Pathological Society

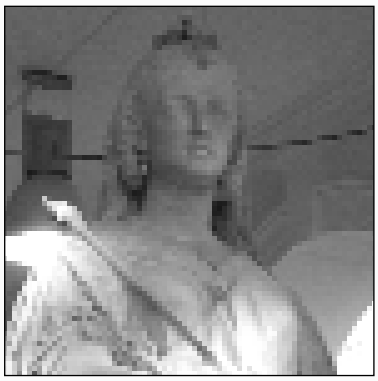
Understanding Disease

Winter Meeting Programme

195th Scientific Meeting
8–9 January 2009
Venue: King's College London

Hosted by the Department of Histopathology King's College London and Guy's & St. Thomas' Hospitals, London

To be held at King's College London, Waterloo Campus, Franklin-Wilkins Building, Stamford Street, London SE1 9NH



KING'S College LONDON

University of London

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PROGRAMME SUMMARY

Thursday 8 January 2009

The Foyer
08.00 **Registration and Coffee** *(coffee is served in the Restaurant)*

2.49 (PAWS) 2nd Floor
09.00–15.00 **Slide Seminar Viewing:** ***Tricky autopsy histopathology***

B.5 – Auditorium
09.15–12.15 **Cytopathology: Joint Symposium with the British Society for Clinical Cytology**

Restaurant 1st Floor
10.45–11.15 **Coffee, Poster Viewing and Trade Exhibition**

B.5 – Auditorium
12.15–13.15 **Trainees Programme: Meet the Experts**
12.15–12.45 *Interstitial lung disease*
12.45–13.15 *Placental examination for non-paediatric pathologists*

Restaurant 1st Floor
13.00–14.00 **Lunch and Trade Exhibition**

B.5 – Auditorium
14.00–16.30 **Plenary Oral Presentations**
16.30 **Pathological Society Undergraduate Essay Prize:** Presentation to Mr A Bamber, Cambridge

Restaurant 1st Floor
15.15–15.45 **Tea and Poster Viewing**

Restaurant 1st Floor
16.30–17.30 **Poster Viewing and Chairman's Rounds**

B.5 – Auditorium
17.30–18.30 **Pathological Society's Goudie Lecture:** Prof NR Lemoine, London

Goldsmiths' Hall, Foster Lane, London EC2
19.30 **Society Dinner**

Friday 9 January 2009

The Foyer
08.00 **Registration and Coffee** *(coffee is served in the Restaurant)*

B.5 – Auditorium
09.00–10.00 **Slide Seminar Review:** ***Tricky autopsy histopathology***

B.5 – Auditorium
10.00–12.30 **Symposium:** ***Advances in haematopathology***

Restaurant 1st Floor
11.00–11.30 **Coffee and Poster Viewing**

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12.30–13.30 **Lunch and Trade Exhibition**

Restaurant 1st Floor
13.30–14.30 **Poster Viewing and Chairman's Rounds**

B.5 – Auditorium
14.30–17.30 **Symposium:** ***Infectious disease diagnostics and pathogenesis***

Restaurant 1st Floor
15.30–16.00 **Tea, Poster Viewing and Trade Exhibition**

SCIENTIFIC SESSIONS INFORMATION

PLENARY ORAL SESSION *[B.5 AUDITORIUM]*

The eight highest-ranked submitted oral abstracts will be presented on Thursday 8 January, 14.00–16.30.

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

POSTERS, VIEWING AND CHAIRMAN'S ROUNDS *[RESTAURANT 1ST FLOOR]*

Viewing:	Thursday 8 January, 10.45–11.15 and 15.15–15.45 Friday 9 January, 11.00–11.30
Chairman's Formal Poster Rounds:	Thursday 8 January, 16.30–17.30 Friday 9 January, 13.30–14.30

Prizes: Poster round chairs will be circulating on Thursday 8 January to select the winners of the Pathological Society Sir Alastair Currie Prize and 2nd and 3rd poster prizes. *Due to shortening of the meeting programme posters not displayed on 8 January will not be considered for the prizes.* Winners will be announced at the Society Dinner on Thursday 8 January.

Note to presenters: Ideally, posters should be in place by 10.45 hrs on Thursday 8 January and removed by 16.00 hrs on Friday 9 January.

Presentation: The presenting author (or another author) must attend the meeting and present the poster during the allocated poster rounds in order for the abstract to be published in the *Journal of Pathology* on-line supplement after the meeting.

SLIDE SEMINAR COMPETITION *Tricky autopsy histopathology*

Slide Case Viewing Times: (via PCs) *[2.49 – PAWS 2ND FLOOR]*

Thursday 8 January, 09.00–15.00

Review Session: *[B.5 AUDITORIUM]*

Friday 9 January, 09.00–10.00

Prize: The winner will be announced at the Society Dinner on Thursday 8 January, the prize being a case of champagne *(at the discretion of the winner, by tradition, this is shared amongst those present!)*.

CONTINUING PROFESSIONAL DEVELOPMENT (CPD)

This meeting has been approved by the **Royal College of Pathologists** for the purpose of Continuing Professional Development.

Credits can be accrued as follows:

Thursday 8 January	Full day 8 credits, Half day 4 credits
Friday 9 January	Full day 7 credits, Half day 3 credits

GENERAL ARRANGEMENTS / ADDITIONAL INFORMATION

SOCIETY DINNER *[Goldsmiths' Hall, Foster Lane, London EC2]*

Thursday 8 January
Tickets are £50 – please book your ticket(s) when registering on-line.
For information on Goldsmiths' Hall visit: http://www.the goldsmiths.co.uk/hall/

TRADE EXHIBITION *[Restaurant 1st Floor]*

Delegates are encouraged to visit the **Trade Exhibition** and are requested to support the companies represented there.

PRESENTATION CHECKING AND PREVIEW *[2.49 – PAWS 2nd Floor]*

INTERNET ACCESS *[2.49 – PAWS 2nd Floor]*

Delegates will be issued with usernames and passwords at the registration desk.

MESSAGES

During the meeting, messages for delegates may be left on the following numbers:
Mobile: 07818 640887

REFRESHMENTS *[Restaurant 1st Floor]*

All refreshments will be served in the Restaurant on the first floor.

BADGES

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

COATS AND BAGS *[Cloakroom]*

Secure facilities will be provided for coats/luggage.

TRAVEL, ACCOMMODATION AND VENUE INFORMATION

Please visit the meeting website for information: http://asp.artegis.com/pathsocjan09

ENQUIRIES

Before the meeting please contact the Pathological Society via:

Tel: +44 (0)20 7976 1260
Fax: +44 (0)20 7930 2981
Email: admin@pathsoc.org

DISCLAIMER

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

FUTURE MEETINGS

2009

26–30 January	Winter School, Kensington Close Hotel, London
June	Pathological Society's 3rd Summer School, Cardiff *(to be confirmed)*
30 June–3 July	Cardiff Pathology 2009 (5th Joint Meeting of the British Division of the IAP and the Pathological Society)

2010

7–8 January	Winter Meeting including Trainees' Programme, Imperial College, London, Kensington Campus
29 June–2 July	Summer Meeting, St Andrews

2011

January	Winter Meeting including Trainees' Programme *(dates and venue to be confirmed)*
10–13 May	Ghent Pathology 2011 (6th Joint Meeting of the British Division of the IAP and the Pathological Society)

REGISTRATION

Registration is via our on-line facility found on our website:
http://asp.artegis.com/pathsocjan09
An email acknowledgement will be sent automatically.

REGISTRATION FEES

Delegate Type	Fee Categories	DAY OR PART DAY *EARLY BIRD Up to and including 24 November 2008*	DAY OR PART DAY *After 24 November 2008*
Pathological Society and BSCC Members* * BSCC medical members and advanced BMS Practitioners / BMS Consultants	Ordinary Members, Consultant and/or equivalent position	£ 80	£ 120
Pathological Society Concessionary Members	Biomedical Scientists; Honorary or Senior Members; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 25	£ 40
Undergraduate Students ❇		£ 25	£ 40
Non-Members	Consultant and/or equivalent position	£ 120	£ 180
Non-Members Concessionary ❇	Biomedical Scientists; PhD Students; Post-Doctoral Fellows, Technicians and Trainees	£ 40	£ 60
Fees include refreshments and lunch			
All delegates and fee categories		Society Dinner £ 50	

❇ CONCESSIONS

Delegates from categories:

UNDERGRADUATE STUDENTS
NON-MEMBERS CONCESSIONARY

must provide an identification document as proof of their student or trainee status, including NTN's where applicable. Proof must be by way of a statement from the Head of Department.
Please email to: **julie@pathsoc.org**

ADVANCE REGISTRATION

Advance registration will close on **Monday 15 December 2008.** Thereafter delegates may only register on-site on arrival at the meeting.

CANCELLATIONS

Please note that we are unable to refund registration fees for cancellations received after **Friday 12 December 2008**.

DELEGATE ENROLMENT (AT THE MEETING)

Enrolment at the Delegate Reception Desk will take place from 08.00 hrs.

08.00 **The Foyer**
REGISTRATION and COFFEE *(Coffee is served in the Restaurant on the first floor)*

09.00–15.00 **2.49 PAWS – 2nd Floor**
SLIDE SEMINAR VIEWING: *Tricky autopsy histopathology*
Cases submitted by Dr P O'Donnell, Department of Histopathology, St Thomas' Hospital, London

09.15–12.15 **B.5 – Auditorium**
CYTOPATHOLOGY: JOINT SYMPOSIUM WITH THE BRITISH SOCIETY FOR CLINICAL CYTOLOGY
Chair: Dr A Chandra, St Thomas' Hospital, London
Dr G Kocjan, University College Hospital, London

PART 1: ***Cytopathology diagnosis enhanced by immediate assessment***

09.15–09.45 **[S1]** *Breast pathology in a one-stop clinic*
Dr T Giles, Royal Liverpool University Hospital

09.45–10.15 **[S2]** *The cytopathologist's role in US-guided transbronchial FNA*
Dr E McLean, Guy's and St Thomas' NHS Trust, London

10.15–10.45 **[S3]** *Paediatric cytopathology – a clinical approach to diagnosis*
Dr Z Pohar Marinsek, Institute of Oncology, Ljubljana, Slovenia

10.45–11.15 **Restaurant 1st Floor**
COFFEE, POSTER VIEWING and TRADE EXHIBITION

B.5 – Auditorium
PART 2: ***Cervical cancer prevention, past and future***

11.15–11.45 **[S4]** *Cervical cancer; a topographic survey of 35 years*
Dr A Herbert, Guy's and St Thomas' NHS Foundation Trust, London

11.45–12.15 **[S5]** *Costs and benefits of cervical screening and HPV vaccination*
Prof J Peto, London School of Hygiene and Tropical Medicine

12.15–13.15 **B.5 – Auditorium**
TRAINEES' PROGRAMME – MEET THE EXPERTS
Chair: Dr I Proctor, University College London

12.15–12.45 **[S6]** *Interstitial lung disease*
Prof AG Nicholson, Royal Brompton Hospital, London

12.45–13.15 **[S7]** *Placental examination for non-paediatric pathologists*
Dr I Moore, St Thomas' Hospital, London

13.00–14.00 **Restaurant 1st Floor**
LUNCH and TRADE EXHIBITION

14.00–16.30 **B.5 – Auditorium**

PLENARY ORAL PRESENTATIONS

Chair: Prof IO Ellis, University of Nottingham
Prof SB Lucas, King's College London, School of Medicine

14.00–14.15 **[PL1]** *Ki-67 labelling index of invasive breast carcinoma: what is the optimal cut-point?*
{P} MA Aleskandarany, AR Green, EA Rakha, SE Elsheikh, RA Mohammed, IO Ellis

14.15–14.30 **[PL2]** *Non-atherosclerotic coronary artery pathology responsible for sudden cardiac death*
{P} S Hill, MN Sheppard

14.30–14.45 **[PL3]** *Effect of diet and microsatellite instability on APC mutation spectra in colorectal cancer*
{P} LJ Gay, MJ Arends, PN Mitrou, R Ball, SA Bingham

14.45–15.00 **[PL4]** *Multiplex quantum dot ISH in tissue microarrays identifies HOXA9 and DNMT3A as unfavourable markers in acute myeloid leukaemia*
{P} E Tholouli, S McDermott, JA Hoyland, C Glennie, R Swindell, JA Liu Yin, RJ Byers

15.00–15.15 **[PL5]** *A20 inactivation by deletion and promoter hypermethylation in MALT lymphoma*
{P} E Chanudet, K Ichimura, RA Hamoudi, J Ferry, J Radford, AG Nicholson, AC Wotherspoon, PG Isaacson, MQ Du

15.15–15.45 **Restaurant 1st Floor**

TEA and POSTER VIEWING

15.45–16.00 **[PL6]** *Identification of pro-angiogenic markers in blood vessels from stroked brain tissue using laser-capture microdissection*
{P} M Slevin, J Krupinski, N Rovira, M Turu, A Luque, M Baldellou, L Badimon

16.00–16.15 **[PL7]** *Novel mutations in GALNT3 provide further evidence that Hyperostosis Hyperphosphataemia Syndrome and Tumoural Calcinosis are allelic disorders*
{P} D Delaney, T Diss, S Hing, P O'Donnell, L Joseph, F Berisha, AM Flanagan

16.15–16.30 **[PL8]** *High performance framework for the rapid analysis of tissue microarrays*
{P} D McCleary, J Diamond, D Crookes, H Grabsch, PW Hamilton

16.30 **B.5 – Auditorium**

PRESENTATION

Pathological Society's Undergraduate Essay Competition Prize
to Mr A Bamber, Cambridge

16.30–17.30 **Restaurant 1st Floor**

POSTER VIEWING and CHAIRMAN'S ROUNDS

CATEGORIES	POSTER NUMBERS	
Autopsy/Forensic	[P1–P8] [1]	
Breast	[P9–P17] [2]	
Cardiovascular/Pulmonary	[P18–P20] [1]	
Cellular/Molecular	[P21–P26] [3]	*(Note: P25 withdrawn)*
Education & Audit	[P27–P34] [4]	*(Note: P35 withdrawn)*
Neonatal/Paediatric	[P36] [1]	
Skin	[P37–P39] [2]	
Technical Advances	[P40–P43] [3]	

Chair: [1] Dr M Osborn, London and Dr P Ramani, Bristol
[2] Dr N Kirkham, Newcastle, Prof S Pinder, London and Prof RA Walker, Leicester
[3] Dr RJ Byers, Manchester and Dr J van der Walt, London
[4] Dr PJ Gallagher, Southampton and Dr C Horsfield, London

17.30–18.30 **B.5 – Auditorium**

THE PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S 5TH GOUDIE LECTURE

Chair: Prof CS Herrington, General Secretary, Pathological Society

[S8] *Molecular pathology: putting pathologists at the cutting edge of personalised medicine*
Prof N Lemoine, Barts and The London School of Medicine

19.30–23.00 **Goldsmiths' Hall, London**

SOCIETY DINNER

Detailed Programme – Friday 9 January 2009

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

08.00 **The Foyer**
REGISTRATION and COFFEE *(Coffee is served in the Restaurant on the first floor)*

09.00–10.00 **B.5 – Auditorium**
SLIDE SEMINAR REVIEW: *Tricky autopsy histopathology*
Chair and Presenters:
Prof SB Lucas, King's College London, School of Medicine
Dr PJ O'Donnell, St Thomas' Hospital, London

10.00–12.30 **B.5 – Auditorium**
SYMPOSIUM: *Advances in haematopathology*
Chair: Dr J van der Walt, St Thomas' Hospital, London
Dr B Wilkins, St Thomas' Hospital, London

10.00–10.30 **[S9]** *Pathology of Castleman's Disease and POEMS syndrome*
Prof A Dogan, Mayo Clinic, Rochester, Minnesota, USA

10.30–11.00 **[S10]** *Molecular techniques in bone marrow trephine biopsy diagnosis*
Prof F Fend, University of Tübingen, Germany

11.00–11.30 **Restaurant 1st Floor**
COFFEE and POSTER VIEWING

11.30–12.00 *AML with mutated nucleophosmin (NPM1): a new corner in the WHO classification*
Prof B Falini, University of Perugia, Italy

12.00–12.30 **[S11]** *The molecular pathogenesis of chronic myeloproliferative disorders*
Prof A Green, University of Cambridge

12.30–13.30 **Restaurant 1st Floor**
LUNCH and TRADE EXHIBITION

13.30–14.30 **Restaurant 1st Floor**
POSTER VIEWING and CHAIRMAN'S ROUNDS

CATEGORIES	POSTER NUMBERS	
Gastrointestinal	[P44–P59] [1]	*(Note: P50 withdrawn)*
Genitourinary/Renal	[P60–P63] [2]	
Gynaecological	[P64–P69] [2]	
Hepatobiliary/Pancreas	[P70–P71] [1]	
Lymphoreticular	[P72–P82] [3]	
Neuropathology/Ophthalmic	[P83] [4]	
Osteoarticular/Soft Tissue	[P84–P87] [4]	

Chair: [1] Dr R Goldin, London and Dr U Mahadeva, London
[2] Prof CS Herrington, St Andrews and Dr P O'Donnell, London
[3] Prof KC Gatter, Oxford and Dr BS Wilkins, London
[4] Prof AJ Freemont, Manchester and Prof JE Martin, London

14.30–17.30 **B.5 – Auditorium**

SYMPOSIUM: *Infectious disease diagnostics and pathogenesis*

Chair: Prof SB Lucas, King's College, London, School of Medicine
Dr U Mahadeva, St Thomas' Hospital, London

14.30–15.00 **[S12]** *Infectious disease pathology: Diagnosing emerging and exotic infections as well as potential bioterrorist events*
Prof S Zaki, Centres for Disease Control and Prevention, Atlanta, USA

15.00–15.30 **[S13]** *HIV, the brain and the final common pathway to dementia*
Prof J Bell, Neuropathology, University of Edinburgh

15.30–16.00 **Restaurant 1st Floor**
TEA

16.00–16.30 **[S14]** *Immune reconstitution disease associated with tuberculosis*
Dr S Lawn, University of Cape Town, South Africa

16.30–17.00 *EBV, Hodgkin's disease and other lymphomas*
Prof H Stein, Charité University, Berlin, Germany

17.00–17.30 **[S15]** *HIV-related pathology: what you are missing*
Prof SB Lucas, King's College, London, School of Medicine

17.30 **THANKS AND FAREWELL**
Prof SB Lucas

ACKNOWLEDGMENTS

as at the time of going to press

The Pathological Society of Great Britain & Ireland
wishes to acknowledge the support of the following companies participating in the
TRADE EXHIBITION

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Abstracts

Plenary

Note: Presenter's name is shown in **bold**

PL1

Ki-67 Labelling Index of Invasive Breast Carcinoma: What is The Optimal Cut-Point?

