induced HO-1 expression and resulted in the activation of the transcriptional factor Nrf2. 2-HC markedly reduced LPS-mediated nitrite, an index of nitric oxide (NO) production, as well as inducible NO synthase expression and TNF-α production. These effects were abolished by blockade of heme oxygenase activity with tin protoporphyrin IX, indicating the involvement of the heme oxygenase system in the anti-inflammatory actions elicited by this polyphenolic compound. We also found that phosphatidylinositol 3-Kinase (PI3K) is a major cellular mediator in 2-HC-induced HO-1 expression. These findings suggest that 2-HC exerts anti-inflammatory actions via up-regulation of HO-1 pathway and provide important elucidations on the mechanisms underlying the anti-inflammatory activities of the HO-1 system.

P28

The Two Promoters of Human *MDM2* Generate Different Transcript Variants That Code For Functionally Different Proteins

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The human 'murine double minute 2' (*MDM2*) gene encodes a protein that binds to p53 and promotes its degradation. It is amplified and/or over-expressed in some cases of glioblastoma. There are many reported alternatively spliced transcripts of the *MDM2* gene for both normal and tumour tissues. The gene has two promoters; the first promoter (P1) is upstream of exon 1 and the second (P2) is in intron 1. It is not known which transcripts originate from the P1 or P2 promoter. P2 has p53-responsive elements and p53 is believed to initiate *MDM2* gene transcription using this promoter. *MDM2* transcripts that derive from the P1 promoter have exon 1 as their 5'UTR, whereas the P2-derived transcripts have exon 2. Exon 3 is common to transcripts from both promoters and contains the start codon. To gain a better understanding of which of the *MDM2* splice variants are expressed in astrocytic gliomas, we have examined a series of glioblastoma derived xenografts and cell lines with known *MDM2* and *TP53* gene status. Primer pairs that exclusively amplify either P1- or P2-derived *MDM2* cDNAs were used to produce products that were cloned and then analysed by PCR-sequencing. We found several previously documented as well as novel splice variants. The newly identified variants resulted mostly from the deletion of entire exons and/or the inclusion of intronic sequences and were not due to splice site mutations. The regions of the mRNA most frequently excluded from the transcript were those coding for the p53-binding domain and the nuclear localisation signal. We are transfecting *MDM2* splice variants into human glioblastoma (GB) cell lines. Initial results indicate that *MDM2* splice forms encode proteins with different functional capabilities.

P29

The association between genetic variant of Luteinizing hormone and the incidence and prognosis of prostate cancer in groups of multi-ethnic origin.

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Introduction: Circulating Testosterone plays an important role in the maintenance and growth of prostate cells. Luteinizing hormone (LH), secreted from the anterior pituitary, signals testicular Leydig cells to secrete Testosterone. A common genetic variant of LH (vLH) has been identified. The prevalence of this variant allele has been estimated worldwide as a carrier frequency of 0% to 53% of Caucasians and is known to be more active than the wild-type protein. Screening for vLH has primarily relied on relative immunoreactoivity in variant-sensitive and insensitive assays. Restriction fragment length polymorphism (RFLP) studies are largely been used to confirm immunoassay results. However, both methods present various limitations and potential bias. We hypothesized that vLH might affect the susceptibility to prostate cancer and we aim to study its relation with the disease in men of different ethnic origins.
Methods: in our international study, we included two groups from the UK population, subdivided into Caucasians and Afro-Carribeans, together with a third population group from the United Arab Emirates, in whom the incidence of prostate cancer is known to be very low, a total of 600 men. We used nested polymerase chain reaction (PCR) and DNA sequencing of LH beta gene region as a definitive test for the mutations in population groups of multi-ethnic origin.
Results: our initial results in the UK population group revealed the absence of these mutations in all healthy individuals tested; however, it was detected in 20% of prostate cancer patients and in 50% of malignant prostate cancer cell lines.**Conclusion:** Our initial results have shown that the genetic variant of LH beta (vLH-beta) gene is more common in patients with prostate cancer. The mutated form detected results in a posttranslational modification that may alter LH bioactivity and hence increase the susceptibility to prostate cancer development.