MA Aleskandarany[1], AR Green[1], EA Rakha[2], SE Elsheikh[1], RA Mohammed[1], IO Ellis[1]
[1]Pathology Department, Molecular Medical Sciences, Nottingham University, [2]Breast Team, Nottingham City Hospital, Nottingham University

Growth fraction of breast cancer can be objectively and reliably assessed using Ki-67 labelling index (LI) by means of immunohistochemistry. Despite the presence of previous studies that used both tissue microarray (TMA) and whole tissue sections to assess Ki-67 LI, there is no consensus agreement regarding the best cut-points correlated with patients' outcome.

Tumour growth fraction of invasive node negative breast carcinomas (n=782) was immunohistochemically assayed using whole tissue sections using the MIB1 clone. Additionally, 200 corresponding cases prepared as TMAs were also studied.

Growth fraction ranged from 0-99% with 10 and 70% chosen as cut-points by examination of the distribution histogram. Highly significant correlation was found between growth fraction and standard prognostic parameters. Moreover, Outcome analysis revealed a relationship between higher growth fraction and shorter disease free interval (DFI, p=0.03) and breast cancer specific survival (BCSS, p< 0.001), independently of other prognostic factors (p=0.01). Using a cross-validation approach (X-Tile bio-informatics software, Yale University, USA), closely comparable cut-points were obtained (9% and 69% for BCSS, and 5% and 70% for DFI respectively). Passing-Bablok fit revealed poor concordance between Ki-67 LI between whole tissue sections and TMAs (p< 0.01).

Categorising breast cancer into three subpopulations, rather than two, based on their LI is more robust in clarifying the relationship between tumour biology and patients' outcome. Moreover, the Ki-67 LI could not reliably be assayed on TMAs primarily due to its heterogeneous distribution.

PL2

Non-Atherosclerotic Coronary Artery Pathology Responsible for Sudden Cardiac Death

S Hill[1], MN Sheppard[1]
[1]CRY Centre of Cardiac Pathology,Imperial College London

Background: Most sudden cardiac deaths (SCD) are due to ischemic heart disease. The concept of non-atherosclerotic coronary artery pathology in sudden death has not been given the attention it deserves. We sought to determine the incidence of this entity and raise awareness amongst cardiologists and pathologists alike. As a referral centre for SCD in the United Kingdom, we have established a database of 1,800 SCD hearts.
Design: Retrospective study of hearts with non-atherosclerotic coronary artery causes of sudden death with detailed histological analysis.
Results: Fifty (2.7%) of the 1,800 cases of SCD were caused by non-atherosclerotic coronary pathology (31 men (62%) and 19 women (38%, age range [8 weeks-71 years]). Twenty four of the 50 cases had anomalous coronary arteries (48%); eight cases had coronary artery dissection (16%); six cases had coronary artery vasculitis (12%); six cases had coronary artery spasm (12%); three cases had idiopathic arterial calcification of infancy (6%); two cases had fibromuscular dysplasia (4%) and one case had a benign tumour occluding the left coronary ostium (2%). Twenty of the 50 patients (40%) were documented to have experienced symptoms such as syncope, chest pain on exertion or breathlessness prior to their SCD. 12 of the patients (24%) died during or immediately after physical exertion.
Conclusions: Non-atherosclerotic coronary pathology can cause sudden death in all age groups particularly younger, male patients. Pathologists need to be aware of these rare causes of sudden death

PL3

Effect of diet and microsatellite instability on APC mutation spectra in colorectal cancer

LJ Gay[1], MJ Arends[2], PN Mitrou[3,5], R Ball[4], SA Bingham[1]
[1]MRC Dunn Human Nutrition Unit, Cambridge, [2]University of Cambridge Pathology Dept., Histopathology, Addenbrooke's Hospital, Cambridge [3]World Cancer Research Fund International, London, [4]Norfolk & Norwich University Hospital Pathology Dept., Norwich, [5]Dept. of Public Health & Primary Care, Strangeways Research Laboratory, Cambridge

Analysis of the mutation cluster region of APC (codons 1276-1556) and MSI were performed on 185 cancers from participants of the European Prospective Investigation into Cancer and Nutrition (EPIC) Norfolk Study, with the aim of relating molecular changes to dietary information collected at the start. For APC analysis, genomic DNA was extracted from formalin-fixed tissue, amplified and sequenced. Overall, 43% cancers had APC mutations with hotspots at codons 1276, 1306, 1415, 1450 and 1556. Comparison of APC mutations by clinico-pathological features (sex, age, BMI, tumour site and Dukes' stage) revealed that proximal colon tumours had more transition point mutations, whereas distal colon tumours had more transversions (P = 0.04). Negative MLH1 protein expression, high MLH1 promoter methylation (>50%) and MSI-High tumours were more likely to be from female cases, proximal in location and early Dukes' stage (P = 0.03, 0.02 and 0.001 respectively). Case analysis of APC and MSI patterns by red and processed meat consumption revealed that cases with processed meat intake above the mean (>25.91g/day) were more likely to have GC to AT transitions (P = 0.05). In conclusion, MSI-High tumours were distinct and only 25% harboured an APC mutation, compared to 47% MSS tumours (P = 0.03), highlighting the different MSI pathway. APC mutation spectra differed by tumour site and were associated with processed meat consumption suggesting a mechanistic link between dietary alkylating agents, such as N-Nitroso compounds, and GC to AT transitions.

PL4

Multiplex Quantum Dot ISH in Tissue Microarrays Identifies HOXA9 and DNMT3A as Unfavourable Markers in Acute Myeloid Leukaemia

E Tholouli[1], S McDermott[2], JA Hoyland[3], C Glennie[4], R Swindell[5], JA Liu Yin[1], RJ Byers[6]
[1]Dept of Haematology, Manchester Royal Infirmary, [2]The Medical School, University of Leeds, [3]Clinical and Laboratory Sciences, University of Manchester, [4]Dept of Histopathology, Manchester Royal Infirmary [5]Dept of Medical Statistics, Christie Hospital, [6]Cancer and Imaging Sciences, University of Manchester

Validation of expression microarray identified prognostic genes is required in clinical samples. We have used a quantum dot (QD) based multiplexed in-situ hybridization (ISH) method in formalin fixed paraffin embedded tissue (FFPET) to identify prognostic genes in AML.

Fifteen tissue microarrays (TMAs) were made using FFPET bone marrow trephines from 240 patients with AML treated at Manchester Royal Infirmary, of which 192 patients were suitable for analysis. Samples were represented in triplicate and a whole blood white cell pellet used as standard. QD-ISH was performed for nine candidate prognostic genes using triplex QD-ISH for: Bcl2, surviving, XIAP; DNMT1, DNMT3A, DNMT3B; HOXA4, HOXA9, Meis1. Signal intensity was measured by spectral imaging and scrambled oligonucleotides used to correct for background staining followed by normalization of expression against the standard. Kaplan-Meier analysis was performed against overall survival (OS) and disease free survival (DFS).

Median age was 52 years and the OS was 43% at 5 years with 80% complete remission (CR). Low expression of HOXA4 was associated with improved OS (p=0.013) and DFS (p=0.025). High expression of HOXA9 (p<0.0001) and DNMT3A (p=0.04) were associated with failure to achieve CR. High expression of Meis1 was of borderline significance for poor response to chemotherapy (p=0.05).

These results demonstrate the utility of the method for identification of prognostic markers in FFPET. The advantages of the method are its application to TMAs, use of archived materials and transferability across a spectrum of malignancies.

PL5

A20 Inactivation by Deletion and Promoter Hypermethylation in MALT Lymphoma

E Chanudet[1], K Ichimura[1], RA Hamoudi[1], J Ferry[2], J Radford[3], AG Nicholson[4], AC Wotherspoon[5], PG Isaacson[6], MQ Du[1]
[1]Department of Pathology, University of Cambridge, UK, [2]Department of Pathology, Massachusetts General Hospital, Boston, MA, [3]Department of Medical Oncology, Christie Hospital, Manchester, UK, [4]Department of Histopathology, Royal Brompton Hospital, London, UK, [5]Department of Histopathology, Royal Marsden Hospital, London, UK, [6]Department of Histopathology, University College London, UK

Background: The acquisition of genetic abnormalities is critical for the development of MALT lymphoma. We recently investigated the genomic profiles of ocular adnexal and pulmonary MALT lymphomas by array-comparative genomic hybridization (CGH) and showed recurrent chromosome 6 copy number changes only in ocular cases.

Purpose: Our study was designed to further characterise chromosome 6 abnormalities in MALT lymphoma.

Results: Chromosome 6 tile-path array-CGH identified the NF-kB inhibitor A20 as the target of 6q23.3 deletion, and the TNFA/B/C locus as a putative target of 6p21 gain. Interphase fluorescence in situ hybridization showed that A20 deletion occurred in MALT lymphoma of the ocular adnexa (8/42), salivary gland (2/24), thyroid (1/9), but not in the lung (26) and stomach (45). Homozygous deletion was observed in 3 cases. A20 deletion and TNFA/B/C gain were significantly associated (P<.001) and exclusively found in cases without characteristic translocation. Mutational analysis of A20 coding sequence did not show somatic mutations. Nonetheless, preliminary pyrosequencing results suggested potential A20 inactivation by promoter hypermethylation in a proportion of cases. In ocular cases, A20 inactivation was associated with concurrent involvement of the orbital soft tissue and the conjunctiva and/or lachrymal glands, or extra-ocular sites at diagnosis, and with adverse clinical parameters, including a shorter relapse-free survival.

Conclusion: The inactivation of A20 may play an important role in the development of translocation negative MALT lymphomas, especially those arising from sites associated with auto-immunity.

PL6

Identification of pro-angiogenic markers in blood vessels from stroked brain tissue using laser-capture microdissection

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Angiogenesis correlates with patient survival following acute ischaemic stroke, and survival of neurones is greatest in tissue undergoing angiogenesis. Angiogenesis is critical for the development of new microvessels leading to re-formation of collateral circulation, reperfusion, enhanced neuronal survival and improved recovery. Here, we have isolated active (CD105/Flt-1 positive; n=5) and inactive (CD105/Flt-1 minus; n=5) micro-vessel rich-regions from stroke-affected and contralateral tissue of patients using laser-capture micro-dissection and compared pro- and anti-angiogenic gene expression using targeted TaqMan microfluidity cards and real-time PCR. Further analysis of key gene de-regulation was carried out by immunohistochemistry to define localization and expression patterns of identified markers. PCR results showed that 7 pro-angiogenic genes (Tie-2, β-catenin, neural cell adhesion molecule (NRCAM), matrix metalloproteinase 2 (MMP-2), tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), hepatocyte growth factor alpha (HGF-α), monocyte chemottractant protein (MCP-1) and C-Kit, a marker of endothelial progenitor cells) were notably up-regulated in CD105 positive microvessel rich regions. Immunohistochemical examination demonstrated strong staining of MMP-2, HGF-α, MCP-1 and Tie-2 in stroke-associated regions of active remodeling in association with CD105 positive staining. This data has identified concurrent activation of key angiogenic molecules associated with endothelial cell migration, differentiation and tube-formation, vessel stabilization and stem cell homing in areas of revascularization. Therapeutic stimulation of these processes in areas of damaged tissue might improve morbidity and mortality from stroke.

PL7

Novel Mutations in GALNT3 Provide Further Evidence that Hyperostosis Hyperphosphataemia Syndrome and Tumoural Calcinosis are Allelic Disorders

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Hyperostosis Hyperphosphataemia Syndrome (HHS) and Tumoural Calcinosis (TC) are rare autosomal recessive metabolic disorders characterised by hyperphosphataemia but otherwise different phenotypes. There is recent evidence that they may represent allelic disorders secondary to germline mutations involving GALNT3 or FGF23: both genes are involved in the regulation of phosphate metabolism. While the diagnosis of TC is readily apparent, HHS mimics a myriad of skeletal conditions including osteomyelitis, osteosclerosis and osteoid osteoma and an inherited disorder is often not considered. We present a family in which one female sibling presented with recurrent multifocal medullary sclerosis. Subsequent clinical history revealed that her older brother had been diagnosed with TC, and serum phosphate was found to be elevated in both.

Materials and Results: Sequence analysis of DNA from the siblings and their parents revealed compound heterozygous mutations involving exon 4 c.842G>A and exon 5 c.1097T>G. 100 control alleles were screened, using PCR and mutation specific restriction enzyme digestion and failed to detect these sequence variations.

Conclusion: This is only the second report of HHS and TC occurring in the same family and therefore provides further evidence that these two phenotypes are allelic disorders. The varied phenotypic expression may be related to compensatory or modifying factors involved in GALNT3 activity. HHS, although rare, is important in the differential diagnosis of multifocal recurrent bone disease and analysis of bone biochemistry, including phosphate, is an important component of the routine work up of bone lesions.

PL8

High Performance Framework for the rapid analysis of Tissue Microarrays

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Tissue Microarrays (TMAs) represent a high throughput technology for biomarker discovery and are being used extensively by research laboratories worldwide. However the need for visual interpretation and manual scoring represents a significant bottleneck and so there is an urgent need for an automated solution. Using specialised scanning hardware, tissue samples can be digitised to produce diagnostic quality digital images (virtual slides) providing enormous opportunities for fully automated TMA analysis. This study investigated the development of a High Performance Cluster (HPC) for parallel processing of TMA cores to allow the high throughput analysis of TMAs. A number of clusters were investigated including several Hewlett Packard benchmarking clusters based in the USA.

The framework was built on a 256 processor cluster, programmed using HP Message Passing Interface (MPI) and based on the manager/worker model where a manager processor is responsible for dividing the workload amongst worker processors. Each worker extracts a core from the virtual slide, analyses the core and stores the result in a TMA Data Exchange Specification compliant database. This cycle is performed until all cores have been processed, significantly speeding up analysis.

A number of image processing libraries have been developed to run inside the framework and preliminary tests show a significant speedup (159x) when using a HPC, making the high throughput automated analysis of TMAs possible for the first time. This combination of TMAs, virtual microscopy, high performance computing and machine vision represents a powerful combination which will underpin high throughput biomarker discovery in tissue-based research.

Abstracts

Posters

Note: Presenter's name is shown in **bold**

P1

Alcohol and Arrhythmic Cardiac Death: A Prospective and Retrospective Study of Post Mortem Cases

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Background: Increasing alcohol consumption within the United Kingdom has lead to an increase in alcohol related deaths. Despite the fact that excess alcohol is a known cause of cardiac arrhythmia, which can in turn lead to death, we have observed from experience that this is not a commonly stated cause of death at post mortem.

Aims: To assess the prevalence of deaths from a presumed cardiac arrhythmia associated with excess alcohol consumption arising in post mortem cases.

Method: Adult post mortems taking place between October 2007 and March 2008 were observed and post mortems having taken place during January 2006 - February 2007 were assessed retrospectively. Routinely recorded data including past medical history and pathological findings in the heart, lungs and liver were documented. All cardiac deaths with evidence of excess alcohol consumption were reviewed.

Results: 1292 post mortems were included. 4 cases were documented to have died from the "classical" scenario of a presumed cardiac arrhythmia associated with evidence of alcohol excess and were certified as such. A further 13 cases were identified in which alcohol associated arrhythmia could have contributed to or caused death. These 17 cases accounted for 1.3% of all deaths surveyed.

Conclusions: Death from a presumed cardiac arrhythmia associated with excess alcohol consumption appears to be an understated cause of death in post mortem cases. This scenario would benefit from becoming a better defined entity with improved recognition by pathologists and the introduction of a term such as SUDAB (Sudden Unexplained Death in Alcohol Abuse).

P2

Alcohol and its Association with Accidental Deaths in the West of Ireland

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We investigate the relationship between alcohol and accidental deaths in the West of Ireland between 2005 and 2007.

692 post mortems were reviewed. Gender, age, cause of death, blood +/- urine levels were recorded.

There were 239 accidental deaths, 75% (n = 180) in men. Alcohol was measured in blood +/- urine in 196 accidental deaths. Alcohol was detected (>10mg%) in 98 cases, more commonly in men (79/98) than women (19/9). The mean level was similar in men (188mg%, range 14-536mg%) and women (189mg%, range 12-240mg%).

Alcohol levels >151mg% were most commonly observed in 18-49 year-olds (44/61, 72%). Road traffic accidents (RTAs) (23/98), suicides (19/98) and drownings (25/98) were the most common accidental deaths associated with alcohol. Alcohol levels >151g% were documented most often in drownings (16/25) and RTAs (13/23). The maority of RTA deaths involved the driver (16/23). The level was >80mg% in 81% (13/16) and >151mg% in 69% (11/16) of these. Three driver deaths (19%) were associated with a level <80mg% Mortality of passengers (3/23) and pedstrians (4/23) was less common.

Alcohol remains a major contriutor to accidental deaths, especially in young men, in the West of Ireland. 19% of driver deaths occur below the legal driving limit. Measurement of alcohol levels in all accidental deaths would facilitate more acurate determination of its role. The burden of alcohol-associated accidental deaths remains a significant challenge.

P3

Examination of the Brain at Postmortem – Comparing Local to National Practice

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AIMS To discover what proportion of post mortem examinations include the brain and in the instances when it is not examined, explain why.

METHODS An initial audit of three local consultants looked retrospectively at one years post mortem reports, to determine in how many the brain was examined, and what the typical reasons for not doing so might be. Following this an anonymous email questionnaire was sent to 118 consultants registered as working in England and Wales and 45 Coroners and Coroners' Officers across England.

RESULTS The three local consultants performed a total of 143 post mortems. One consultant examined all brains whilst the other two only examined a proportion (46% and 81%). In the patients where the brain was not examined, the reason was that a cause of death had been found elsewhere, though this was not always due to a massive event causing instantaneous death (MECID).

Of the national survey, 29 pathologists performed post mortems currently, of which 24 reported always examining all brains. The remaining 5 reported examining 50 – 95 % of brains. 18 of the 45 Coroners' departments completed the questionnaire. Twelve (67%) expected the brain to be examined in every case, five (28%) felt it was up to the pathologist to decide, and one answered 'N/A'.

CONCLUSION There exists considerable variation in the interpretation of whether all brains should be examined by both pathologists and coroners.

P4

An Autopsy Case Report of Haemopericardium from a Ruptured Aneurysm of the Left Coronary Sinus of Valsalva

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Sinus of Valsalva aneurysms are uncommon clinical entities which may be predisposed towards by either congenital or acquired factors. Only 1% of such aneurysms arise from the left coronary sinus of Valsalva (LCSV), with the remainder arising from the right or non-coronary sinuses. Here we report an autopsy case of a 59-year-old Caucasian female with a known LCSV aneurysm diagnosed as an incidental finding following investigation of respiratory symptoms. On her last admission she underwent elective excision of a suspicious right adnexal mass which was also thought to be contributing towards a recently diagnosed DVT. On the second post-operative day she developed tachycardia and tachypnoea which did not respond to medical management. She continued to deteriorate and went into cardiac arrest from which she could not be resuscitated. On post-mortem examination it was found that the LCSV aneurysm had ruptured directly into the left atrium with its subsequent rupture, resulting in a haemopericardium and cardiac tamponade.

P5

Current Causes of Maternal Death in London; Comparison with UK Data

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Maternal deaths in the UK are uncommon (14/100,000 maternities in 2003-5). All such deaths are reported to the Confidential Enquiry into Maternal and Child Health (CEMACH), which reports triennially. Since 2002, most maternal death autopsies in London have been performed at one London centre, using RCPath Guidelines full protocol.
We compare these data (n=60) with the recent CEMACH data (2003-5, n = 377) for causes of death.
Results: London demographics: median age 30 yrs (range 17-42), 43% black, 28% obese (BMI=>30). Half had Caesarian section, with 25% undergoing a peri-mortem section.
The leading causes of maternal direct and indirect (non-psychiatric) death (n, %). In London: genital tract sepsis (12, 20%), cardiac (10, 17%), post-partum haemorrhage (PPH, 6, 10%), eclampsia (6, 10%), venous thrombosis and pulmonary embolism (VTE & PE, 5, 8%), amniotic fluid embolism (AFE, 3, 5%), dissection of aorta (3, 5%), thrombotic thrombocytopaenic purpura (TTP, 3, 5%), illicit drug toxicity (2, 3%).
UK/CEMACH data: cardiac (48, 13%), VTE & PE (41, 11%), cerebral haemorrhage (22, 6%), eclampsia (18, 5%), sepsis (18, 5%), AFE (17, 5%), PPH (14, 4%), epilepsy (11, 3%), ectopic pregnancy (10, 3%).
Comment: the different rankings of causes of death reflect sample size and a different population of London vs rest of UK (eg higher non-white %). Sepsis and TTP seem underestimated nationally. It is important to screen for sepsis by culture and perform full histopathology in maternal deaths.

P6

Should the Spleen be Ignored as a Marker of Infection?

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Introduction: Acute splenitis (also known as the 'septic spleen') has traditionally been depicted as a state in which the spleen is enlarged, soft and congested as a result of systemic infection. The few studies that have tested this concept have found mixed results and some workers feel that acute splenitis may not reflect sepsis.
Aims: The purpose of this study is to examine the association between splenic appearance and gross infection and to determine whether the spleen should be ignored as a marker of infection at autopsy.
Methods: The reports from consecutive autopsies between January and May 2007 were examined. Splenic weight, consistency and the presence or absence of infective foci were noted for each subject.
Results: One hundred and seventy-one autopsy reports were included. The average spleen weight in those with infection was lower than the average weight in the non-infection group (141gms versus 168gms; $p<0.05$).Diffluent (very soft) spleens were significantly more common in subjects with evidence of infection compared to those without (78% versus 14%; $p<0.0001$).
Conclusion: The appearance of the spleen at autopsy yields valuable information and should not be ignored. Macroscopic evidence of infection is associated with prominent softening of the parenchyma. Splenic weight is less useful as a marker, but may be reduced in infection.

P7

Cosmetic Camoflage Techniques and Facial Identification in the Forensic Mortuary

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Recognition of facial features remains central to formal identification procedures in the United Kingdom and viewing of the body is an integral part of the early grieving process. Difficulties arise when there is signficant facial trauma or disfiguring post mortem changes. These include the adverse impact of viewing on the individual, when facial trauma is present, and the misunderstandings that can develop when post mortem features are mistaken for marks of violence.

Cosmetic camoflage is used in specialist clinical settings, such as burns units, and formal training is required to successfully apply the skin toned make-up products. We have introduced this technique into a regional forensic mortuary and present, photographically, examples of effective masking of various facial injuries, such as bruising, abrasions and lacerations, along with post mortem changes including chemical burns, putrefaction and pronounced hypostasis, from a variety of forensic cases. If necessary, these cosmetic products can be easily removed after viewing.

Our experience indicates that cosmetic camoflage offers a significant benefit to relatives, as part of the facial reconstruction process, in appropriate autopsy cases.

P8

Establishing a Cause of Death in Inconclusive but Suspected Cases of Myocardial Infarction by Measuring the Troponin I Level

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An assay for myocardial damage-specific troponin I is one of the few tests carried out to detect very early myocardial infarctions and is used in the clinical setting to help diagnose and monitor myocardial injury. An event leading to ischaemic damage causes an early release of cardiac troponin I, the level remaining elevated for several weeks. However, its use in evaluating myocardial damage in postmortem samples has not yet been clearly established. The aim of this investigation is to establish a suitable reference value of measuring cardiac Troponin I in postmortem blood samples taken from cadavers showing significant signs of cardiovascular disease but no obvious histopathological evidence of acute myocardial infarct. A suitably raised troponin I level would add weight to determining the cause of death as being attributed to acute MI.
The study will evaluate cardiac Troponin I in blood samples obtained from the femoral vein of 400 cadavers, using the combined platform Abbott Architect Ci8200.
55 cases have had postmortem troponin I tested, 28 with acute MI or ischaemic heart disease on death certification. 85.7% of the suspected MI cases had raised troponin I.
The results obtained so far indicate a direct correlation between the anatomic findings of the postmortem examination and the value of troponin I in the blood sample.

P9

Pre-operative ultrasound and FNA stages accurately the axilla in early breast cancer.

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Introduction:Preoperative assessment of axillary nodes is now a routine part of the management of patients with early breast cancer. This usually involves imaging followed by FNA or core biopsy of suspicious nodes.

Materials and Methods: Operative pathology was reviewed from 83 patients identified from hospital records who had suspicious axillary ultrasound and subsequent FNA and its accuracy was assessed. Notation of FNA results was based on breast screening guidelines with the suffix ”n”.
Results: Our results are shown in Table 1:

Correlation between axillary FNA cytology and axillary node histology

Result	No. of cases	Sample/Sentinel Node	Clearance
True positive (C5n)	41	3	38
True negatives (C1n &C2n)	24	20	4
Unconfirmed positives (C5n)	2	0	2
False negatives (C1n&C2n)	13	5	8
Suspicious (C3n&C4n)	3	0	3
Total	83	28	55

Sensitivity is 92% and Specificity is 76 %. The Positive Predictive Value is 0.95 and the negative predictive value is 0.65. Two of the “True” positive cases showed a nodal chemotherapy response without viable tumour. The two unconfirmed positive cases had undergone neoadjuvant chemotherapy but showed no nodal chemotherapy response.

Conclusion: Preoperative FNA of axillary lymph nodes has a high positive predictive value. The lower negative predictive value suggests that for small metastases FNA is less reliable. Our results provoke discussion about the correct notation for the recording of negative and unsatisfactory results for axillary staging FNAs.

P10

Relationship of Src to Cell Adhesion Proteins in Breast Cancer

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The tyrosine kinase Src is important in invasion and metastasis of cancer cells, including breast, and can downregulate E-cadherin – catenin interactions promoting invasion. Data on the relationship of Src to cell adhesion proteins in human breast cancer is limited.

Immunohistochemistry was used to determine the expression of Src, phosphorylated Src (PSrc), E-cadherin, α and β catenin, and p120 in 94 breast cancers and interrelationships determined.Src was detected in 96% of Infiltrating Ductal Carcinomas (IDC), 65% having >50% cells with moderate staining; Infiltrating Lobular Carcinomas (ILC) had weak staining of <50% of cells. There were no correlations with grade, node status, Oestrogen Receptor and cell adhesion proteins. PSrc staining was perinuclear, nuclear and cytoplasmic, and was present in >50% of cells in 80%, 10% and 40% of IDC respectively, but in 15%, 10% and 0 of ILC. Nuclear and cytoplasmic staining related to negative node status (IDC). Presence of nuclear PSrc related to extent of E-cadherin(P=0.012) and p120 (P=0.019) and extent of cytoplasmic staining related to extent of E-cadherin (P=0.049), β catenin (P=0.04) and α catenin (P=0.012).

Expression of Src and PSrc differs between IDC and ILC, paralleling expression of cell adhesion proteins. In IDC Src related to cell adhesion proteins levels when phosphorylated and in a specific cellular location . That with the correlation with node negative status does not support a role for Src in metastasis of breast cancer.

P11

OSNA® Intra-Operative Sentinel Node Analysis is Feasible at a District General Hospital

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Sentinel node (SN) biopsy is the axillary staging procedure of choice in invasive breast carcinoma. Reliable intra-operative analysis of nodes is desirable as it allows immediate progression to axillary dissection in positive cases, sparing the patient a second procedure. Results with imprint cytology and frozen sections are inconsistent.

OSNA® (one step nucleic acid amplification) is a new automated commercial system that rapidly provides quantitative measures of cytokeratin (CK) 19 mRNA. We took part in a multicentre study investigating the accuracy and feasibility of intra-operative use of OSNA to detect metastases in SNs.

Three laboratory staff members were trained over a one month period during the technical phase of the study. During the intra-operative phase 35 patients were enrolled, yielding a total of 69 SNs. Alternate slices of the node were analysed by either OSNA® or processed for histology. Our average times from receiving the node in the laboratory to telephoning a result was 29 minutes for one node, 38 minutes for two nodes, 44 minutes for three nodes, and 47 minutes for four nodes. When compared to histological and immunohistochemical analysis, OSNA was 96.8% specific and 83.3% sensitive with a concordance in excess of 95%.

Our results have indicated that intra-operative analysis of SNs using OSNA is feasible in a District General Hospital setting. Turn-around times were acceptable to the surgeons who proceeded with the breast operation whilst the SN was being analysed.

P12

The Reliability of commonly used EGFR Antibodies in Breast Cancer

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Epidermal Growth Factor Receptor (EGFR) is a member of the family of type I tyrosine kinase growth factor receptors and is implicated in progression of many cancers. Head and neck tumours, colorectal and breast neoplasms have all been associated with aberrant EGFR expression. EGFR forms heterodimers with other members and binds several ligands responsible for downstream activation of cancer cell proliferation. EGFR comprises an extracellular region, a single transmembrane region and a cytoplasmic tyrosine kinase domain. There are several drugs that specifically target the EGFR receptor, either licensed for clinical use or undergoing trials. Some are chimeric monoclonal antibody inhibitors targeting the extracellular domain (cetuximab (Erbitux), panitumumab (Vectibix)), whilst others are small tyrosine kinase inhibitors (lapatinib (Tyverb, Tykerb), gefitinib (Iressa), erlotinib (Tarceva)), actively competing for the ATP-binding site of the intracellular domain. Novel monoclonal drugs in clinical development include zalutumumab, nimotuzumab and matuzumab. Currently, unlike HER2 there is no reliable immunohistochemical quantatative assessment to identify those patients most likely to benefit from these novel drugs. There are several commercially available antibodies that target either the intracellular or extracellular domain of EGFR. We have selected five of these antibodies and undertaken immunohistochemical staining of 94 cases of breast tumours in tissue microarrays. We have thus explored the expression of EGFR in normal and neoplastic tissues and demonstrated variation in expression. We wish to highlight the need for a reliable marker to optimally identify patients for these new drug therapies.

P13

Guy's & St Thomas' Breast Research Tissue and Data Bank

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The Guy's & St Thomas' Breast Research Tissue and Data Bank has accrued both tissue and data for the specific purposes of translational research since 1975. At the outset specimens were received fresh, sliced and fixed to optimise morphology (which has subsequently proved beneficial for DNA, RNA and protein preservation). In parallel, detailed patient history was taken and subsequent disease events and treatments recorded for the lifetime of the patient. Searchable databases hold demographic, pathological, clinical and outcome data from over 10,000 breast cancer patients. The tissue bank holds formalin fixed, paraffin embedded primary breast tumours from almost 6000 patients, with matched frozen tissue from more than 2000 of these. Other resources include a paired tumour and peripheral blood DNA bank from more than 1500 unselected breast cancers and a Tissue Micro Array (TMA) Bank of 1200 sequential tumours for high throughput analyses.
High quality tissue preservation and preparation techniques and data acquisition are paramount for research purposes. The Bank works to standardised methods with emphasis on quality checks and audit.
The Bank is a Human Tissue Authority licensed establishment and an NRES approved Research Tissue Bank. Tissue and data are available to any investigator (local, national or international) with a scientifically valid and funded study, confirmed by the Access Committee.
Services provided by the Bank include immunohistochemistry, antibody optimisation, TMA construction, nucleic acid extraction, laser micro dissection and slide scanning. Tissue and data from the Bank have been used in hundreds of studies described in peer-reviewed journals

P14

Audit of Needle Core Biopsy Diagnosis in a Symptomatic Breast Unit

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BACKGROUND: The use of breast needle core biopsies has increased in recent years as a diagnostic modality for both symptomatic and screen detected breast lesions. Although many publications assess its performance in screening programmes, data from purely symptomatic units are less readily available.

AIMS: We reviewed the reports of all breast core biopsies performed in our recently established breast symptomatic unit over 1 year to determine i) The percentage of cases in each B category (B1-B5; as described in the NHSBSP UK guidelines). ii) To specifically examine the borderline subgroups B3 and B4.

RESULTS: 403 biopsies were retrieved. The most common category was B2 (58%) followed by B5 (30.5%) with the remaining groups as follows: B1 (5.7%); B3 (4.5%); B4 (1.2%). Of the B3 cases, the majority were papillary lesions (44%) and fibroepithelial lesions (28%). Seventy-two percent of B3 cases underwent a subsequent surgical procedure. Of the resampled papillary lesions, 71.4% were benign intraductal papillomas on excision, 1 showed DCIS (14.3%) and 1 showed ADH (14.3%). Seventy-five percent of fibroepithelial lesions in the B3 group were subsequently reported as benign phyllodes tumours and 25% as fibroadenoma. All of the 4 B4 cases had further sampling with a diagnosis of malignancy in 2 cases (50%).

DISCUSSION: This audit provides preliminary data on the performance of needle core biopsy in the setting of a breast symptomatic unit and confirms that this modality can provide a definitive diagnosis in the majority of cases.

P15

Malignant Phyllodes Tumour with Liposarcomatous Differentiation, Invasive Tubular Carcinoma, Ductal and Lobular Carcinoma in Situ

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We report the case of a 43 year-old woman who presented with a lump in her right breast that enlarged over 5 months. She had a diagnosis of Non-Hodgkin's Lymphoma in 1998, which was treated with chemoradiotherapy. A diagnosis of Phyllodes tumour (PT) was made on core biopsy and a wide local excision performed.

Histological examination revealed a malignant PT with stromal overgrowth, nuclear pleomorphism and brisk mitotic activity. Liposarcomatous differentiation and ductal carcinoma in-situ were present within the tumour. Invasive tubular carcinoma and lobular carcinoma in-situ were seen in the surrounding breast.

Liposarcomatous differentiation is uncommon in PTs and co-existing carcinoma is even rarer with <30 reports. Review of the literature reveals that co-existing carcinoma occurs in malignant PTs (n=16), benign PTs (n=7) and in PTs of unspecified malignant potential (n=8). Co-existing invasive carcinoma is more frequent (n=17) than in pure in-situ tumour (n=11). Carcinoma is more common within benign PTs; whereas in malignant PTs, it is more often found surrounding the PT or in the contralateral breast. Previous radiotherapy treatment is reported in two cases.

This case highlights the diverse pathology that can occur with PTs, which should be considered when evaluating biopsies and excision specimens. The aetiology underlying the development of co-existing carcinoma is unclear. However, the rarity of previous radiotherapy suggests it is incidental. While prognosis is determined by the PT, management decisions should take presence of invasive carcinoma into account.

P16

Audit of B3 breast needle core biopsies over a 27 month period and correlation with histology on excision specimens

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An audit of B3/ uncertain malignant potential breast needle core biopsies undertaken over a 27 month period with respect to biopsy histology and correlation with histology following excision.

136/2296 (6%) of total biopsies were B3. 29 (21%) B3 biopsies were AIP, 23 (17%) radial scars (RS), 21 (15%) papillary lesions (PL), 20 (15%) ALH/LCIS, 14 (10%) columnar cell change (CCC) with atypia, 12 (9%) fibroepithelial lesions/phylloides (FEP), 17 (13%) other eg.hamartoma, spindle lesions.

84/136 (62%) cases went on to excision including 16/ 29 (55%) AIP, 14/23 (61%) RS, 10/21 (48%) PL, 13/20 (65%) ALH/LCIS, 12/14 (86%) CCC with atypia, 9/12 (75%) FEP, 10/17 (59%) 'other'.

On excision, 7/16 (43%) AIP showed malignant histology (6 DCIS, 1 invasive), 4/14 (28%) RS (1 DCIS, 3 invasive), 5/13 (38%) ALH/LCIS (2 DCIS, 3 invasive), 6/12 (50%) CCC with atypia (3 DCIS, 3 invasive), 1/9 (11%) FEP and 4/17 (24%) 'other' exhibited malignant histology. One PL showed atypia on excision but not invasive carcinoma.

In total 27/84 (32%) B3 biopsies excised were malignant. AIP, CCC with atypia and ALH/LCIS showed greatest association with malignancy. We conclude that AIP and CCC with atypia, RS, FEP and PL should continue to be excised. All cases, in particular ALH/LCIS, require MDM discussion and accurate correlation with radiology prior to excision. Findings were similar to previous trials (Dillon et al. 2006, Lee et al. 2003).

P17

Pleomorphic Lobular carcinoma in situ (PLCIS); a clinical and pathological review

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PLCIS is a recently recognized variant of LCIS often identified at breast screening through the detection of mammographic calcification.

We aimed to review clinical and pathological findings in a series of PLCIS diagnosed by needle core biopsy (NCB) in order to further understand its nature and pathological characteristics.

Seven cases with a NCB diagnosis of pure PLCIS were identified. Complete histopathological information at NCB and final excision was collated for all cases.

In six cases, PLCIS was the original diagnosis. One case was diagnosed after MDT review and E-cadherin immunohistochemistry following an initial diagnosis of high grade DCIS. Five were categorized B5a, one "B3" and one was not categorized. All cases demonstrated histological calcification in association with comedo necrosis. All cases underwent conservative surgery. At final histology, all cases were seen to be associated with conventional LCIS. One case also had associated microinvasive lobular carcinoma.

To conclude, PLCIS may mimic DCIS and give rise to uncertainty regarding "B" categorization. On subsequent excision, there is usually associated LCIS of conventional type. Of interest, the risk of invasive malignancy following immediate surgical excision may not be significantly higher than for conventional LCIS.