P30

Osteoprotegerin is strongly expressed in the intratumoural endothelial cells of gastrointestinal carcinomas

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Osteoprotegerin (OPG) is a protein, physiologically involved in control of bone growth, which has been shown to act as a decoy receptor for tumour necrosis factor related apoptosis inducing ligand (TRAIL) and thus to act as a tumour cell survival factor *in vitro*. We have shown that OPG is strongly expressed in intratumoural endothelial cells in 37% of breast cancers, is not expressed in endothelial cells outside the tumours and has a significant association with increasing tumour grade. We have also shown that OPG acts as a survival factor for endothelial cells *in vitro*. We postulate that OPG in intratumoural endothelial cells is a potential therapeutic target for anti-vascular therapy in human cancer and a survey of its expression in different human cancers is warranted, in this study we look at OPG expression in gastrointestinal cancers. 100 oesophageal cancers (24 squamous, 76 adenocarcinomas), 20 samples of non-neoplastic oesophageal squamous epithelium and gastric body mucosa, 20 colorectal adenomas, 80 colorectal cancers and 50 hepatic metastases from colorectal cancer were arrayed in triplicate in tissue microarrays and immunohistochemistry for OPG was performed. OPG was expressed in the nucleus of non-neoplastic glandular mucosa in Barrett's oesophagus, colorectal mucosa and bile ducts. It was not expressed in any endothelial cells in normal tissues including background liver tissue 5mm from hepatic metastases. There was strong expression of OPG in the intratumoural endothelial cells in 60% of the gastrointestinal cancers and the colorectal adenomas with high grade dysplasia. This provides further evidence of the specificity of OPG expression in intratumoural endothelial cells and its potential as a therapeutic target.

P31

Ethanol Does Not Affect Expression Of The Genes Of The Ubiquitin-Proteosome Pathway In Rat Skeletal Muscle

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Myopathy affects up to two thirds of all alcoholics. Histology correlates with symptoms and shows selective atrophy of type II muscle fibers. Ethanol exposure reduces muscle protein and ribonucleic acid (RNA) content. Loss of protein may result from changes in proteolysis, protein synthesis or both. Acute intraperitoneal administration of ethanol has been shown to inhibit some of the activities of the ubiquitin-proteasome proteolytic pathway in rats. However, the mechanism of this effect is unclear.
To investigate the effect of acute ethanol exposure on expression of the major genes of the ubiquitin pathway in skeletal muscle, rats were exposed to ethanol (75 mmol/kg body weight; i.p.; 2.5h). Controls were injected with identical volumes of 0.15 mol/l NaCl. The mRNA levels of the major genes of the ubiquitin pathway were assessed by Northern blotting. The complementary deoxyribonucleic acid probes encoding UBLarge and UBSmall, C2 and C8 20S proteasome subunits and 14-kDa E2 and 18S ribosomal RNA (rRNA) were used. Data (as mean $\pm$ SEM) in arbitrary units (AU) were as follows:
There was no significant effect of alcohol on the levels of UBLarge, UBSmall, E2 k14L, k14S, C2 or C8 mRNA.

P32

Parkin Expression Varies Between Regions Of The Brain In Rats *In Vivo* But Is Not Affected By Ethanol Or Gender

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Chronic alcohol excess results in brain atrophy and impaired cognitive function. Changes within the ethanol-exposed brain appear to be site-specific and vary with gender. Perturbed protein degradation may account for these effects of ethanol. Alcohol excess can impair proteolysis mediated by the ubiquitin–proteasome pathway. However, the mechanism is unclear. The gene product of parkin is the ubiquitin E3 ligase, an important component of the ubiquitin–proteasome pathway. Abnormalities of this gene have been implicated in Parkinson's and parkin has been found in neurofibrillary tangles in Alzheimer's. The aim of this study was to assess the impact of chronic ethanol exposure on expression of the parkin in the brain in vivo. Male and female rats were subjected to chronic ethanol feeding for 6 weeks. The levels of parkin mRNA in different regions of the brain were assessed by reverse transcription-polymerase chain reaction (RT-PCR). Data (as mean + SEM) in arbitrary units were as follows:

Marked inter-regional differences in brain parkin mRNA levels were observed. The lowest levels were in the cerebellum, but the reason for this is unclear. Ethanol did not affect the levels of parkin mRNA in the brain. There was no difference between males or females.

P33

Endotoxin Reduces The Inhibition of Skeletal Muscle and Jejunal Seromuscular Protein Synthesis Induced By Acute Ethanol Administration In Rats *In Vivo*

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Both gram negative sepsis and acute alcohol toxicity inhibit protein synthesis and result in loss of protein. Endotoxaemia has also been reported to initiate some of the pathological lesions seen in alcoholism. We hypothesized that during alcohol exposure, endotoxin administration would further inhibit protein synthesis. To investigate this rats were treated with either endotoxin (3 mg/kg; i.p.), ethanol (75mmol/kg; i.p.) or both for 3 hours. Controls were treated identically and injected with 0.15 mol/l NaCl i.p. Fractional rates of protein synthesis (k_s, % skeletal muscle protein renewed/day) were measured in skeletal muscle and the seromuscular layer of the jejunum with [^{3}H]phenylalanine. Data (as mean, n=5-8) were as follows:

Marked inter-regional differences in brain parkin mRNA levels were observed. The lowest levels were in the cerebellum, but the reason for this is unclear. Ethanol did not affect the levels of parkin mRNA in the brain. There was no difference between males or females.

P34

A web-based aid to facilitate the introduction of trainees to breast pathology

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Getting trainees started in pathology presents challenges. Very rapidly they need to grasp an understanding of disease processes, the basics of macroscopic description of specimens and microscopy. An expanding curriculum and a shortened training period compounds this problem as does a shortage of consultants to deliver hands-on tuition.
A web-based training handbook has been written that facilitates structured learning of breast pathology and integrates the clinical / pathology interface. It also includes departmental tissue-handling protocols. The manual is stand-alone in that trainees can pick a topic and study a fully illustrated web page. The "alt" feature of the browser is utilised to provide additional mouse-over information when looking at photomicrographs and image mapping could enhance this further. Numerous hypertext links allow cross-reference within the site e.g. to "Immunohistochemistry" or "Special types of cancer". External links could be added easily if the pages were published on line. The site is dynamic and evolving and new pages are being added frequently.
Slide sets are linked to the web site with the potential for multiple-choice type questions, explanations of differential diagnoses and links to the "correct answer" pages with further reading and illustrations. Scottish pathology trainees have commented positively about the value of this new resource built on freely available software and local teaching material. The presentation includes discussion of the essentials of good web design to maximise educational benefit and a demonstration of the web site in action.

P35

An Audit Of Frozen Sections

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Objectives: To assess the number and types of frozen sections reported by the department, the details included within a frozen section report and the identification of discrepancies between frozen section and H&E diagnoses.
Methods: All 195 cases reported over a ten month period were included and the request forms examined. The presence within the report of the date, time, diagnosis, signature and documentation of to whom the report was given was assessed. The frozen section and subsequent H&E slides and reports were reviewed and compared.
Results: 59% of cases were sent for the evaluation of malignancy and 34% for infection. Clinicians supplied a contact number in 90% of cases. In 6 cases (3%), the pathologists did not document any details on the back of the request form. Of the remaining 189 cases, 75% included the date in their report, 86% the time, 99% documented a diagnosis, 91% were signed, and 77% stated to whom the report had been issued. Complete correlation between the frozen section and H&E diagnosis was found in 192 cases (98.5%). The discrepancies within the remaining three cases were found on review to be due to differences in sampling (malignancy x 2, ganglion cells x 1).
Conclusions: The use of frozen sections to evaluate infection is questionable and may not warrant the use of technical and consultant resources. The majority of consultants demonstrate consistently high standards in their reporting of cases. The introduction of a standardised stamp maybe useful in prompting the documentation of specific details. All frozen sections should be reviewed alongside the H&E.

P36

Supporting Undergraduate Teaching in Histopathology with Virtual Microscopy

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We described an E-learning system exploiting virtual microscopy to support postgraduate training at the last meeting of the Society. Undergraduate teaching has distinct requirements, with concentration on basic concepts and little assumed prior knowledge. The developed system addresses this by bringing together the interactivity of virtual microscopy and more familiar elements of histopathological e-learning systems - such as pertinent still images.
The e-learning platform we have developed for undergraduate comprises two interfaces to the same information. The consultant-access system is password protected and allows teaching staff to structure materials into topics mirroring the course timetable. Any number of slides with associated history and macroscopic images can be associated with each topic. Given the difficulty of identifying salient regions of slides (for novices), still images of slide regions are included alongside hints and comments. The student-facing interface simply presents this information in a systematic way to the student. Investigations are currently underway into the use of XML annotation files to overlay text and diagrams upon the virtual slide, although this makes use of proprietary virtual microscopy applications and is not proving as easy to manage cross-platform.

Acknowledgement: Software development was supported by a teaching development grant from the University of Leeds.

P37

Pathnet– A Novel Use Of Internet Technology For Post-Graduate Histopathology Education

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Pathnet (http://www.pathnet.org.uk) is a novel collection of web applications to facilitate collaboration and exchange of educational materials between the Histopathology Training Schools. All Year One Histopathology trainees are enrolled, and form the majority of the 258 registered users along with interested Consultant Histopathologists and Specialist Registrars. All users are able to modify the site contents, by uploading educational material (including presentations, word documents and images). Trainees are encouraged to share interesting case reports by uploading case reports (using a provided template). Pathnet also incorporates Tapir, a pathology image database which allows users to submit pathology images with associated descriptions. The database currently contains over 2500 images, indexed using MeSH (Medical Subject Headings) for rapid searching. Also provided is a facility for the user to annotate the images to emphasise key features.
Q&A Café provides pathology video footage for trainees within Pathnet. Trainees can then describe what the video shows and where appropriate give a differential diagnosis online. Participation is encouraged, as response are anonymised and trainees are unable to see other trainees' responses or the 'correct answer' until they have submitted a response themselves.
Pathnet uses innovative educational technology to provide a novel online learning environment for trainee histopathologists.