P18

Establishing a Pathology Laboratory to Investigate Sudden Cardiac Death

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Background: Most sudden cardiac deaths (SCD) are due to ischemic heart disease. In the young it is due to inherited cardiac disease such as cardiomyopathy. Our Institute has been a referral centre for SCD in the United Kingdom. As a result of this work, a charity called Cardiac Risk in the Young (CRY) funded a unit specifically to investigate the cardiac pathology of these sudden deaths in order to help families with obtaining a specific diagnosis of the cause of death and refer them for cardiac screening.

Design: Retrospective study of hearts in sudden death with detailed histological analysis.

Results: Our referral pattern yearly has increased to 250 hearts per year Our turn around time for issuing a report is 2 weeks from the receiving of the heart. The diagnosis includes mainly normal heart indicating that channelopathies are very important in the cause of young sudden deaths. Idiopathic left ventricular cardiomyopathy as well as cardiomyopathies come next with hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy predominating. All these entities are hereditary and screening of family members is essential in order to avoid further deaths.Conclusions: Families and the public are becoming aware of sudden cardiac death and wish to obtain a rapid and specific cause of the death. As a result of the establishment of the CRY Cardiac Pathology Unit, we are able to make rapid specific diagnoses and help families come to term with a very traumatic event and assist with family screening.

P19

Sudden Cardiac Death in Young Adults: Spontaneous Coronary Dissection can be Missed: A Study of 7 cases

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Background: Spontaneous coronary artery dissection is a rare cause of death seen largely in young women, with many cases occurring in the early post-partum period.

Design: A retrospective study showed a total of 7 cases with this condition

Results: 4 women and 3 men with an age range of 26 to 40 years. All deaths were sudden and only one patient having chest pain,8 weeks post-partum. 4 of the hearts were considered as 'normal' hearts by the referring pathologist. In one heart, it was difficult to be certain if it was dissection or a post-mortem thrombus in the coronary artery. All cases showed a thrombus in the vessel which took careful analysis to determine that the thrombus was actually in the wall and not the lumen. All cases were examined histologically and they confirmed acute dissection of the coronary arteries, with more than 2 arteries affected in 3 cases. Histological features of myocardial ischaemia were noted in 4 cases.

Conclusion: The macroscopic changes of spontaneous dissection in the coronary arteries can be difficult to detect and can be easily mistaken for post-mortem clot or a thrombus overlying an atheromatous plaque. All such cases with thrombus in the arteries, especially in young adults should be examined microscopically for dissection.

P20

Aspergillus Pericarditis with Tamponade in a Renal Transplant Recipient

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Invasive Aspergillosis (IA) is an important opportunistic infection in immunocompromised individuals typically presenting as pulmonary disease. Amongst solid organ transplants, renal allografts have the lowest incidence of IA (0.4-5%). Aspergillus pericarditis is a rare extra pulmonary complication of IA, with the vast majority of cases reported in haematological malignancies. It is predominantly fatal and diagnosed at autopsy. We report the first published case of antemortem diagnosis and successful treatment of Aspergillus pericarditis presenting as cardiac tamponade in a renal transplant recipient.

A 48 year old man was stable for nine years on tacrolimus monotherapy. In 2006 he presented with Autoimmune Haemolytic Anaemia and then Guillain-Barre syndrome. He was treated with IV immunoglobulin initially, then prednisolone with good response and mycophenolate mofetil later for steroid sparing. Subsequently he became dyspnoeic. At bronchoalveolar lavage Pneumocystis jiroveci, Cytomegalovirus and Aspergillus were detected by PCR. Aspergillus fumigatus complex $<1 \times 10^3$ cfu/ml was grown on culture. He improved with appropriate antimicrobial therapy including caspofungin. In 2007 he had a pericardial tamponade. At thoracoscopic creation of pericardial window a visceral pericardial mass was excised. Pericardial fluid PCR and histopathological tissue examination confirmed Aspergillus organisms. He was successfully treated with Voriconazole.

Potent immunosuppression regimes are associated with serious opportunistic infections including Aspergillus. In this first reported case of its kind in a renal allograft recipient we show that a high degree of clinical suspicion, appropriate investigation and accurate diagnosis through histological and molecular techniques are vital for successful outcomes.

P21

Cell cycle markers in clinical oncology: diagnostic and predictive targets

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Analysis of the complex and redundant pathways that control proliferation, differentiation, apoptosis and DNA damage response by global genome wide analysis is an intensive area of investigation aimed at identifying unique molecular signatures of prognostic and predictive significance in cancer. An alternative approach is to focus on the cell cycle machinery, which acts as an integration point for information transduced through upstream signalling pathways. Recently we have shown that mutliparameter analysis of core regulatory proteins involved in G1-S and G2-M cell cycle phase transitions provides a powerful biomarker readout for assessment of tumour cell cycle state, information that can be exploited in tumour prognostication and as a predictor of therapeutic response to cell cycle phase specific chemotherapeutic agents. Moreover we have shown that the DNA replication licensing machinery, a core regulator of the G1-S transition, is a potent anticancer target as a result of the abrogation of a novel licensing checkpoint that normally operates in G1 phase. The checkpoint is p53 dependent and negatively regulates two proliferation-associated signalling pathways (details of which will be presented) which leads to the inhibition of S-phase inducing CDKs and arrest in G1 phase. An understanding of the signalling pathways involved in the molecular workings of the licensing checkpoint will be important for selecting patient groups that are likely to respond to this new form of therapeutic intervention.

P22

A 20 year analysis of endometrial hyperplasia and carcinoma; in women less than 40 years

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BACKGROUND: The focal nature of the endometrial atypia and the disappointing lack of reproducibility of the WHO classification together with the potential of conservative management in young women prompted us to look at our own data in these patients.

AIM and METHOD: Data was retrieved from the co-path database between 1988 and 2008,
to assess epidemiology and morphology of endometrial hyperplasia and carcinoma diagnosed in our institution in patients under 40 years of age.

RESULTS: We found 58 cases of endometrial hyperplasia and 15 cases of endometrial carcinoma. Specimens comprised: 61 biopsies, 11 total abdominal hysterectomies with or without bi- or unilateral salpingooophorectomy and 1 myomectomy.

The average age was 33 years with no significant difference between those with and without atypia (34 vs 32 years). Clinical presentations ranged from irregular bleeding, infertility and obesity. 16 (27%) had polycystic ovarian syndrome.

43% were hyperplasia without atypia while 53% showed atypical hyperplasia. 3% showed atypical complex hyperplasia where carcinoma could not be excluded.

There were15 cases of endometrioid carcinoma (EC) with an average age of 34 years. 6/15 (40%) were grade 1 EC; 7/15 (47%) were grade 2 EC; 2/15 (13%) were grade 3 EC.

CONCLUSION: We highlight the frequency of hyperplasia and EC in women less than 40 and reemphasize the important of correctly diagnosing atypical hyperplasia/carcinoma in these women as some may be eligible for fertility preserving treatment if diagnosed at an early stage.

P23

The segregation of mutant mitochondria in human stem cells

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Cytochrome c deficient colonic crypts, due to deleterious mutations in mitochondrial DNA (mtDNA) can be visualized using immunohistochemistry. The frequency of deficient crypts is <1 per 10000 in those under 40 years but rises to between 1 and 10% in those over 80 years. Epithelial stem cells contain between 1000 and 10000 molecules of mtDNA (P molecules) and the majority of the mitochondria must express the mutation for staining to be positive. Conversion from one mutant molecule to homoplasmy could occur by genetic drift but it would take in excess of P DNA replications. In this poster an alternative model is proposed. A single deleterious mutation occurs in one mtDNA molecule in one mitochondrion. Loss of the other mtDNA molecules from that organelle occurs over a number of years leading to a mutant mitochondrion in which all its DNA molecules express the deleterious mutation. During subsequent epithelial cell divisions the progeny of the mutant mitochondrion stay close together and are segregated in clusters. The result is progression to homoplasmy can occur in approximately log P epithelial cell divisions. The model is consistent with the hierarchical model of stem cell genesis in which the total number of stem cell replications is <60. The model is also consistent with the fact that deleterious mutations in mtDNA do not increase from generation to generation because the 30 to 40 cell divisions in oogenesis are sufficient for complete segregation of mutant mitochondria.

P24

mRT-PCR – a Rapid Realistic Alternative to Immunocytochemistry in the Early Diagnosis of Malignant Effusions

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Carcinoma of Unknown Primary (CUP) study aims to use multi-plexed reverse transcriptase RT-PCR on RNA extracted from malignant materials from patients with metastatic disease. PCR primers and hybridisation probes for use in the mRT-PCR assay will be targeted at tissue-specific markers.

We have already used this technique for determining the presence of metastatic disease in sentinel lymph node samples detecting CK-19 and mammaglobin1 in nodes with metastatic breast cancer.

Here, we investigate the feasibility of the use of mRT-PCR to determine the primary cancer site in patients with malignant effusions. Adoption of this innovative technique used in conjunction with liquid based cytology will surplant immunohistochemistry in cancer diagnosis, markedly reducing unnecessary bed occupancy, costly radiological tests and investigative biopsies.

P25

Abstract withdrawn

P26

SOCS-3 is widely expressed in normal tissues and demonstrates modulation of expression in inflammation

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Suppressor of cytokine signalling (SOCS) proteins are intracellular inhibitors of cytokine signalling that act in a classical negative feedback loop. Up-regulation of SOCS proteins by one particular cytokine can lead to the inhibition of signalling by other cytokines. We validated commercially available polyclonal serum against SOCS-3 and demonstrated the expression pattern of SOCS-3 in normal tissues. By means of immunostaining, we tested the hypothesis that expression of SOCS-3 by macrophages and dendritic cells shows modulation in various types of inflammation.
In normal tissues, SOCS-3 is expressed in both the nucleus and cytoplasm of a wide range of cell types, particularly macrophages, dendritic cells, lymphocytes and some epithelia. We compared the numbers of macrophages and dendritic cells that expressed SOCS-3 between tissues showing acute, chronic or granulomatous inflammation and their normal counterparts. We demonstrated SOCS-3 expression by an increased proportion of macrophages and dendritic cells in the majority of these conditions, particularly in inflammatory conditions of the gastro-intestinal tract. Although there was some statistically significant variation between the amount by which SOCS-3 expression increased in different types of inflammation, there was no clear trend, suggesting that SOCS-3 regulation in vivo is a complex phenomenon that can be modulated by a large number of stimuli in the cell's immediate environment.

P27

Systems Thinking - a Method for Embedding Pathology in the Undergraduate Medical Curriculum

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Specific pathology learning opportunities have been reduced or eliminated in many medical undergraduate courses with the introduction of integrated problem-based curricula. Systems thinking is a set of methodologies that looks at the entirety of a topic ('the system') and defines elements of the system which will enable its behaviour to be predicted. Four undergraduate medical students brought self-selected topics to a series of workshops. Initial faciltated sessions to capture all possible factors in the system produced an average of 70 elements in about 20 minutes. Factors were then clustered into related groups. Relationships between factors were explored and codified by directional arrows. Key subsections of the overall system were selected for further investigation by causal loop diagrams. Reinforcing and balancing loops within the subsystem were identified and the behaviours of the system were predicted in a semi-quantitative manner. Some of the casual loop diagrams were converted into system dynamics models, using proprietory software, to enable quantitative predictions of system behaviour over time. A final 'flight simulator' model with detailed annotations was constructed for some systems which enabled other students to explore the behaviour of the system using onscreen 'controls' and dynamic graphs. The students engaged well with the project, were suprised at how much knowledge they had on topics when using the facilitated methods and said that they understood the systems, and the role of any relevant pathological mechanisms in that system, much better at the end of the project.

P28

Audit of Oesophageal and Gastric Cancer Biopsy Reporting

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Background: The histological features of malignancy found in oesophageal and gastric biopsies may predict lymph node metastasis and survival. However, specific features are not reported uniformly. Histological type, differentiation including Lauren classification, invasion of submucosa and double reporting are perhaps the most important factors to be included in these reports. The aim of this study is to audit the reporting of gastric and oesophageal cancer biopsies and to determine the adherence to published guidelines.
Methods: All gastric and oesophageal biopsies containing malignancy over 1 year were identified (1/6/2007 to 31/5/2008). Each report was evaluated against criteria set out by the Royal College of Pathologists and the British Society of Gastroenterology.
Results: 98 oesophageal cancer biopsies and 50 gastric cancer biopsies were evaluated. Other than the histological type, biopsies were not reported consistently. A minority of reports commented on submucosal invasion, lymphovascular invasion or Lauren Classification.
Conclusion: There is considerable variation in the reporting of gastric and oesophageal cancer biopsies. Specific proformas will be piloted at John Radcliffe Hospital with the aim of improving reporting standards and to further investigate the clinical value of the criteria.

Table 1: Results.

Cancer and Histopathological Feature	Percentage of Reports Commenting on the Histopathological Feature
Oesophageal	
Type	99%
Differentiation	71%
Adjacent Non-malignant Epithelium	73%
Invasion of the Submucosa	22%
Vascular and/or Lymphatic Invasion	5%
Double Reporting	71%
Gastric	
Type	100%
Differentiation	64%
Lauren Classification	34%
Invasion of the Submucosa	20%
Vascular and/or Lymphatic Invasion	2%
Double Reporting	86%

P29

Audit of Completeness of Excision of Malignant Melanomas by Dermatologists and General Practitioners at Maidstone and Tunbridge Wells NHS Trust

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Clearance of excision margins is paramount in the management of malingnant melanomas.
In this study, we audited the rate of margin involvement in primary excisions of all malignant melanocytic lesions which were reported in the histopathology department at Pembury and Maidstone Hospitals between 01.01.07 and 31.12.07. The excisions were performed by dermatologists from various regional hospitals, including Pembury and Kent and Sussex district general hospitals, and a number of general practitioners (GPs).

We analysed 75 histopathology reports for malignant melanocytic lesions; 46 (61%) of which were excised by dermatologists and 29 (38.6 %) were excised by GPs. We found that while 37 (80.4 %) of the lesions removed by dermatologists were completely excised, only 6 out of 29 (20.7 %) lesions removed by the GPs were completely excised. In addition, clinical suspicion of melanomas in general practice (17.2 %) was lower than that seen in dermatology clinics (76 %). Other skin malignancies, such as basal cell carcinoma, were suspected by GPs in 14 % of cases and in 10 % by the dermatologists

We conclude that clinical diagnosis of melanoma in general practise is challenging, therefore, the primary excision of these lesions tends to be incomplete when compared to hospital based dermatologists.

P30

An Audit of the Management of Bone and Soft Tissue Sarcoma in a Single Region and the Influence of a Nationwide Managed Clinical Network for Sarcoma

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Sarcomas should be managed in specialist centres by a multidisciplinary team. In areas with geographically dispersed populations it is presumed that Managed Clinical Networking achieves a critical mass of specialists whose expertise optimises care.

AIM: Audit the management of sarcomas in a geographically large area by comparing patient outcomes for those managed in a specialised sarcoma centre in contrast to non-specialised hospitals and audit the effectiveness of a nationwide managed clinical network for sarcoma.

STUDY DESIGN: Retrospective assessment of referral and patient care pathways as well as outcomes following sarcoma surgery before and after the establishment of a clinical network. Data retrieved from patient case records, pathology reports and a computerised sarcoma database.

RESULTS: 524 individual primary sarcoma cases were identified. A random selection of cases pre- and post network were audited. Networking is associated with a 33% reduction in referral time to hospital appointment (median 1 week from 3 weeks); 50% reduction in waiting time for diagnostic imaging (median 2 weeks from 4 weeks); an increase in the numbers of planned surgeries (78% from 54%; p=0.01) including pre-operative imaging, staging and pre-operative core biopsies (72% from 53%; p=0.05). This is reflected in an increase in the numbers of clear surgical margins (85% from 50%; p=0.02) and a dramatic reduction in the rates of local recurrence (13% from 80%; p=0.012).

CONCLUSION: Specialised multidisciplinary team working and the managed clinical network for sarcoma positively influences patient management and outcome.

P31

How Reliable is Ultrasound Guided Axillary Lymph Node FNA in Breast Cancer Staging?- Guy's and St Thomas' Hospital Experience

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Ultrasound Guided Fine Needle Aspiration (FNA) of Axillary Lymph Nodes is increasingly employed in pre-operative staging of breast carcinoma. The aim of this audit was to determine the diagnostic accuracy of lymph node cytology in breast cancer patients who attended our hospital between January 2007 and August 2008. Cytology results were correlated with subsequent histology.
A total of 82 aspirates of indeterminate, suspicious and metastatic appearing lymph nodes were performed. Nine cases were excluded because of the inadequate/suboptimal nature of the samples. Histological correlation was available in 49 out of 73 cases. These were 15 sentinel node biopsies, 8 lymph node core biopsies and 26 axillary clearances. Thirty cases had positive cytology, out of which 29 were confirmed on follow up histology giving a Positive Predictive Value of 97%. The single false positive case had posed difficulty for cytology interpretation. This was later explained by the presence of widespread sinus histiocytosis in the Axillary Clearance Specimen. Five cases with negative cytology were subsequently proven to be positive, giving a false negative rate of 14.7%. A further 14 cases that were reported as negative on FNA were confirmed to be so on histology. The overall sensitivity was 85.3% and specificity 93.3%.
In 25 of the 34 cases with Lymph Node Metastases, a Sentinel Node Biopsy was avoided by FNA cytology. In conclusion, Ultrasound Guided Lymph Node Cytology is a simple, sensitive and cost effective tool for pre-operative breast cancer staging.

P32

An audit of Lymph Node Fine Needle Aspiration – Do Clinicians Act on Pathologists' Reports?

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Aim: To determine whether there is appropriate follow up following fine needle aspiration (FNA) of a lymph node, when the cytological findings are suspicious or suggestive of lymphoma.

Method: Using the laboratory computer records system, APEX, and a SNOMED search for lymph node FNA specimens, a list of reports from January 2005 to August 2008 was obtained. Each report suspicious of or suggestive of lymphoma was reviewed and the follow-up details recorded.

Results: A total of 1275 lymph node specimens were included. 110 cases were reported as suspicious or suggestive of a primary lymph node malignancy, i.e. lymphoma, and 76 (69%) of these had a follow up excision of the node. There was no follow-up in 17 cases (15%). There were 197 inadequate cases in the total sample, 23 with a clinical suspicion of lymphoma. Of these, there was no follow up in 11 cases (48%).

Conclusions: The findings of only 15% with no surgical follow up, when the pathologist has suspicions of lymphoma, although low is still worrying. The percentage of no follow up after an inadequate FNA result with a clinical suspicion of lymphoma is higher and more concerning. The pathologists' report can offer advice regarding surgical excision or follow up and in the majority of these cases, it is acted upon. It is the pathologist's responsibility to provide a result which is helpful and useful to the clinician, but ultimately it is the clinician's responsibility to ensure that this is acted upon.