P38

An Audit of Renal Biopsy Diagnosis in Two Renal Units

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The distribution of renal biopsy diagnoses for a service will depend on: the characteristics of the populations served; the biopsy policy of the medical staff; and the diagnostic preferences and accuracy of the reporting pathologist(s). The distribution of diagnoses should be within expected ranges; an excess or absence of a particular diagnosis may identify problems with diagnostic procedures or with selection of patients for biopsy.

Biopsy diagnosis were audited in two renal units for the year 2002 by categorising all 384 medical renal biopsies for the indication for biopsy and the final histological diagnosis using the biopsy request form and the report.

Indications for biopsy were: nephrotic syndrome: 24%; chronic renal failure: 23%; acute renal failure: 21%; proteinuria: 11%; others: 10% or less each.

Incidence of individual diagnoses: IgA nephropathy: 13%; crescentic/segmental necrosis: 10%; diabetic nephropathy: 9%; membranous: 8%; FSGS: 7%; minimal change: 6%; immune complex/post infective: 5%; membranoproliferative: 4%; ATN: 4%; others: 3% or less each.

There were differences between the units in the indication "chronic renal failure" (9 vrs 31%) and in the diagnoses "diabetic nephropathy" and "membranoproliferative GN" (12% vrs 7% and 0.7% vrs 6% respectively). These differences require investigation.

The incidences determined here offer a benchmark against which other units may audit.

P39

Development of Web-based Interactive Pathology Computer-Assisted Learning Programs (PathCAL)

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The previously reported set of computer-assisted learning programs in pathology and medicine (PathCAL) has been redeveloped as a Web-based application of 117 tutorials on a wide range of topics. The programs retain their original core educational design, based on principles of learning psychology, but have been substantially expanded in functionality, accessibility, utility, reflexivity and adaptability to incorporate animations, streamed video sequences and more varied self-assessment. Every self-assessment interaction is recorded, allowing tutors to assess the quality of student learning. The web-based authoring interfaces (Edinburgh Reusable Object Sequencer (EROS)) allow the material to be adapted easily according to feedback, evolving scientific knowledge and educational practice. Changes are immediately available to users. Evaluation at the end of each program elicits electronic feedback in support of quality assurance. The number of authorised users worldwide is limited only by the capacity of servers delivering the programs. Multiple authors can collaborate, irrespective of geographical location. The programs are available to medical students in Edinburgh and Cambridge Universities. In 2003 till October 2005 the logged-in sessions recorded each year from Edinburgh and Cambridge together numbered 3533, 13435 and 10303, with over 3000 per month in Nov and Dec 2004; users numbered 527, 1010 and 904. In evaluation studies in 2003-04,100 of 177 respondents cited PathCAL among the three best things in year 2 of the medical course at Edinburgh in terms of helping them learn and in 2004-05, 146 (96%) of 152 respondents strongly agreed or agreed it helped them learn, which was higher than any other learning method. Evaluation studies over nine years showed consistent high student satisfaction with PathCAL. The system is becoming more widely available to subscribing universities and medical schools in the UK via JISC Collections (www.pathcal.ac.uk).

P40

Development Of A Web-Based System For A General Histopathology External Quality Assurance Scheme

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The North West Regional Histopathology External Quality Assurance (EQA) started in 1990 and has used the glass slide based method since its inception. There are 118 participants in 28 centres across the North West of England, Merseyside and North Wales. There are 2 circulations of 16 slides per year (12 'scoring' and 4 educational). In the 2 most recent circulations (Spring and Autumn 2005), glass slides were circulated normally, in parallel with a web-based (Slidepath) system that allowed participants to view cases online and submit diagnoses. Haematoxylin and eosin stained sections were digitised by Aperio and were placed on a password protected anonymised website. In Spring 2005, 46 of 118 participants (39%) registered for use of the Slidepath system and of these, 42 (91%) submitted online diagnoses. The scoring was based on the written diagnoses. The consensus meeting used the web-based material for part of the discussion. Participants using the system commented favourably on the quality of images and the ease of use of the Slidepath software. Difficulties were reported with poor resolution of some low power images. These were later rescanned and the improved methodology has been incorporated into the Autumn 2005 circulation. Problems were encountered with information technology systems in host NHS departments, causing slow access and in places prevented by firewall restrictions. These were partly alleviated by contact with trust IT personnel and by using more modern equipment. This initial study demonstrates that it is possible to conduct an EQA scheme online. A further double blind study is planned for Spring 2006 in which the feasibility of replacing glass slides for part or all of a circulation will be considered, possibly permitting the use of more biopsy (as opposed to resection) material.

P41

On-line virtual slide library for training and education in liquid based cervical cytology

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Liquid based cytology (LBC) for cervical screening has been recognised by the NICE who recommend that the technique is introduced UK wide by 2008. This puts pressure on cytology laboratories to ensure high quality training and quality assurance in this new technique. Some of these problems can be alleviated through the use of on-line training methods and in particular the use of virtual cytology slides. Virtual slides (VS) are high resolution digital scans of the entire slide, can be viewed on-line by a web-based or client server application and provide a valuable medium for the delivery of on-line pathology education.

This study has developed an on-line VS library of over 200 liquid-based cervical cytology specimens (SurePath®) which are delivered to the user via a VS on-line pathology content manager, *PathXL®*. LBC slides were scanned using an Aperio T2 slide scanner at x40 magnification and served using an Aperio ImageServer. Each slide is digitally annotated to highlight the key diagnostic fields and cells of interest. These can be viewed as a feature list and on request the user can be driven to the pertinent areas of the slide. A series of questions are available on each slide against which the user can be scored for training, self-directed learning, self assessment, examination or for quality assurance. The system also permits the delivery of on-line streaming instructional video demonstrating how an experienced cytologist arrived at the diagnosis for every case. Supplementary features include the automatic on-line screening of slides.

PathXL® as an on-line VS archive enhances education in LBC. We are currently developing other on-line education resources in other diagnostic specialties including breast, urine and pleural fluid cytology and breast, cervical, prostate and soft tissue tumour histopathology.

P42

Computerised Decision Analysis and Virtual Slide Library for e-Learning and Quality Assurance in Urinary Cytopathology

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Urinary or bladder wash cytology is currently recommended as an integral part of diagnosis/follow-up of urologic tumours. It is however a subjective procedure. InView© is a tool for storing diagnostic knowledge on cases, viewing virtual slides of those cases and assessing ones ability to correctly interpret all of the key morphological features and reach the correct diagnosis. This is based around a Bayesian belief network and membership function architecture with an interface that leads the user through the diagnosis process. An InView© module was constructed for diagnosis in urine cytology. The diagnostic alternatives (benign, atypical, suspicious, malignant) and a set of diagnostic clues, necessary to make the diagnosis were defined. Reference images are presented to the user to help them grade each clue. InView© is designed to record a diagnostic assessment and construct a diagnostic graph that shows how each clue was assessed, its impact on the diagnosis and how the final diagnosis was arrived at. Here a series of 20 urinary cytology specimens were assessed using InView© by an experienced cytopathologist and a diagnostic assessment on each case stored. Each case was also scanned as a virtual slide allowing users to examine the slide on-screen, assess the slide under the direction of InView and compare their performance against that of an expert.

The InView© system can be used in three ways: 1) As a valuable training tool where trainees can compare their performance against a recognised expert, and identify inaccuracies in their diagnostic assessment. 2) In quality assurance, allowing a more precise assessment of diagnostic interpretation and comparison against a gold standard or a cohort of QA programme contributors. 3) As a diagnostic decision support system for more experienced cytopathologists in making difficult decisions.

P43

Morphological changes to the uterus seen in response to neonatal exposure to genistein and diethylstilbestrol.

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The effects of neonatal exposure to diethylstilbestrol (DES; 2µg and 0.002µg) and genistein (GEN; 100µg), on the morphology of the murine uterus were investigated at various stages of development in CD-1 female mice. Pups were exposed by subcutaneous injection on post-natal days (PND) 1-5 inclusive, and animals were sacrificed at PND's 8, 12, 17, 30 and 50. The uterine weight was taken, one horn processed for light microscopy and the other snap frozen for genomic analysis. Treatment with 2µg DES and 100µg GEN produced broadly similar effects consisting initially of a reduction in the number/maturity of uterine glands and an increase in stromal connective tissue seen at PND's 8 and 12, followed by a recovery at PND17 and to some extent PND30. Changes at PND50 included increased stromal connective tissue and intra-epithelial gland proliferation of the uterine epithelium. In contrast, treatment with 0.002µg DES produced different changes. At all time-points some uteri showed the presence of epithelial basal cells, although the incidence appeared to reduce with time. Early changes included epithelial hyperplasia (PND8), increased stromal connective tissue (PND's 8 and 12) and reduction in the number / maturity of the uterine glands (PND's 8 and 12). Squamous metaplasia of the uterine epithelium was seen from PND30 onwards, a change unique to this treatment group. Genomic analysis showed differential expression of some genes, including Trp63, between the two DES dose groups. These changes suggest perturbation of the genome during compound exposure resulting in altered cell phenotype at the time points described. The changes apparent after exposure to 0.002µg DES are consistent with the known carcinogenic potential of DES and may suggest dose dependency.