P33

Achilles' Foreskin

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Great importance was attached to the foreskin in ancient Greece. The prepuce was valued aesthetically more than the penis and could be portrayed as occupying two thirds of the length of the whole penis. A long, tapering foreskin was a feature of male beauty and elegance. Display of the glans penis, by contrast, was at best a faux pas and at worst the action of a coarse buffoon. Nakedness was a natural state for the Greek male, particularly during athletic performance. To avoid accidental exposure of the glans and to keep the penis under some sort of control during the sprint relay, the athlete bound the foreskin with the 'kynodesme'. This was a thong bound around the foreskin distal to the end of the glans and then secured around the waist.
Greeks and Romans viewed with abhorrence the removal of the foreskin and circumcision was banned at various times in the Roman empire. An inadequate foreskin became an abnormality to be treated by the medical profession through medicine, physical means or surgery. The foreskin still rouses great passion in the present age. The kynodesme has still its enthusiastic proponents, and the aesthetic subtleties of foreskin length are emphasized by an index of 10 gradations. The normal and pathological in anatomy and behaviour are constructs of their age. We must beware of being persuaded of new pathologies, such as vulvo-vaginal 'abnormalities', that then require medical intervention.

P34

Evaluating Student Learning Styles and Approaches to Teaching and Learning in a Traditional and E-Delivered Curriculum

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Background. Delivering high quality learning to increasing numbers of students is a problem facing in many UK Medical Schools. An innovative approach to help solve this problem has been developed in the undergraduate pathology curriculum at our institution. The traditional lecture-and–tutorial based course has been replaced by an e-learning course built on digitally recorded lectures supported by on-line assessments and interactive tutorials.
Aims. To evaluate the learning styles orientation and approaches to learning of third year undergraduate medical students prior to the introduction of an e-course in pathology and at the end of the first year of virtual learning.
Methods. At the conclusion of the traditional pathology syllabus, all third year students (n=168) completed a questionnaire (adapted from the ETL Project, Edinburgh) assessing learning styles, motivation and experiences of learning. Similarly, 221 students completed the same questionnaire at the end of the first year of the e-delivered pathology course.
Results and Conclusion.The majority of medical students in both groups had high internal motivation to study medicine, consistent with expectations. Most students appeared to have a deep approach to learning, with a marked tendency to constructivist model knowledge acquisition. The course content was generally felt to be beneficial in developing knowledge required for clinical practice but there was a wider range of responses to this question in the e-learning cohort. This response may suggest anxiety among students when information is presented in a new form. There was no gender difference in the results.

P35

Abstract withdrawn

P36

An Interesting Case of Granulomatous Inflammation of the Placenta

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We present a case of granulomatous inflammation around the decidual vessels of the placental membranes. A 29 year old female with a history of hypertension during pregnancy and fits underwent an emergency C-section at 32 weeks gestation. The preceding MRI scan showed features suggestive of posterior reversible encephalopathy syndrome (PRES), a condition associated with pregnancy-induced hypertension (PIH). The macroscopic appearance of the singleton placenta was unremarkable except for a small focus of retroplacental haemorrhage. Microscopically, scattered well-circumscribed granulomas were present within the subchorion and attached decidua, closely associated with decidual vessels. Occasional multinucleated giant cells were noted. Special stains were negative for mycobacteria (ZN stain) and fungi (Grocott) and polarisation showed no foreign material. The mother and baby were both well post-partum.

The cause of the granulomas in this patient is not readily apparent. The differential diagnosis of granulomatous inflammation includes bacterial and fungal infection, sarcoidosis and foreign material. Decidual granulomas have been reported in patients with PIH, however this may reflect an immune vasculitis unrelated to PIH. Alternatively, the inflammation may represent a reaction to an infectious pathogen not identified on routine histochemical staining. This case highlights an uncommon histological pattern of placental inflammation and the importance of careful microscopic examination. In the future, a pathogen may become apparent through more advanced immunohistochemical or molecular testing. Until such a time clinical investigations to exclude causes of granulomatous inflammation should be undertaken.

P37

Melanoma Reporting in 2003 and 2007 at University College London Hospitals (UCLH): Are we complying with the National Minimum Data Set?

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The Royal College of Pathologists has introduced a National Minimum Data Set (NMDS) for reporting melanoma. Our aims were to document the number of melanoma cases reported in 2003 and 2007, to examine if an NMDS has been filled in and to examine the contents of the reports and to see whether all the MDS parameter have been reported.

Any report coded as melanoma in 2003 and 2007 was included in the audit, from the 1st January to the 31st December in each year. Any of the NMDS items that have not been mentioned in the report are considered to be missing.

In total 24 and 34 melanoma reports have been audited in 2003 and 2007 respectively. The mean age was 60 years (28 –82) for 2003 and 66.5 years (28-94) for 2007. Only two NMDS has been completed in each year. Size of the lesion was documented in two thirds of the reports. Microscopic parameters such as Breslows thickness were well reported but border of the lesion and vascular invasion were not documented in most of the reports. We recommend that the NMDS should be filled in each case and all the parameters should be reported even if they are not present (negative reporting). This would provide a standard way of reporting and would provide a valuable database for future audit and research in this difficult area. Re-audit after implementation of this recommendation.

P38

Malignant melanoma in Cornwall. Is the population getting smarter?

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We have compared trends in malignant melanoma (MM) over a decade in Cornwall, which has the highest annual number of new cases in Britain. A British Cancer Research Campaign promoting earlier recognition of MM began in July 1987. Several studies have since examined whether there has been any change in features of melanoma. This study looked at factors that might indicate changes in incidence or behaviour.

All cases of primary, cutaneous MM occurring in central and west Cornwall in 1996 and 2006 were retrieved from the histopathology database. Lentigo maligna was excluded. A database was constructed including the information recommended by the Royal College of Pathologists. A consultant pathologist reviewed each case to ensure consistency in data and to add information omitted in the original report.

Between 1996 and 2006, cases of MM increased from 79 to 91. There was no significant difference in the mean Breslow thickness between the two years. MM was located on typical body sites in the Cornish population consistent with national data. Significantly more people over 60 were diagnosed with melanoma in 2006, compared with 1996.

Decreasing Breslow thickness would be the best indicator of earlier, improved diagnosis. No such change occurred between 1996 and 2006. No changes occurred in body site, suggesting there had been no change in behaviour related to sun exposure. The reason for the increase in MM in those aged over 60 was not evident.

P39

Vaccination Induced Cutaneous Pseudolymphoma – A Case Report

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Cutaneous pseudolymphoma is not a specific disease but rather an inflammatory response to known or unknown stimuli that results in a lymphomatous-appearing but benign accumulation of inflammatory cells.
We present a case of a hypersensitivity reaction resulting in a cutaneous B-cell pseudolymphoma, 3 months following the second dose of Hepatitis B vaccination. A 24 year old Afro-Caribbean female presented with a large hyperpigmented, lichenified, non-tender granulomatous plaque on the right upper forearm which was itchy, indurated and warm. Similar smaller lesions also appeared on the left upper arm after the initial presentation. Her blood profile was normal, however, a skin biopsy revealed a dense nodular dermal and subcutaneous lymphomatoid infiltrate with no evidence of epidermotropism. Immunohistochemical analysis demonstrated nodular aggregates of CD20+ B-cells associated with scattered reactive follicles (bcl-2 negative) and a second population of interfollicular CD3+ T-cells. PCR gene rearrangement studies showed no evidence of monoclonality and elemental analysis failed to demonstrate the presence of aluminium. Patch and skin prick testing were negative.
Differential diagnoses considered were cutaneous B-cell pseudolymphoma, primary cutaneous follicle center lymphoma, primary cutaneous marginal zone B-cell lymphoma or cutaneous involvement of a systemic lymphoma. Detailed morphological, immunohistochemical and genetic studies excluded a neoplastic process and staging revealed no evidence of systemic lymphoma.

P40

Tips for Making a User Friendly Tissue Microarray

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Tissue microarrays (TMAs) are an established research resource for high throughput translational research studies. However, there is little inter-laboratory standardisation thereby template design, orientation cores and standards of section cutting vary considerably. This can lead to significant difficulties with evaluation and poor use of a precious resource.
A few simple steps in preparing and sectioning the TMA, can improve both efficiency and whole evaluation experience.
Areas to core must first be marked on an H&E section. This section must correspond to the current face of the wax block. Often sections have been cut after the original H&E, so marking the latter is not an accurate representation.
Donor blocks should be re-embedded to ensure block depth and thereby physical core length is consistent for placement in the recipient block.
TMA core diameter is determined according to structure being sampled. 0.6mm diameter stylets are suitable for invasive tumours, whereas features such a ductal carcinoma in-situ or tonsil follicles may require 2.0mm.
The shape, size and layout of the grid, must be such that orientation of the section is incontrovertible to both technical and pathological staff.
Asymmetrical grid patterns with control tissue cores incorporated within the array help considerably when cores have moved or are missing.
Accurate documentation relating core location to tissue identification is paramount. Software and scanning systems are rapidly developing to meet the needs of those who make and use TMA's. However, the basic principles for good TMA production will continue to be a prerequisite.

P41

A Novel Approach to Automate Identification and Assignment of Cores on Tissue Microarrays

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Tissue Microarrays (TMAs) represent a potentially high-throughput platform for biomarker investigation in tissue samples. Combining virtual microscopy and algorithm development, it is now possible to automate the analysis of tissue core characteristics and biomarker density using high performance platforms that can significantly speed up analysis. This study seeks to automate assignment of segmented cores with their corresponding row/column position, so that subsequent analysis can be attributed to the appropriate tissue/patient sample and associated clinical, pathological and treatment metadata. The algorithm utilises a convex hull approach which identifies the spatial domain of the cores within the TMA array by identifying the cores that lie on the edge of the TMA. Corners of the TMA can be identified by a search along the cores on the convex hull and all internal cores can be identified by a method of triangulation from a given corner. Triangulation provides the basis for a dedicated spatial search algorithm which can identify and assign specific cores to their appropriate row/column and can recognise missing or incomplete cores. In preliminary results the algorithm proves to be reliable for automatically "de-arraying" a wide range of TMA samples including the ability to identify missing cores. In addition, this algorithmic platform provides a robust framework for managing more complex TMA artefacts such as missing rows/columns and highly skewed/stretched arrays. This provides the link-pin between virtual TMA slides and image analysis, establishing TMA technology as a truly high performance platform for tissue biomarker analysis.

P42

Compression in Virtual Microscopy: How low can you go?

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Virtual slides are high resolution images of tissue specimens and can result in images in excess of 20GB in size when stored uncompressed. There are a number of compression algorithms available to reduce image size however lossy compression also reduces image quality impacting on visual inspection. The aim of this study was to establish which compression technology is most effective at compressing virtual slides and to quantify how much they can be compressed without compromising image quality.
Images were compressed using jpeg and jpeg2000 at a non-linear rate biased towards higher compression rates. Images were assessed by visual inspection by experienced scientists/pathologists who used a tool specifically designed by the author to display the original image and an image of an unknown compression on screen. The pathologist recorded the extent to which any differences could be seen between the compressed and uncompressed images on a linear scale from 1 – 4.
Results show that jpeg2000 is a superior compression algorithm, compressing the images to a smaller file size with less obvious compression artefacts, however compression time is 3x slower r than jpeg. Images can be compressed significantly, reducing file size by a factor of 40 without the majority of pathologists noticing any differences between the compressed image and the original. By compressing images not only do we free up valuable hard disk space but we also significantly speedup the online delivery of virtual slides, bringing virtual microscopy one step closer to routine use in clinical pathology.

P43

The Northern Ireland Virtual Tissue Archive (NIVTA)

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Tissue banking allows for the extensive collection of well classified and appropriately stored tissue samples that are linked to well defined clinical and pathological information. Presently, an element of tissue banking involves storing large volumes of microscopic glass slides, which are prone to loss or breakage, and can be viewed in only one location at a time. Virtual microscopy overcomes this problem by providing a virtual image of the tissue section for storage and review. The Northern Ireland Virtual Tissue Archive (NIVTA), has been established as a key centralised resource to support tissue-based translational research. Tissue samples for bio banking, clinical trials, biomarkers studies and tissue-based research are scanned, anonymously stored and linked with clinico-pathological staging information. NIVTA digitally scans slides using a bank of scanners, stored centrally and managed using the PathXL virtual slide platform. These can be instantly retrieved from storage using authorised access and viewed on-line using a dedicated web-based PathXL viewer anywhere in the world. To date, in excess of 25Terabytes of virtual slide cases have been stored. Virtual slides facilitate transnational collaboration on tissue based research and enable external pathologists to review, score and digitally annotate material from multiple locations, without physically sending any glass slides. They also provide a platform for the automated quantitative analysis of tissue biomarkers, which will offer a more reliable and objective approach to tissue biomarker discovery. NIVTA provides a reliable institutional model for centralised virtual tissue archiving for a range of tissue research activities.

P44

Oncological Superiority of Cylindrical Abdominoperineal Excision for Low Rectal Cancer Confirmed in a European Multicentre Study

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Standard APE for low rectal cancer is associated with worse outcomes than anterior resection for higher rectal tumours. This is due to increased CRM involvement and intraoperative perforations caused by a combination of anatomical and surgical difficulties. We have previously shown in a small two-centre series that extended perineal dissection in the prone position results in a cylindrical specimen removing more tissue around the tumour and significantly reducing CRM involvement and perforations.

Several European colorectal surgeons have adopted the cylindrical technique with varying degrees of experience. We received the pathological reports and specimen photographs of 150 cylindrical APE specimens from 7 different surgeons in 6 European centres and compared them to a series of 114 standard specimens from one centre.

Cylindrical surgery removed more tissue in the distal 12 slices of the specimen (mean difference 895mm^2 per slice, 95% CI 794mm^2 to 996mm^2, $p<0.0001$) and was associated with lower CRM involvement (19.6% vs. 43.4%, $p=0.0007$) and perforations (8.3% vs. 24.8%, $p=0.0011$) compared to standard surgery. For patients who had received pre-operative therapy, the rates of CRM involvement (14.9% vs. 36.0%, $p=0.0045$) and perforation (3.7% vs. 24.0%, $p=0.0001$) were similarly reduced.

We have shown in a large multicentre European series that cylindrical APE removes more tissue around low rectal tumours resulting in reduced CRM involvement and perforations. Urgent consideration should be given to changing surgical practice in order to improve patient outcomes.

P45

The Expression Pattern of Pericentrin and Aurora Kinases in Gastric Cancer

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Background: Aurora kinases A and B (AURKA and AURKB) and Pericentrin are implicated in centrosome cycle regulation. We hypothesised that aberrant expression of these proteins may be related to tumour progression and patient survival in gastric cancer (GC).

Methods: We investigated the protein expression of AURKA, AURKB, Pericentrin and Ki67 in 147 GC by immunohistochemistry. The relationship of the expression frequency of individual proteins to centrosome number, Ki67 expression, clinicopathological data, DNA ploidy and patient survival was analysed.

Results: High expression of nuclear Pericentrin was associated with poor patient survival ($p<0.036$), DNA aneuploidy ($p=0.006$) and diffuse type GC ($p=0.029$) whereas high levels of cytoplasmic Pericentrin was associated with intestinal type GC ($p=0.004$) and patient age ($p < 0.001$). No other associations were found.

Discussion: This is the first study reporting a relationship between the subcellular expression pattern of Pericentrin and clinicopathological data in GC. Our study was unable to confirm a relationship between AURKA and AURKB expression and patient survival as advocated in the published literature. However, as AURKA and AURKB were expressed in the majority of primary GC in our series, further functional studies in GC cell lines are warranted to establish whether the expression of these proteins is related to response to aurora kinase inhibitors.

P46

Pre-operative Imatinib treatment of GIST abolishes immunostaining for c-kit – A diagnostic pitfall

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We describe a case of imatinib treated gastric tumour in a 64 yr old male with proximal gastrectomy. Microscopically, the tumour was composed of coarse fascicles of spindle cells with elongated blunt-ended nuclei in the submucosa, extending focally into the muscularis propria. The tumour cells were positive for actin and desmin, but did not express S-100 protein, CD34, CD117 or bcl-2. The case was therefore misdiagnosed as a typical leiomyoma rather than a GIST. It was recognised at a subsequent clinicopathological meeting that the patient had a firm diagnosis of GIST based on a previous biopsy which was highly cellular with numerous mitosis and unequivocally CD117 and CD34 positive. Unbeknown to the pathologist reporting the gastrectomy, the patient had been treated with Imatinib.

GISTs commonly express mutated KIT and mutated platelet-derived growth factor receptor alpha. The activity of these kinases provides the malignant cells with growth and survival signals which is very effectively turned off by Imatinib. Imatinib exerts its activity through blockade of the adenosine triphosphate–binding site of KIT. It inhibits proliferation and promotes apoptosis in GIST cells by interrupting tyrosine kinase–mediated intracellular signaling.

This case demonstrates that a pathological complete response could be achieved with pre-operative Imatinib therapy and abolishes immunohistochemical staining for CD117. This emphasises the importance of having clinical and treatment history prior to making a histological diagnosis.

P47

Should Examination of Surgical Doughnuts in Colorectal Adenocarcinoma Specimens Still be Routine Practice?

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The RCPath standards and datasets for reporting cancers "Dataset for Colorectal Cancer (2nd Edition)" specifies that there is no necessity for histopathological examination of doughnuts from stapling devices if the main tumour is greater than 30mm from the cut end of the main specimen. The practice at our institution was to examine all specimens regardless of tumour distance to cut end. Such specimens typically contain many staples. Removal of the staples and the associated distortion, as well as processing and orientation difficulties can then make histopathological assessment potentially unreliable.

We conducted a retrospective review of 180 patients who underwent resection of primary colorectal adenocarcinoma over a 2 year period. Seventy-six specimens came with doughnuts. One case was excluded due to pseudomyxoma peritonei. In 38 cases the tumour was less than 30mm from the cut end, with 2 cases having involved cut ends. None of the 76 cases had tumour involvement of the doughnut.

We propose that in view of the technical difficulties in specimen preparation, the subsequent unreliablility of histopathological assessment and the additional time and material resources involved in both these activities, surgical doughnuts should only be examined if there is proven involvement of the cut end.

P48

Bowel Screening Programme, First Year's Results Analysis

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The bowel screening program was initiated in November 2006 in the London region and was based at our Hospital.

The purpose of this retrospective audit was to assess the number of cases that were found to have pathology by the screening program, to evaluate the extra workload created and to assess the number of days it requires for the pathology service to authorise a report.

In the year 2007, 12542 individuals were invited to participate but only 6577 (54%) of them took part. From those, 370 individuals had a positive faecal occult test and proceeded to have colonoscopy. From the 370 colonoscopies performed 164 were normal and the remaining 206 had colonic pathology.

From the above 206 “positive cases”, 173 (100%) have been reviewed by our study. 107 (64%) had low grade adenomas, 12 (7%) had both low grade adenomas and hyperplastic polyps and 17(10%) had adenocarcinoma. 9 (6%) cases had both adenocarcinoma and low grade adenomas, 17 (10%) had hyperplastic polyps and 5 (3%) had inflamed mucosa.

The average turn around time was 1.55 working days. The extra workload for the consultants was calculated to 169 “College working” hours. The extra workload for the laboratory staff was 172 hours.

The study has pointed out that our facility has similar results with the NHS BSP pilot scheme and has identified the areas where new resources have to be engaged in order to continue providing first-rate pathology services

P49

Dysplasia-Associated Lesion or Mass (DALM) Vs. Sporadic Adenoma – What Are the Current Guidelines and Do We Employ Them Correctly?

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Background: Endoscopical examination often fails to differentiate between adenoma-like DALMs and sporadic adenomas in patients with inflammatory bowel disease. The pathologist is often called upon to assist with the final diagnosis. Traditionally adenoma-like DALMs have been treated with colectomy, whereas sporadic adenomas required polypectomy only. The literature suggest that the following features might assist in differentiating the 2 entities:

Feature	DALM	Sporadic adenoma
History of IBD	Yes	Yes/No
Glandular architecture	Disorganised	Regular
p53	+	-
Bcl-2	-	+

Methods: A computer database in a large teaching hospital generated a list of 8440 patients with inflammatory bowel disease, adenoma or adenocarcinoma over a 10 year period. Twenty-two patients with ulcerative colitis with either associated dysplasia and/or adenocarcinoma were identified. The slides were reviewed for above-mentioned histological and immunohistochemical features.

Results: Subjective review of 53 adenomatous polyps in patients with ulcerative colitis showed 32 polyps with regular and 21 polyps with disorganised glandular architecture. Immunohistochemistry with p53 and Bcl-2 was reviewed:

p53/Bcl2	Regular architecture	Disorganised architecture
Pos/Neg	8	5
Neg/Pos	2	3
Pos/Pos	1	4
Neg/Neg	0	0

Conclusion: Histological and immunohistochemical features suggested above were not always useful in differentiating these two entities. Furthermore, recent molecular studies have also shown that adenoma-like DALMs and sporadic adenomas have similar molecular profiles. Data also suggest that adenoma-like DALMs could be managed by polypectomy. It raises the question of significance in differentiating these two pathological entities in future.

P50

Abstract withdrawn

P51

Interactions Between Oesophageal Squamous Cells and Fibroblasts in Response to Acid Exposure

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Exposure of the oesophageal mucosa to gastroduodenal refluxate is a key factor in the development of Barrett's Metaplasia (BM), with NF-κB activation in response to refluxate exposure thought to induce CDX2 expression. However there is limited data on the effect of acid on NF-κB activation in primary human oesophageal squamous (HOS) cells, and no data on the response of underlying fibroblasts (HOFs) or on paracrine interactions between these cells. We examined the effect of acid exposure on primary cultures of HOS and HOF cells. We also performed experiments where media conditioned by HOSs exposed to acid was applied to HOFs and vice versa. Metabolic activity assays showed HOSs are relatively resistant to acid, consistent with their protective barrier role, while HOFs rapidly lost viability. In contrast acid exposure (pH7 - pH4 ≤120 minutes) did not activate NF-κB in fibroblasts but did in HOSs. Analysis of this revealed HOS activation of NF-κB when exposed to pH 4 for 30 to 120 minutes. Moreover, when HOSs were subjected to short pulses at pH5 (which was itself insufficient to translocate NF-κB), a soluble factor was released that triggered the activation of NF-κB in HOFs. These results are the first to show a downstream effect in fibroblasts in response to exposure of epithelial cells to acid pulses of a similar duration to those encountered during reflux. Significantly this paracrine interaction is observed at a pH that does not cause a detectable NF-κB response in the epithelial cells themselves.

P52

Glycine Conjugated Bile Acids are Toxic to Oesophageal Cells in a pH Dependent Manner

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Exposure of the oesophageal mucosa to bile salts is thought to play a key role in the development of oesophageal adenocarcinoma. In-vivo studies on the effect of these insults have typically used cells lines derived from established Barrett's metaplasia or carcinoma, and there is a lack of systematic data on the effect of bile salts on oesophageal squamous cells. Using primary human oesophageal fibroblasts (HOF) and immortalised oesophageal squamous (HET1A) cells we studied the effects of a range of bile salts both at neutral pH and pH 4. Each bile salt was used singly and in a physiologically representative mix at 0.4mM. Cell metabolic activity was measured by MTT-ESTA assay. In both cell types treatment with bile salts at neutral pH caused an increase in cell metabolic activity from between 110-145% of control, with taurodeoxycholate having the strongest effect. A similar response was seen when cells were treated with bile salts at pH 4, except with the glycine-conjugated bile salts glycochenodeoxycholate and glycodeoxycholate, both of which caused a profound drop in metabolic activity to between 6-15% of control, indicative of significant toxicity. The increased metabolic activity in response to bile salt exposure is likely to indicate either cell proliferation or a cellular stress response. These data emphasise the differential effects of the various bile salts, and the impact of pH on these effects. These factors should be taken into account when considering the role of reflux in the pathogenesis of Barrett's metaplasia.

P53

A Histological Comparison of Tissue-Engineered Oesophageal Mucosal Models

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The development of Barrett's metaplasia and oesophageal cancer is influenced by complex microenvironmental factors which existing cell culture systems fail to recapitulate. There is accordingly demand for ex-vivo models which more realistically model the oesophageal mucosa. Although a variety of approaches have been described few systematic studies have been reported. We compared two different matrices for supporting cell growth: acellular porcine oesophagus (APO), and collagen I. We also compared two oesophageal epithelial sources: primary human oesophageal squamous cells (HOS) and the HET1A telomerase immortalised oesophageal cell line. Human oesophageal fibroblasts were incorporated into all models. All models were cultured at air/liquid interface for 10 days. Tissues were examined histologically to assess epithelial attachment to the underlying matrix, epithelial maturation, and the penetration of fibroblasts into the matrix. Both scaffolds supported the regeneration of a multilayered epithelium. This attached well to the APO scaffold but only loosely to collagen. On both scaffolds HOS grew into a stratified epithelium showing basal proliferation and progressive maturation. HET1A cells showed little evidence of maturation and proliferation was seen throughout the epithelium. Fibroblasts penetrated the collagen but were not seen in the APO. Culture systems using collagen are unlikely to recapitulate normal interactions between cells and the basement membrane, or between epithelia and fibroblasts. Although convenient, immortalised cells do not appropriately recapitulate the process of cell maturation. 3D models will be of value in investigating Barrett's metaplasia and oesophageal cancer, but their design should take such factors into account.

P54

Gastric Antral Vascular Ectasia (GAVE) Forming Multiple Pseudopolyps Requiring Gastrectomy: An Atypical Macroscopic Appearance

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Gastric antral vascular ectasia (GAVE) is a rare localised vascular disorder that is responsible for up to 4% of non-variceal upper-gastrointestinal bleeding. It generally presents with chronic iron-deficiency anaemia. Less commonly, there may be overt gastrointestinal bleeding in the form of melaena or rarely haematemesis. Classically, GAVE has a unique macroscopic appearance including prominent erythematous longitudinal stripes that are visible endoscopically: the "Watermelon" stomach. However, unlike the present case described, it does not typically form polypoid nodules.

We describe a case of GAVE in a 78 year-old man who had a gastrectomy for gastrointestinal bleeding refractory to other treatments. Examination of the total gastrectomy specimen identified a brown nodular area in the antrum measuring 110 x 60mm containing polypoid nodules up to 30mm in diameter. Microscopically the antral mucosa showed villiform hyperplasia of the surface glandular epithelium with elongation of gastric foveolae, some of which were thrown in to complex folds with focal dilatation of the glands. The surface of the polypoid areas showed extensive ulceration with fibrinous exudate. In addition, there were numerous vascular structures of varying caliber within the lamina propria and the submucosa. Characteristically, the lamina propria contained vertically orientated smooth muscle cells and fibroblasts. Also, prominent microthombi were present within the superficial small vessels.

GAVE is an under-recognized condition that may be misinterpreted as antral gastritis on mucosal biopsies. Wider recognition of the clinical and histopathological features is required to allow early diagnosis and non-surgical treatment.

P55

Expression of p53, Ki-67, iNOS and eNOS in Barrett's Oesophagus cases with dysplasias, negative for dysplasias and adenocarcinomas

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Aims :To compare the expression of p53, Ki67, iNOS and eNOS in Barrett's oesophagus and identify markers expressed early in the disease which can predict patient prognosis.
Methods:54 cases in 4 groups were investigated to examine the immunohistochemical expression of p53, Ki-67,iNOS and eNOS. **Results**: p53 and Ki67: For both these markers the low grade/negative groups had significantly lower levels than theose of high grade and adenocarcinoma groups (p53: chi-square=39.792, df=3, p<0.001, Ki67: chi-square=42.642, df=3, p<0.001)
i-NOS & eNOS A significant difference in i-NOS levels was seen across the groups using Kruskal Wallis (Chi-Square=56.552 df=3 p<0.001) and descriptive analsyis indicates that I_NOS may be useful in distinguising both low from high grade, and high grade from adenocarcinoma. In contrast, analysis showed that e-NOS is a poor marker of disease stage overall.
Conclusion: Ki-67 and p53 may be useful in identifying patients who develop high grade dysplasia / adenocarcinoma. Therefore Ki-67 and p53 warrant further research using a prospective study design. i-NOS should be investigated similarly.

P56

PET Positive and Pretty

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We report the incidental finding of a ganlioneuroma presenting as a large positron emission tomography (PET) positive nodule in the retroperitoneum of a 71 year old patient with known metastatic malignant melanoma.
Following the finding of two possible deposits of metastatic melanoma on CT and FDG-PET scans in a left para-aortic lymph node and the right adrenal a resection was undertaken under general anaesthesia by a consultant hepato-biliary surgeon at the Royal London Hospital. At the time operation, a 16mm lymph node was felt in the small bowel mesentery which was resected in view of the history.
Macroscopic examination revealed a normal adrenal gland and two nodules measuring 27mm and 16mm in largest dimensions retrieved from the paraaortic region and small bowel mesentery respectively. Cut surface of the larger nodule was tan and homogenous and the smaller nodule was pale white and homogenous.
Microscopic examination of the larger nodule showed a circumscribed lesion composed of interlacing fascicles of bland spindle cells with interspersed large polygonal cells which had abundant eosinophilic cytoplasm and a paracentral nucleus. No pleomorphism, necrosis, mitoses or atypia was seen. The morphological features were typical of a ganglioneuroma. No features of malignancy and no evidence of metastatic melanoma was seen. The second, smaller nodule showed features of a lymph node with metastatic malignant melanoma.
This case highlights the pitfalls in imaging and the importance of histological examination in the diagnostically straightforward but therapeutically important distinction between benign and malignant neoplasms.

P57

Audit of Departmental Reporting of Colorectal Cancer

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Detailed reporting of colorectal cancer resection specimens is essential in confirming the diagnosis, determining prognosis and assisting clinicians in deciding on the next stage of treatment for the patient. It is, therefore, essential that the information in the report is communicated to the multidisciplinary team in an accurate, understandable and concise manner. The completion of standardised proformas, that contain the core data items, has been demonstrated to facilitate this and their use is strongly recommended by the Royal College of Pathologists.

I audited all free text colorectal cancer reports from 2007 against the core items in the minimum dataset from the Royal College of Pathologists in order to ascertain whether free text reporting was sufficiently detailed in the department.

47 resection specimen reports were reviewed. The areas which were less well reported pertained to the changes introduced to the minimum dataset in September 2007, in particular, macroscopic grading of the plane of resection in anterior resection specimens and microscopic assessment of tumour involvement of the non-peritonealised resection margin. Furthermore, it was found that there were discrepancies in the assignment of the relevant TNM stage and Duke's category.

On the basis of these results it was recommended that a proforma or crib sheet should be kept near the cut-up bench to ensure all the necessary macroscopic details are recorded correctly and that implementation of supplemental proforma reporting would guarantee that the core data items are recorded accurately and in full.

P58

Vascular Malformation with Unusual Morphology in the Caecum

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We report a vascular malformation in the Caecum with unusual microscopic features.

A 15 year old male presented with abdominal pain and intussusception. A right hemicolectomy was performed. The specimen macroscopically revealed a 25mm ulcerated lesion in the Caecum which on slicing showed extension to the subserosa but without perforation. Microscopic examination showed a transmural, somewhat lobular vascular proliferation composed of small calibre vessels without cytological atypia.

This case was referred to paediatric and soft tissue pathologists who agreed to the benign nature of the lesion. However the diagnoses ranged from secondary reactive changes to haemangioma, and a vascular malformation. Following a clinicopathological correlation and review of literature, the features were interpreted as being consistent with a vascular malformation. The patient was discharged and is well to date (1 year post operatively).

Vascular malformations are errors in morphogenesis. Though there are numerous reports in literature, only few have detailed microscopic descriptions. The most common histological feature is dilated vascular channels, either localised to the submucosa or extending transmurally. This case is unique in that it is composed mainly of small calibre vessels which showed a lobular growth pattern. The distribution argued against a lobular capillary haemangioma.

Our literature study shows a general lack of detailed microscopic descriptions of vascular malformations and absence of consistent terminology or classification for such lesions in the gastrointestinal tract, necessitating further research in this area. We highlight the need for detailed histopathological description of all possible such cases which would aid research.

P59

Semi-Quantitative Assessment of Immunohistochemical Staining for Mismatch Repair Proteins in HNPCC

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Introduction: Hereditary Non-Polyposis Colorectal Cancer (HNPCC) is caused by mutations of DNA Mismatch Repair (MMR) Genes. Mutation Carrier Identification is essential as screening reduces mortality. Immunohistochemical (IHC) staining of the MMR proteins is increasingly used, concerns remain regarding sensitivity.

Methods: Tumour sections from 51 MMR Mutation Carriers and 17 controls were stained on an automated platform with antibodies against MLH1, MSH2, MSH6 and PMS2. Staining intensity and percentage positivity were recorded, on 0-3 and 0-4 scales respectively, and multiplied for an overall 0-12 score per slide. ROC curves of staining performance were evaluated. The sensitivity and specificity of each score for each antibody stain was plotted, and optimum cut offs calculated.

Results: The area under the MLH1 ROC curve was 0.885 (95% CI 0.778 – 0.991). The area under the MSH2 ROC curve was 0.817 (95% CI 0.675 – 0.959). For MLH1 staining, a score of 2 or below gives a sensitivity of 94.1% (95% CI 71.3 – 99.9) and a specificity of 88.2% (95% CI 71.3 – 99.9) for identifying MLH1 Mutation Carriers. For MSH2, a score of 6 or below gives a sensitivity of 83.3% (95% CI 58.6 – 96.4) and specificity of 64.0% (95% CI 49.2 – 77.1) for identifying MSH2 Mutation Carriers.

Discussion: This study validates IHC against the largest group of Mutation Carriers to date and supports a Semi-Quantitative Slide Assessment Method.

P60

Tissue Validation of Potential Biomarkers for Prostate Cancer

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Prostate cancer (CaP) is a significant cause of illness and death in Irish males. Marked disease heterogeneity is associated with CaP. Current detection strategies do not detect the disease at an early stage and cannot distinguish aggressive versus non aggressive CaP leading to over-treatment of the disease and associated morbidity. This indicates CaP as an appropriate disease to pursue novel markers for disease detection.

Zinc-α-2-glycoprotein (ZAG), Proteasome Subunit β Type 6 (PSMB-6) and Kininogen-1 (KNG-1) were found to be upregulated in the serum of CaP patients following proteomic analysis. The purpose of this study was to determine if ZAG, PSMB-6 and KNG-1 were also upregulated in prostatic tumour epithelial cells in the tissue of CaP patients.
Immunohistochemical analysis was performed on a 50 case CaP tissue microarray in which areas of Gleason grade (G) 3, 4, 5 and benign prostatic hyperplasia (BPH) were sampled for each case where available.

ZAG expression in epithelial cells of the prostate was inversely associated with malignancy. PSMB-6 was not expressed in prostate epithelium. However, strong PSMB-6 expression was noted in stromal and inflammatory cells around BPH and tumour nests with increasing intensity around higher grade tumours (G5). There was little or no KNG-1 expression in prostate epithelium.

These preliminary results suggest ZAG and PSMB-6 as possible biomarkers in assisting CaP diagnosis and prognosis.

P61

A Self-directed Learning Package in Bladder Cancer Pathology using Virtual Microscopy

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Recognition, understanding and interpretation of morphological patterns are important skills for medical students. This study developed an on-line virtual slide-based course on bladder cancer histopathology. One hundred and twenty slides of bladder tissue/cytology were digitally scanned using an Aperio Scanscope and hosted online using PathXL™ as a virtual slide content management system. A range of lesions were identified, tabulated and organized into 3 progressive educational levels. Lectures corresponding to each level were delivered by a pathologist. Special stains or immunocytochemistry were used to highlight or discriminate important features. Key features were annotated for self directed learning. Multiple choice question (MCQ) assessments tested competency at each of three levels. Level 1 covered normal cells, layers and related structures typical of bladder biopsies; Level 2 non neoplastic lesions; namely inflammatory and pre-neoplastic and Level 3 malignant lesions, staging, grading, metastasis and anti-tumour immunity. A final assessment containing 30 questions was used to assess understanding of morphology. A Case Study assessment was employed to measure understanding of clinicopathologic correlations. Students completed a questionnaire at the end of the course.

Eleven questionnaires were returned. Nine students reported that the annotated images enhanced their ability to recognise morphological features; seven that virtual microscopy was complimentary, but should not replace lectures; seven that their experience with PathXL™ increased their interest in pathology; and ten that they logged on more than five times to view annotated images. Virtual microscopy is a valuable adjunct to traditional teaching methods in undergraduate pathology courses.

P62

Monodermal Testicular Teratoma with Predominant Cartilaginous Differentiation

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Mature teratomas are rare in the testis, comprising only 2.7 -7% of testicular tumours. Usually derivatives of all three germ layers are encountered, commonly neural tissue, cartilage and different types of epithelium. However, a few show differentiation of one germ layer only. We present a monodermal teratoma showing a predominant cartilaginous differentiation in a 51-year-old man. Macroscopically there was a well-circumscribed glistening white tumour mass confined to the testis. The tumour was composed almost exclusively of well-formed mature cartilage with very tiny collections of S100 positive cells of neural crest origin. Our initial differential diagnosis was a primary testicular chondroma, but due to our extensive sampling of the tumour, a very minor secondary component of benign neural crest cells were identified. Hence, we consider this to be exclusively monodermal teratoma with predominant cartilaginous differentiation. There are two previous case reports of pure cartilaginous teratoma. It may be possible that these reports have not identified such minor secondary components.
Pathologists must be aware that regardless of their appearance, post pubertal teratomas have a higher incidence of subsequent metastasis and the cellular composition of metastases might differ from the primary tumour.