P44

Audit of Fine Needle Aspiration Cytology in the Diagnosis of Thyroid Nodules

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A retrospective review of 434 patients who had fine needle aspiration cytology (FNAC) for the evaluation of thyroid disease during 2003-4, has compared the effectiveness of FNAC with or without ultrasound guidance. For 69 patients, the cytology was compared with histological examination of resected thyroid tissue.

24 (6.4%) of the 373 ultrasound-guided aspirates were inadequate, compared with 8 (13.1%) of the 61 aspirates performed without guidance (p=0.043). 331 patients were assessed as having non-neoplastic diseases (nodular colloid goire, simple cysts, thyroiditis) on FNAC.

50 patients had FNAC reported as suspicious of neoplasia due to cytological atypia or features suggestive of a follicular neoplasm. 14 malignant cytological diagnoses were made including 8 papillary carcinomas, 2 metastatic carcinomas, 2 lymphomas and 2 anaplastic carcinomas.

Histological examination revealed 6 follicular carcinomas in the 27 cases with suspicious cytology. One false positive diagnosis of papillary carcinoma was identified and there were 2 false-negative biopsies (one follicular carcinoma in a nodular goitre, and one lymphoma). Overall sensitivity was 83.3% and specificity was 98.2%.

The results indicate that ultrasound-guided FNAC of thyroid nodules results in a significantly reduced inadequate rate for aspirates, and that FNAC is a reliable predictor of final histology.

P46

The β subunit of hCG may have a role in anti-apoptosis, and in tumour invasion of cervical squamous carcinoma

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The expression of the beta subunit of human chorionic gonadotrophin (hCG β) in patients with cervical squamous cell carcinoma was investigated with respect to tumour cell apoptosis. Seventy samples from patients with cervical squamous cell carcinoma (biopsy and/or curettage specimens) were immunohistochemically stained for beta-hCG. Apoptosis was evaluated by both morphological characteristics and by the TUNEL technique.
hCG β staining was observed in different cancer stages and different histological grades. Sixty one (87%) of the cervical carcinomas were beta-hCG positive, of which 29 (47%) were invasive. The beta-hCG reactivity was predominantly confined to peripheral tumour cells at the stromal-epithelial interface, and the intensity of the stain was stronger in the invasive lesion. It was uniformly absent from adjacent non-neoplastic epithelium, and from control cervices. TUNEL positive staining for apoptotic cells was significantly less in the tumours where beta-hCG expression was greater than 50% of the tumour tissue section.
Lymphatic spread was also observed in the majority of the cases where positively stained tumour cells were found within the lymph vessel. However, beta-hCG positive staining was also observed in endothelial cells of the newly formed blood vessels, suggesting that the expression of hCG-β protein may be associated with tumour angiogenesis.
In conclusion, beta-hCG expression correlates with reduced tumour cell apoptosis, and can act as a marker of tumour behaviour such as invasion and dissemination, and hence for prognosis and treatment.

P47

Microarray CGH Analysis of Adult and Juvenile Pilocytic Astrocytoma Shows a Common Pattern of Alteration

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Pilocytic astrocytomas ('PA', WHO Grade I) account for nearly 25% of childhood brain tumours, the most common solid tumour of childhood. Previous studies found few genetic changes in this common childhood tumour, with no obvious pattern to reported abnormalities. It was hoped that the increased sensitivity of aCGH screening would provide more insight into the genetic alterations characterising this tumour type.

The genomes of PA cases (n=45) from children (<15yrs, n=32) and adults (15yrs+, n=13) were assessed using microarray CGH, with clones spaced ~1Mb apart across the genome. The most common finding was trisomy of at least one chromosome, occurring in 36% of cases. The most frequent changes were trisomy 5 in 27% and trisomy 7 in 24% of cases. Trisomy 5 and/or 7 occurred in 94% of all cases with any trisomy. Interphase FISH and microsatellite analysis were used to validate these findings in a subset of tumours. This is the first genome-wide study to show this pattern of chromosomal alteration in pilocytic astrocytomas.

Furthermore, there was a statistically significant (p=0.02) difference in the occurrence of trisomies between juvenile and adult cases of PA (25% and 62%, respectively), possibly suggesting different tumourigenic pathways leading to these histologically similar entities.