P63

TRA-1-60 stem cell marker is expressed in human foetal and adult kidney and upregulated upon tubulointerstitial damage

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The tubular epithelium of the kidney is susceptible to injury from ischemia, nephrotoxins, inflammation and immune disorders, but has the ability to recover from insult. Understanding the cellular and molecular basis of nephron repair is critical for the design of new therapeutic approaches. There is evidence that intrarenal epithelial cells can participate in repair of injured tubules but it is not clear whether all cells have equal regeneration potential or whether a resident population of progenitor or stem cells exists. TRA-1-60 epitope expression is linked to pluripotency in human ES cells and is lost upon differentiation. We studied distribution of TRA-1-60 epitope on serial sections of human foetal and adult kidneys. In foetal kidneys between CS21 and 10 weeks of gestation it was abundantly expressed on the apical surface of ureteric bud and collecting duct epithelium. In the cortex of adult kidney we found small populations of positive cells, which were confined to tubules expressing epithelial membrane antigen (EMA) that are distal to the proximal tubule. In tubulointerstitial injury there was a dramatic increase in TRA-1-60 staining, still confined to cells in EMA expressing structures. Dual staining showed that TRA-1-60 positive cells co-expressed transcription factor Pax-2 and proliferation marker Ki-67. Collectively these observations show that human ES cell marker TRA-1-60 is expressed in epithelia of human foetal and adult kidney and suggest that in adult kidney it may identify a population of cells contributing to tubular repair.

P64

Expression pattern of the activated leucocyte cell adhesion molecule ALCAM/CD166 as a diagnostic and prognostic marker in endometrial cancer

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ALCAM (CD166) is an immunoglobulin superfamily cell adhesion molecule and has been implicated in tumourigenesis and tumour progression in melanoma, prostate and breast cancer. Endometrial carcinoma is the most frequent malignancy of the female genital tract. The present study was designed to investigate the expression pattern of ALCAM in the normal human endometrium and in endometrial carcinomas.
In the present study, immunohistochemistry and western blotting were performed on a series of 20 normal samples, 15 hyperplasias and 40 endometrial carcinomas to investigate the expression pattern and cell-type specific localization of ALCAM and to correlate it with clinico-pathological data.
Strong ALCAM expression with a consistent cytoplasmic localization was observed in 80% of normal samples of the proliferative and secretory phase (score 8-12). Most of the hyperplasias showed the same result. Moderate (score 4-7) cytoplasmic and membranous ALCAM expression could be observed in 50% of the low grade endometrioid carcinomas. With increasing malignancy grade, low ALCAM expression or complete loss could be observed. Down-regulation (score 0-3) occurred preferentially in 40% of the analyzed high grade endometrioid carcinomas as well as in serous and clear cell carcinomas.

Our data suggest that ALCAM expression is disturbed in endometrial carcinoma. At present, we can only speculate about the molecular mechanisms underlying our results. The expression pattern of ALCAM in endometrial tissue indicates that it might play a role in the pathogenesis of endometrial cancer and seems to be useful as an independent diagnostic and prognostic marker for such lesions.

P65

Concordance of grade in endometrial adenocarcinomas between biopsy and hysterectomy specimens

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Aims: Compare concordance when grading endometrial carcinoma in biopsy and hysterectomy specimens and assess inter-observer variability in grading. In addition, our local practice was compared with the available literature.

Standards: Concordance of FIGO grade of endometrial adenocarcinomas in biopsy and hysterectomy specimens. J Mitchard, L Hirschowitz. Histopathology 2003, 42, 372-378.

Methods: A retrospective audit was conducted within our pathology department. Data was collected from the Trust Pathology database from September 2006 to September 2007 on the following criteria: type of biopsy specimen, type of carcinoma in biopsy and hysterectomy specimens, grade of both samples, type of hysterectomy specimen and reporting pathologists of the specimens. Data was also collected on whether samples were MDM and peer-reviewed. Any changes in grade were recorded as a consequence of review. Our results were compared with the available literature.

Results: The overall concordance between the hysterectomy and biopsy samples was 81%. 4/58 biopsies were low grade, but were all upgraded on the hysterectomy specimen, resulting in 0% concordance for grade 1 samples. 51/58 biopsies were high grade, with grade 2 samples showing 90% concordance, and 77% concordance for grade 3 specimens. Biopsies revealing other subtypes had 100% concordance. There was low inter-observer variability with an overall concordance of 78%.

Conclusions: The concordance of grading within our department was high for high grade specimens but was low for low grade samples. This is consistent with current literature and has potential implications for patient management.

P66

Ruptured Tubal Hydatidiform Mole

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Background: Ruptured ectopic gestation is a life threatening medical emergency and an important cause of maternal mortality especially in developing countries. However, the occurrence of hydatidiform mole in ruptured ectopic pregnancy is uncommon.

Method: A consecutive analysis of patients with hydatidiform mole in ruptured tubal gestation over an 8-year period in a tertiary hospital. The H& E stained histology slides of patients were reviewed and only cases which fulfilled the diagnostic criteria of hydatidiform mole are presented.

Result: Of a total of 93 females with ectopic gestations, only five had ruptured tubal hydatidiform mole. Their ages ranged from 20-37years. They all presented with acute abdominal symptoms (abdominal pain associated with tenderness, vomiting and varying periods of amenorrhoea) which necessitated emergency surgical intervention. Intraoperative findings revealed ruptured and or leaking tubal gestation. One of the females also had multiple uterine fibroids. The excised tissue specimens sent for histology showed hydatidiform mole characterized by circumferential trophoblastic proliferation, hydropic degeneration and stromal karyohexis. Patients' serial human chorionic gonadotrophin (HCG) levels were monitored before discharge.

Conclusion: Ruptured tubal hydatidiform mole is uncommon and less than 50 cases have been reported in literature. Strict histologic criteria are important in diagnosis and serial HCG levels must be monitored in individual patients to forstall development of malignant trophoblastic disease especially in patients in developing countries who are often lost to follow-up.

P67

Low Grade Endometrial Stromal Sarcoma with Epithelial Differentiation Mimicking Endometriosis

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Low grade endometrial stromal sarcoma may be a difficult tumour to diagnose especially on curetted specimens. The tumour cells closely resemble normal endometrial stromal cells with minimal nuclear atypia and mitotic activity. The site of occurrence in the uterine corpus is a useful suggestion for such tumour type, but when present at extra uterine sites it maybe more difficult to recognise. In addition a variant with epithelial differentiation has been recently described which mimics both endometriosis and low grade adenosarcoma. A characteristic translocation t (7; 17) (p15; q21) resulting in fusion of JAZF1 / JJAZ1 genes has been reported in classic low grade endometrial stromal sarcoma.

Here we describe a 52 year old female who presented with a pelvic mass showing very minimal cytological atypia mimicking endometriosis clinically and histologically.Several curetted specimens were interpreted as endometriosis. The ultimate diagnosis of Low grade Endometrial Stromal sarcoma with epithelial differentiation was possible on hysterectomy specimen only. Here we also discuss the differential diagnosis with other benign/ low grade spindle cell lesions of the uterus and the possible role of t (7; 17) in confirming the histological diagnosis.

P68

Audit of VIN Histopathology Reporting

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Careful reporting of vulval biopsy specimens is important for determining the management, prognosis and follow up of patients with vulval intraepithelial neoplasia (VIN). The type and grade of VIN, assessment of margins and minimum distance from the resection margins, where applicable, and the presence or absence of invasion should be recorded for VIN histopathology reporting. The aim of this audit was to determine whether all reports fulfil these minimum criteria. This audit was carried out retrospectively by using a computer based search to retrieve the reports of all VIN specimens over a period from January 1991 to June 2008: cases coded as invasive carcinoma were excluded. The total number of VIN histopathology reports was 143. Only 2.8% (4/143) of the reports fulfilled the above criteria. The type of VIN was mentioned in only 4.2% (6/143) of reports. All reports mentioned the grade of VIN. Seventy nine (55.2%) reports commented on the completeness of excision but 43% (34/79) did not mention the minimum distance from the resection margins. 76.2% (109/143) of the reports commented on the absence of invasion. In conclusion, there is a need to improve the content of reports on biopsies containing VIN lesions. In particular, with increasing recognition of differentiated and undifferentiated VIN, specific identification of the type of VIN is important if these entities are to be properly understood.

P69

Ovarian Yolk Sac Tumour in a Seventy Year Old Woman

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Ovarian yolk sac tumours (endodermal sinus tumours) are malignant germ cell neoplasms which as described by Teilum are thought to arise from totipotential cells which undergo selective differentiation towards the yolk sac or vitelline duct. They usually occur in children or young adults and are rare after the age of 45 years. We present here a case of an ovarian yolk sac tumour occurring in a 70 year old female.

The ovary contained a malignant neoplasm with solid and microcystic areas, foci of necrosis and frequent mitoses. Peri-vascular structures with appearances similar to Schiller-Duval bodies were present. The cells were strongly positive for AFP, pancytokeratin MNF116 and focally for inhibin. The appearances were of a tumour showing extensive yolk sac differentiation.

Rare cases of ovarian yolk sac tumours have been described in post menopausal women. They occur in association with ovarian surface epithelial – stromal tumours and are of uncertain histogenesis. It is postulated that the mechanism in such cases is different from that of yolk sac tumour in the younger age group. Rather than arising from germ cells, there is a process neometaplasia whereby somatic carcinomas acquire germ cell differentiation. The neoplastic cells are therefore transformed cells of somatic origin.

P70

Is a selective approach to gallbladder histopathology justifiable?

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Introduction: Gallbladder specimens are routinely sent for histological examination regardless of their macroscopic appearance. This audit aims to find out if a selective approach to processing these specimens can be adopted based on the macroscopical appearance.

Standards: The results of the audit were compared with an audit undertaken in a Blackpool Hospital.

Methods: A search was conducted for all gallbladder specimens processed by the histopathology laboratory between 2003-2008. A further search was undertaken for a histological diagnosis of dysplaisa and carcinoma.

Results: The total number of gallbladder specimens was 4145. Two cases (0.048%) of primary adenocarcinoma of the gallbladder were detected with both cases showing a tumour macroscopically. One case showed focal high-grade dysplasia. Fourteen cases showed low-grade dysplasia. Four cases showed cytological atypia. In one case the dysplasia was involving the cystic duct and in 2 cases the surgical margin was not identified.

Discussion:

The number of specimens received is substantial and contributed greatly to the workload of the department. It is estimated that the cost of processing a single gallbladder specimen is £18 (not including salaries), putting the cost of processing the 4145 specimens at £74,610. We can conclude from the results that it is unlikely that a frank tumour would be missed however, cases of dysplasia would prove to be more difficult to assess at cut-up. Taking this into consideration together with the current climate of increased litigations, it is recommended that gallbladder specimen histology should continue to be undertaken.

P71

Expression of Trefoil Factor Family (TFF) Peptides and Gastrokine (GKN)-2 in Normal and Diseased Human Pancreas

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Trefoil factor family (TFF) peptides TFF1, 2 and 3 have roles in restitution following mucosal injury in the gastrointestinal tract. Elsewhere, expression is seen in mucinous epithelia. In the pancreas, TFF1 and 2 are up-regulated in chronic pancreatitis (CP) and PanIN. Reports have suggested TFF3 to be expressed at low levels in islets and act as a β-cell mitogen *in vitro*. We explored expression of TFFs in normal and diseased human pancreas. Normal, chronic pancreatitis, pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine tumours were studied. Isotopic in-situ hybridization was performed using 35S-labelled riboprobes complimentary to hTFF1, 2 and 3 and TFF2-binding peptide blottin (GKN-2) mRNAs. Probe binding was revealed by autoradiography. Immunohistochemistry was performed for TFF3. In normal pancreas, rare expression of all TFF mRNAs was seen in interlobular ducts. Reactive ducts in CP showed moderate expression of all three TFFs, but not GKN2 mRNAs. Incidental PanIN occurred in 8 blocks, of which 4 exhibited strong TFF1 and 2 and weak TFF3 expression and 1 weak GKN2 expression. Strong expression of all TFFs was seen in well-differentiated PDAC, with weaker expression in poorly-differentiated areas. Weak TFF3 expression was seen rarely in islets. TFF3 immunostaining revealed discordant, strong staining in normal islets as well as concordant staining in other areas. Neuroendocrine tumours showed no expression.
In summary we found mRNA expression of all TFFs in normal interlobular ducts with intensification in CP and increased expression of all three TFFs in well-differentiated PDAC.

P72

Plasmacytoid Dendritic Cells (PDC) in B-Cell Post-Transplant Lymphoproliferative Disorders (B-PTLD), HIV-Associated B-Cell Lymphomas and Immune Competent Diffuse Large B-Cell Lymphomas (IC-DLBCL)

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Background: Post-transplant lymphoproliferative disorders (PTLDs) are a group of lymphoproliferative disorders that develop in the background of immune suppression. Plasmacytoid dendritic cells (PDCs) that home close to the High endothelial venules in the lymph nodes secrete type I Interferon which stimulates the cytotoxic function of CD8+ T cells and NK cells.

Purpose of the study: We intended to investigate whether B-PTLDs and HIV-associated B-cell lymphomas significantly differ from IC-DLBCL with respect to infiltration by PDCs and to correlate the impact of Epstein Bar Virus (EBV) association on PDC infiltration.

Method and description of the results: We carried out immunohistochemistry for expression of CD123 and BDCA2 and In-Situ hybridization for EBV-EBER on tissue microarray slides prepared from 19 cases of B-PTLD, 14 HIV-associated B-cell lymphomas (7 Burkitt lymphoma, 7 Diffuse large B-cell lymphoma (DLBCL)), and 40 Cases of Immunocompetent (IC)-DLBCLs. Cells positive for CD123 and BDCA2 were counted and expressed as cells/mm2. B-PTLD had significantly higher CD123+ cells and BDCA-2+ cells as compared to IC-DLBCL (p=0.02 each). Among the B-PTLDs cases, 14 were EBV-associated and 5 were EBV-negative. EBV-negative PTLDs had significantly higher numbers of CD123+ and BDCA-2+ cells as compared to EBV-positive PTLDs (p=0.09 and 0.016 respectively).

Conclusion: Tissue samples from B-PTLD (especially EBV-negative) have significantly higher numbers of plasmacytoid dendritic cells (PDCs) as compared to immunocompetent DLBCLs.

P73

Profound EBV driven lymphoid hyperplasia of rectal tonsil mimicking high grade lymphoma

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A 38 year old immunocompetent male presented with acute rectal bleeding and at endoscopy there was ulceration of the anterior rectum. Rectal biopsy showed ulcer slough with an underlying infiltrate composed of large pleomorphic lymphoid cells, many with prominent nucleoli. There were admixed eosinophils and small lymphocytes, but classical Reed-Sternberg cells were absent. Immunohistochemistry showed that these atypical lymphoid cells expressed CD30, and that many were positive with EBER in-situ hybridisation. The cells were negative with CD20, CD3, CD15, CD45, CD79a, ALK-1, Bob-1 and IgM, and showed weak positive staining with Oct-2 and PAX-5. PCR demonstrated a polyclonal picture for IgH, Igκ and TCRγ. There was no evidence of systemic disease and PET scan showed extensive diffuse activity localised to the rectal mucosa.

The features were those of an EBV-driven lymphoid hyperplasia of the rectal tonsil, although a diagnosis of high grade lymphoma was initially considered. Whilst the palatine tonsil is well-known to show ulceration and prominent lymphoid proliferation in infectious mononucleosis, similar EBV-related changes in the anorectal tonsil are poorly described.

P74

Bone marrow biopsy involvement by Lymphoma

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In order to evaluate the morphological features of bone marrow involvement by Non-Hodgkin's and Hodgkin's lymphoma, 450 consecutive cases of trephine biopsies involved by lymphoma were reviewed to assess percentage of marrow involvement, pattern of involvement, presence of associated changes like reactive germinal centres, stromal fibrosis, granulomatous response, neoplastic follicles, and whether there was discordance with subtype or grade of lymphoma seen in the related lymph node biopsy, where applicable. Correlation with immunohistochemical, aspirate, flow cytometric and molecular findings was made wherever possible.

Amongst other findings, a paratrabecular pattern of involvement was commonest overall and was seen in 85% of follicular lymphomas, whereas an interstitial pattern of infiltration was most frequently seen in lymphoplasmacytic lymphoma (68%). Intrasinusoidal infiltration was most often seen in cases of splenic marginal zone lymphoma. High grade lymphomas (Diffuse large B cell lymphoma and Burkitts) which invoved the marrow were more likely to have extensive infiltration often with a diffuse pattern. Bone marrow necrosis was also seen most often in diffuse large B-cell lymphoma (24% of cases) and Burkitt's lymphomas (22%). 8% of follicular lymphomas showed the presence of neoplastic germinal centers and reactive germinal centers were seen most commonly in marginal zone lymphomas. A granulomatous response was most often seen in Hodgkin's lymphoma.

Analysis of the results showed that most subtypes of lymphoma exhibited characteristic patterns of marrow involvement which may be helpful in suggesting the likely diagnosis. We have also correlated the histological findings with other haematological data.

P75

To B or not to B: T Cell Lymphoma with Aberrant CD20 Expression

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INTRODUCTION: Haematological malignancies are currently classified by the WHO according to lineage, with stratification of non-Hodgkin lymphomas into B cell neoplasms, and T and NK cell neoplasms. CD20 and CD3 immunostains are routinely used to identify B and T cell lymphomas respectively, with the use of additional immunomarkers where necessary.

CASE REPORT: We report a case of an 84-year -old male with a 6 week history of a left neck mass with associated localised pruritus. A skin ellipse was removed from the area which showed extensive replacement of the dermis and subcutaneous tissue by a lymphocytic infiltrate which involved skeletal muscle. Tumour cells showed a T helper cell phenotype (CD3, CD4, CD5 positive) but were also positive for B cell markers CD20, Bcl6 and Mum1. PCR of DNA extracted from paraffin embedded material was positive for clonal T cell receptor gene rearrangements but negative for clonal immunoglobulin gene rearrangement supporting a diagnosis of T cell lymphoma with aberrant CD20 positivity. Treatment was commenced with CEOP-R chemotherapy and after 5 cycles there has been a dramatic clinical response with resolution of the neck mass.