P48

EphB2 is a Prognostic Factor in Colorectal Cancer

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Screening for targets of the Wnt pathway with oligonucleotide microarrays revealed that the level of expression of EphB2 was increased in colorectal cancer compared to normal. The aim of this study was to perform a detailed analysis of EphB2 expression in colorectal tissues. In addition, we sought to evaluate EphB2 expression as a prognostic factor in colorectal cancer.
Expression of EphB2 was examined in normal colon (n=28), cell lines (n=20), colorectal adenomas (n=148), primary cancers (n=28), and metastases (n=39) using immunohistochemistry. In addition, a series of primary cancers and matched normal (n=342) with outcome data were profiled in tissue microarrays. The intensity of EphB2 expression was assessed in the entire series by immunohistochemistry, and in a subset by in situ hybridization. Overall and recurrence-free survival were correlated with EphB2 protein expression in retrospective subset analyses.
Epithelial EphB2 expression was shown at all stages of colorectal tumourigenesis, including the base of all normal crypts, 77% of adenomas, 82% of primary cancers, and 64% of metastases. Although homogeneous expression was observed in adenomas, the pattern of staining was focal (mean 25%) in most malignant lesions. Patients whose tumour stained 2+ for EphB2 expression (versus 0/1+) exhibited significantly prolonged overall survival: mean duration of survival, 2,514 versus 1,044 days; hazard ratio, 0.45; 95% confidence interval, 0.18-0.95 (P=0.035).
In summary, EphB2 is expressed in normal crypts, colorectal adenomas, primary cancers, and metastases. High levels of EphB2 expression are associated with a longer mean duration of survival in colorectal cancer.

P49

Impact of VEGF Expression, THBS-2 Expression and Microvessel Density (MVD) on the Treatment Effect of Bevacizumab

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Bevacizumab is a monoclonal antibody to VEGF; in a phase III trial in metastatic colorectal cancer (mCRC), addition of bevacizumab to first-line irinotecan, 5-fluorouracil, and leucovorin (IFL) significantly prolonged median survival. The aim of these retrospective subset analyses was to evaluate VEGF, THBS-2 and MVD as prognostic factors and/or predictors of benefit from bevacizumab.
In the pivotal trial, 813 patients with untreated mCRC were randomized to receive IFL plus bevacizumab or placebo. Of 312 tissue samples collected (285 primaries, 27 metastases), outcome data were available for 278 (153 bevacizumab, 125 placebo). Epithelial and stromal VEGF expression were assessed by *in situ* hybridization (ISH) and immunohistochemistry on tissue microarrays and whole sections. Stromal THBS-2 expression was examined by ISH on tissue microarrays. MVD was quantified by Chalkley count. Overall survival was correlated with these variables in retrospective subset analyses. In all subgroups, estimated hazard ratios (HRs) for risk of death were <1 for bevacizumab-treated patients regardless of the level of VEGF expression or MVD. Patients with a high THBS-2 score showed a non-significant improvement in survival following bevacizumab treatment (HR with 95% confidence intervals = 0.11 [0.02-0.51]) compared to patients with a low score (0.65 [0.41-1.02]); interaction analysis P = 0.22. VEGF expression, THBS-2 expression, and MVD were not significant prognostic factors.
These exploratory analyses suggest that in patients with mCRC addition of bevacizumab to IFL improves survival regardless of the level of VEGF expression, THBS-2 expression, or MVD.

P50

Routine Elastic Staining Assists Detection of Vascular Invasion in Colorectal Cancer

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Vascular invasion (VI) is an independent prognostic factor in colorectal cancer (CRC). Some studies have recommended elastic stains to facilitate the recognition of VI, however, the usefulness of routine staining in CRC is not clear and this is not widely performed. The aim of this study was to determine the value of routine elastic staining of CRC specimens. 498 cases of CRC were included in this study (65, 215 and 218 Dukes' A, B and C). In 208 cases, VI was assessed using elastic stains that were introduced as a routine staining in CRC. As a control, 290 cases in which VI was assessed solely on H&E staining were included.
Vascular invasion (VI) was detected in 198 cases (40% of the whole series); 11 (16.9%), 62 (28.8 %) and 125 (57.8%) in Dukes A, B and C respectively There was a statistically significant increased detection of VI in the elastic stained group; 46.2% in the test group compared to 35.5% in the control group ($p<0.05$). Particular increase was noted in Dukes' stage A and B and in rectal tumours ($P<0.05$). Elastic stains are useful and practical in evaluation of VI status in CRC, and we recommend implementing these stains in routine pathological practice.

P51

Small-scale genomic abnormalities on specific chromosomes in sporadic colorectal cancers are associated with poorer survival.

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The influence of large-scale chromosomal instability (CIN) and microsatellite instability (MSI) on the survival of sporadic colorectal cancer (CRC) patients is controversial and requires further investigation. Although many studies have failed to show an association between microsatellite instability and survival, others have shown improved survival and different responses to 5-fluorouracil treatment by microsatellite unstable CRC compared to stable CRC. The aim of this study was to investigate whether there is any relationship between small-scale chromosomal changes and the survival of CRC patients. To answer this question we analysed the chromosomal changes of >100 sporadic colorectal cancers using high resolution 1Mb array-CGH. The primary tumours were evaluated for micro-deletions or -gains and these were correlated with survival of patients who received adjuvant chemotherapy and/or radiotherapy or neither. We also investigated whether small-scale genomic changes could be used to stratify patients with Dukes' Stage B or C CRC into groups with different risks of recurrence or survival. Both microsatellite stable cancers with large-scale aneuploidy and near-diploid cancers with microsatellite instability showed small regions of DNA copy number change involving one or a few genes only. Losses involving specific loci within chromosomes 18q and 8p were associated with a higher risk of recurrence and a poorer survival. Despite the fact that there was no correlation between microsatellite instability and tumour recurrence, MSI was associated with improved survival. We conclude that small-scale genomic abnormalities on specific chromosomes in sporadic colorectal cancers involving the loss of one or a few genes are associated with poorer survival.

P52

Proteomic Profiling of the Epithelial and Stromal Components of Matched Normal and Colonic Carcinomas using Protein Microarrays

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Introduction: Colorectal carcinoma does not have a single specific biomarker that can detect and predict disease behaviour. Consequently, combinations of expression markers may be useful in diagnostics and prognostics. Moreover, it is likely that the complex interaction between tumour epithelium and stroma is a key facilitator in sustaining tumour growth.
Methods: Colectomy specimens from 36 patients with colorectal carcinoma were included in the study. Epithelium and stroma of normal and cancerous colonic tissues were isolated by laser capture microdissection of fresh-frozen specimens. Using reverse phase protein microarrays, cell lysates were probed for 62 phospho-specific and total protein antibodies and relative protein concentrations were calculated.
Results: There was striking heterogeneity in protein expression between the patients and between the epithelial and stromal tissue types. Supervised and unsupervised clustering analysis indicated that signalling pathway portraits of tumour epithelium and stroma were more similar than their normal tissue counterparts.
Conclusions: This is the first study to perform isolated functional mapping of the epithelial and stromal components of colorectal cancer at a phosphoproteomic level. The greater similarity between protein expression in tumour epithelium and stroma supports the hypothesis of tumour-stromal cross talk and underscores the future potential to target tumour stroma therapeutically.

P53

Glucose Transporter 1 (Glut-1) expression and cellular localization in early colorectal neoplasia.

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Background: Glucose Transporter 1(GLUT-1) is a high affinity glucose transporter. Increased glucose uptake and utilization is one of the metabolic characteristics of tumour cells. Elevated levels of GLUT-1 have been reported in many human malignancies however the significance of GLUT-1 location and levels of expression in colorectal cancer (CRC) cases with corresponding adenomas has not yet been elucidated.
Design: The object of this study was to investigate the expression and localization of GLUT-1 in CRC specimens and adenomas using tissue microarrays and immunohistochemisrty. To date, we have analysed 106 CRC (Dukes A & B) and 21 adenomas (11 are contiguous to carcinoma and 10 separate). Four 6mm cores from each sample were scored and assessed for percent positivity and cellular localisation. Results were correlated with clinicopathological features.
Results: 96/106 CRC cases (91%) showed positive GLUT-1 immunostaining and 10 cases (9%) were negative. Three patterns of staining were observed, supranuclear, membranous and a mixed pattern of expression. GLUT-1 expression in CRC showed supranuclear staining in 37 cases (38%), membranous in 44 cases (46%) and mixed in 15 cases (16%). In the adenomas examined, 14 displayed supranuclear staining, 3 with membranous and 4 were negative for GLUT-1 expression. The 3 cases with membranous staining were all contiguous adenomas and 2 of which had high-grade dysplasia. The carcinomas, which developed in these patients, showed either a membranous or mixed pattern. Comparison of GLUT-1 expression and clinicopathological characteristics in all cases revealed significant associations between high GLUT-1 expression and Dukes stage B ($p < 0.001$), high T stage ($p<0.001$), level of invasion ($p=0.005$) and peritoneal involvement ($p=0.006$).
Conclusion: Our findings indicate that both the increased and cellular location of GLUT-1 may be useful determinants of neoplastic progression in CRC. We hypothesise that translocation of GLUT-1 from supranuclear to a mixed to membranous pattern may correlates with CRC disease progression.