DISCUSSION: Our case is one of only a small number of reported cases of T cell lymphoma coexpressing CD20 and illustrates a potential pitfall in diagnosis. It again raises the question of whether this is an aberration of antigen expression as a consequence of malignant transformation, or whether these unusual cases represent malignant transformation of a normal population of T lymphocytes which coexpress CD20.

P76

Audit of Bone Marrow Trephine Specimen and Processing Quality in a Regionalised Haemato-oncology Service

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We surveyed bone marrow trephine collection and processing practices among a regional network of haematologists linked to a specialist haematopathology service. Within this network, trephine specimens are processed in 14 hospitals, a proportion being referred centrally for review. We identified the extent of bone marrow trephine practice at each hospital, grade of staff performing biopsies, needles used and methods for fixation and decalcification. Wide variations were found, including use of 7 needle types of differing gauge, and 5 decalcification protocols. We then performed a retrospective audit of trephine quality using sections cut and stained in the referral laboratory. We used published and locally agreed standards of specimen adequacy and assessed quality of a range of stains. Generally adequate quality was found but with wide variation and sub-standard results for some hospitals. Guidance was proposed, accommodating different local priorities for turnaround and preferred stains. The results were presented to participating haematologists and to technical staff at the referral laboratory. The audit was repeated after 3 years. Specimen quality had been maintained or improved in almost all hospitals. Staining quality in the referral laboratory also improved, reflecting minor technical changes that increased tolerance of stains for varying fixation/decalcification methods. One hospital changed its decalcification method between audit rounds and one more has done so since the second round. Overall, raising awareness of variation associated with collection and decalcification methods led to improvements without need to impose a single approach throughout the network.

P77

Prospective Evaluation of new CD19, CD30 and CD7 Antibodies for Fixed Tissue Immunohistology

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In our laboratory handling numerous, diverse haemato-oncology specimens, we evaluated 3 new monoclonal antibodies prospectively. For 3 months, new anti-CD19 (BTS1E) was added to our "basic lymphoid" immunostaining panel alongside CD20 and CD79a, new anti-CD30 (JCM182) to our "Hodgkin's panel" alongside BerH2 and new anti-CD7 (LP15) to our "T cell panel" alongside existing clone CD7-272. Sections immunostained with new and established antibodies were scored as cases were reported. For CD19, 110 cases permitted analysis of results according to referring hospital, tissue and diagnosis. Overall, BTS1E gave weaker staining than CD20 or CD79a, not significantly influenced by processing variations although decalcification of bone marrow was adverse. However, results in many preparations revealed a wider spectrum of B cells than CD20 and were often easier to assess than CD79a. CD19 immunostaining offers comparability with fluorescent immunophenotyping and provides an additional B cell marker for complex lymphoid proliferations and those with down-regulated CD20. JCM182 out-performed BerH2 in almost all 26 cases stained. Interpretation was straightfoward although large perifollicular CD30+ve cells are more apparent with JCM182. For CD7, our study included sufficient cases (7) only for anecdotal comment. However, LP15 performed well, giving higher scores than CD7-272 and no spurious nucleolar staining. Our strategy provided a simple and cost-effective evaluation of CD19-BTS1E. It was less successful for CD30-JCM182 and CD7-LP15. Retrospective analysis of pre-selected specimens remains the preferred approach for evaluating antibodies applicable to a low proportion of routine cases.

P78

The Grey Zone Lymphoma Post-transplantation

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Introduction: The distinction between a nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL) and a T cell/histiocyte rich B-cell lymphoma (T/HRBCL) is difficult but has very important therapeutic implications. Whilst immunohistochemistry (IHC) usually resolves this, there is a subset with substantial overlap making it virtually impossible to differentiate these conditions - this has been referred to as the 'grey zone'. We present such a case further complicated by the presence of an immunosuppressed environment. Case history: A 33-year old male presented with cervical lymphadenopathy 5 years after liver transplant for autoimmune hepatitis. An 18mm node was excised. Histology showed diffuse architectural effacement with vaguely nodular areas comprising L & H type cells. Typical Reed-Sternberg cells were also present. The background showed small lymphocytes, histiocytes and occasional eosinophils but no epithelioid histiocytes. IHC excluded classical Hodgkin's lymphoma and anaplastic large cell lymphoma. EBV was negative thereby excluding EBV-positive post-transplant lymphoproliferative disease (PTLD). IHC features pointed towards NLPHL as well as T/HRBCL. Discussion: NLPHL with T cell-rich nodules has recently been described. The stage at presentation and frequency of B symptoms is similar to T/HRBCL but if stage is matched, the clinical outcome is similar to NLPHL. Our case fulfilled all the criteria for this entity. As a subset of EBV-negative PTLD may behave as EBV-positive PTLD, in view of the limited stage, our patient was treated with rituximab and reduction in immunosuppression resulting in complete remission.

P79

A Study Evaluating the Reporting and Correlation of Bone Marrow Biopsy (BMB) Versus Flow Cytometry (FC) in Lymphoproliferative Disease (LPD)

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Introduction: Bone marrow (BM) investigation is vital in LPD staging as it indicates stage IV disease requiring more intensive treatment. The current "gold standard" is BMB with immunocytochemistry. BMB assesses the amount, cytomorphology, immunophenotype and architecture of LPD. FC quantifies a cell population by detecting abnormal antigen coexpression.
Aims: 1. to investigate the correlation of FC versus BMB in LPD. 2. To identify the role and limitations of FC as a tool in the diagnosis and staging of LPD. 3. to contribute to integrated reporting of haemato-oncological diseases in our hospital.
Methods: We retrieved BMB reports involved by LPD from April 2007-April 2008 and stratified them according to histological diagnoses. Their FC results were retrieved from ULTRA database. These were compared to investigate inconsistencies and to see whether some LPDs showed a better correlation than others.
Results: 151/367 BMBs showed LPD. FC was available for 147 cases. Concordance was seen in 110 (74.8%) and 31 (21.1) had positive BMB and negative FC. Six (4.1%) had negative BMB with positive FC where FC detected very low level involvement by a skewed kappa-lambda ratio. There was a huge discrepancy in plasmacytic percentages but FC determined monoclonality of low level infiltrates.
Conclusion: FC is vital in staging LPD but is not useful in Hodgkin's lymphoma or T/histiocyte rich B-cell lymphoma. Negative FC in follicular lymphoma and diffuse large B cell lymphoma does not exclude BM involvement.

P80

HHV-8-positive endothelial proliferations: reports of five cases and discussion of the minimum diagnostic criteria for Kaposi's Sarcoma

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Kaposi's sarcoma (KS) is a vascular neoplasm that arises in association with HHV-8 infection, generally, but not exclusively, in HIV+ patients. We describe five HHV-8+ endothelial proliferations in HIV+ patients that fail to efface tissue architecture and we consider the minimum morphological/ immunophenotypical features required for a diagnosis of KS.

We present the case of a 40year old HIV+ man, admitted with fever, who died 10 days later with presumptive diagnoses of Listeria monocytogenes meningitis and active chronic hepatitis B, although no autopsy was performed, due to the risk of infection. A lymph node biopsy, performed to investigate widespread low volume lymphadenopathy, demonstrated follicular lysis, in keeping with HIV, and focally prominent sinus endothelial proliferation that was HHV-8+ CD31+ CD34+ LYVE-1+ and DC-SIGN/ DC-SIGNR- and did not efface the lymph node architecture or extend beyond the lymph node capsule. A liver biopsy failed to demonstrate hepatic Kaposi's sarcoma.

We describe a further four cases of HHV-8+ endothelial proliferation, occurring in HIV+ male patients (three in the skin and one in liver), that fail to efface the architecture of the tissue and do not show significant dissection of collagen.
These cases raise questions about whether all HHV-8+ endothelial proliferations should be regarded as Kaposi's sarcoma. Philosophically, one might imagine a biological continuum between HHV-8 infected endothelial cells and an obviously malignant neoplasm. No clear minimum diagnostic criteria for Kaposi's sarcoma are currently available. We discuss possible diagnostic criteria that might be used.

P81

Two Cases of Histiocytic Necrotising Lymphadenitis without Granulocytic Infiltration with some Atypical Features – An Expanding Spectrum

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The first case was a 35 year old lady who presented with an isolated enlarged inguinal lymph node which showed expansion of the paracortex due to patchy necrosis with nuclear debris, histiocytic aggregates (myeloperoxidase positive) and admixed atypical CD8 and CD56 positive lymphoid cells. CD56 staining was undertaken on two cases of Kikuchi's disease with typical clinical presentation that showed only rare CD56 positive cells. Though a predominance of CD8 positive lymphocytes is known, CD56 expression has not been reported in Kikuchi's disease. In view of lymphoma being included in the possible differential diagnosis, it is useful to know the immunoprofile in some atypical cases. The patient is well five months post initial biopsy.

The second case was that of a 34 year old male with a solitary submental lymph node and bilateral malar skin rash. Morphological examination confirmed necrotising histiocytic lymphadenitis with the histiocytes staining for myeloperoxidase. In addition to atypical CD8 positive lymphocytes, there were atypical B-blasts (polytypic) in the paracortex. There was no periadenitis. Serology for lupus erythematosus was negative. A skin biopsy from the cheek showed necrotic epidermis with a mixed, predominantly histiocytic, inflammatory infiltrate in the dermis alongwith fibrinoid necrosis in a dermal vessel. Immunoflouroscence showed positive staining for IgM, C3 and Fibrinogen. Since the initial description by Kikuchi in 1972, there have been rare reports of skin involvement and of temporal association with lupus lymphadenitis. This case highlights the limitations of histological examination and the importance of follow-up in diagnosis.

P82

Detection of Hypermethylation of Tumour Suppressor Genes in Ocular Adnexal Lymphoma Using Multiplex Ligation-Dependent Probe Amplification

H Ma[1], ACY Lo[2], DSH Wong[1,2], BE Damato[1], SE Coupland[1]
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Ocular adnexal lymphoma (OAL) occur in the orbit, lacrimal gland and drainage system, conjunctiva and eyelid. OAL comprise 8% of all extranodal non-Hodgkin lymphomas. Extranodal marginal zone B-cell lymphoma (EMZL) is the largest subtype of OAL, accounting for 60-70% of all OAL. Follicular and diffuse large B-cell lymphomas each accounts for approximately 10% of OAL. We examined the methylation status of multiple tumour suppressor genes (TSGs) in OAL.
Formalin-fixed paraffin-embedded OAL, including both EMZL and non-EMZL OALs, were examined. DNA was extracted and purified from paraffin blocks, and only those containing intact DNA were selected for subsequent analysis using methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) (29 EMZL and 25 non-EMZL OALs). ME001B and ME002 MS-MLPA kits were used for detecting CpG methylation in up to 35 candidate TSGs in total. Reactive lymphoid hyperplasia cases were used as references for the MLPA analysis.
CpG hypermethylation in patient samples was determined when statistical significance of standard error > 0.1 as compared to the reference samples. Eight tumour suppressor genes including CDH13, WT1, MSH6, IGSF4, DAPK1, ESR1, p14-ARF and RAR-beta have shown frequent hypermethylation in 65% of the 29 EMZL OALs. Similar CpG hypermethylation patterns were observed in non-EMZL OALs. Validation of this data is currently in progress using pyrosequencing. Correlation of this data with clinical presentation and follow-up may reveal epigenetic markers of prognostic value in these OAL.

P83

Multiplex-Ligation Probe Amplification of Choroidal Melanoma

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[1]*University of Liverpool,* [2]*Liverpool Women's Hospital*

Choroidal melanoma is fatal in 50% of patients, because of hepatic metastasis. The most important predictor is monosomy 3. Since 1999, we have tested this chromosome with fluorescence in situ hybrization (FISH). Our audit of 355 cases revealed deaths despite normal FISH, because our centromeric probe missed partial deletions. In 2007, we started using multiplex-ligation probe amplification (MLPA), which simultaneously analyzes 30 loci on chromosomes 1p, 3, 6 and 8. MLPA is more informative and less expensive than FISH, requiring smaller samples, which can be formalin-fixed and paraffin-embedded.

Between January 2007 and July 2008, we tested168 choroidal melanomas with MLPA. The patients had a mean age of 61 years. The tumours had a median diameter of 14.4 mm and a median height of 6.5 mm. The primary treatment was: enucleation (79), radiotherapy (60); local resection (27) and photodynamic therapy (2). Histology was possible in 160 cases. FISH was attempted in 93 cases and was successful in 69. Monosomy 3 with FISH was confirmed by MLPA, which also demonstrated loss of 1p and 6q and gains in 8q. MLPA also revealed partial deletions of chromosome 3 that were missed with FISH. Several tumours showed equivocal MLPA results, which FISH showed to be due to tumour heterogeneity.

MLPA produces more information than FISH and requires smaller samples. In addition it identifies partial deletions missed with centromeric FISH probes. FISH is required in some cases to determine whether equivocal MLPA results are caused by tumour heterogeneity.

P84

Immune Cell Subsets in Necrotizing Fasciitis: An Immunohistochemical Analysis

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Background: Neutrophilic inflammation is a common diagnostic feature of necrotizing fasciitis (NF). Current thoughts concerning pathogenesis of this disorder have emphasized the importance of T-lymphocytes and other immune cells in the pathways leading to injury, specifically superantigen-mediated toxin release by bacterial antigens. In order to assess the anatomic basis of immune activation, immune subsets of NF were enumerated in situ.

Design: The records of the Massachusetts General Hospital Pathology Department were searched from 2004-2007 for the diagnostic term "necrotizing fasciitis" in soft tissue specimens. We performed immunohistochemistry to analyze the cells: T-lymphocytes (CD3), histiocytes (CD68), Langerhans cells (CD1a), dendritic cells (Factor XIIIa), and endothelium (CD31). Cells were enumerated by consensus conference as negative, 1+ (<10%), 2+ (10-50%), and 3+ (>50%) staining of the mononuclear infiltrate.

Results: CD3+ T-lymphocytes were present in all cases, and they accounted for 10% of the mononuclear cell infiltrates in 5/13 patients. CD68+ macrophages were present in all cases, and accounted for >50% of the infiltrate in 10/13. Factor XIIIa+ cells accounted for greater than 10% of cells in 10/13. CD1a+ cells were present in 3/13 cases where they accounted for <10% of cells. CD31 revealed negative to <10% staining in 13/13 cases.

Conclusion: Mononuclear cell inflammation was found to be a common feature of NF. The presence of substantial numbers of CD3+ lymphocytes and accessory cells in the early lesions of NF support the current notions with respect to its pathogenesis.

P85

Mammary-Type Myofibroblastoma- Case Report

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Myofibroblastoma is a benign myofibroblastic tumour of the breast. It occurs in a wide age group but most often in the sixth and eight decades. Myofibroblastoma typically occurs as a solitary, mobile, slowly growing lesion, most often present for several months. It is generally a well circumscribed and composed of fascicles of spindle cells having features of myofibroblasts, with intervening hyalinized collagenous stroma and a variably prominent component of adipose tissue. The spindle cells characteristically express both CD34 and desmin. The standard treatment is marginal excision.Extra mammary myofibroblastoma is a rare benign spindle cell lesion resembling the breast counterpart but occurring in extramammary sites like groin, trunk and vagina. We report an extra mammary-type myofibroblastoma in the inguinal region of a 40-year-old female patient. The tumour was morphologically and immunohistochemically identical to myofibroblastoma of breast. Its occurrence at this site raises a speculation that these lesions might be arising along the embryonic milk line.

P86

Involvement of FGFR/RAS/MAPK Pathway in Non Skull Base Chordoma

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Little is known about chordoma pathogenesis. We previously showed that transcription factors, brachyury and ETS2 are highly expressed in chordomas. In lower vertebrates brachyury is regulated by FGFR/RAS/MAPK/ETS2. The aim of this study was to investigate the role of FGFR/RAS/MAPK/ETS2 in chordoma pathogenesis. Methods: A tissue microarray with 50 chordomas was examined for expression of FGFR1-FGFR4 by IHC and results validated by western blot analysis for phosphorylated FRS2-alpha, a hallmark for FGFR activation. Interphase FISH was employed to investigate brachyury amplification and ETS2 amplification and/or re-arrangement. 16 chordomas with available frozen tissue were examined for the common mutations in K-RAS (exons 2, 3), B-RAF (exons 11, 15), and the four FGFRs (FGFR1: exons 3, 6, 11, 12, 14; FGFR2: 5, 7, 11, 12; FGFR3: 2, 4, 5, 6, 7, 8, 9; and FGFR4: 7, 9, 16). Finally, brachyury and its promoter were screened for mutations. Results: 70% of chordomas showed immune reactivity for at least one of the four FGFRs. Western blot analysis of 8 selected cases validated the presence of phosphorylated FRS2-alpha. 6% of cases showed a minor gain of brachyury. There was no evidence of ETS2 amplification or gene rearrangement. No mutations were detected in any of the screened FGFR genes, in the brachyury gene and its promoter. Conclusion: FGFR is activated in chordoma. No mutations were detected in the genes analysed in the FGFR/RAS/MAPK/ETS2 which explains the tumourigenesis of chordoma.

P87

Expression of Large and Small Tenascin C Splice Isoforms in Human Meniscus

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Whilst the investigation of new roles for Tenascin C in matrix turnover, cell adhesion and the pathogenesis of various disease states has continued to progress in recent years, the expression of this molecule in human meniscus and contribution to the development of tissue changes associated with degenerative joint disease has been less studied..

We have used immunohistochemistry with a panel of monoclonal antibodies that recognise common and alternatively spliced domains to investigate the expression of large and small Tenascin C isoforms in human menisci from individuals undergoing partial meniscectomy for meniscal tear and from normal and osteoarthritic knee joints.

Our results show that the small splice isoform appears to be expressed constitutively in both normal human meniscus and menisci showing degenerative changes. Large splice isoforms are expressed more specifically in those areas showing degenerative changes histologically. There was a variety of patterns of immunoreactivity including both pericellular staining and areas of dense homogenous matrix staining.

We propose that these findings support the idea that Tenascin C has a role in normal extracellular matrix turnover and that the large splice isoform of Tenascin C is involved in the tissue attempts to repair damaged menisci.

Abstracts

Speakers

Note: Presenter's name is shown in **bold**

S1

Breast Cytopathology in a One-stop Clinic

T Giles[1]
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There are distinct benefits to both patients and health care providers in utilising a one stop breast diagnostic service for symptomatic patients for which cytology is the most suitable pathological modality. In order for cytology to remain effective in supporting this service it must be of a demonstrable high standard and readily available. In recent years core biopsies have been increasingly used in many departments where fine needle aspiration cytology was previously submitted. This is not universal, however, and there is significant variation in the diagnostic pathway between centres which is perhaps partly explainable by rationalisation of limited resources depending on local expertise.

Whilst establishing a reliable, definitive diagnosis of symptomatic breast disease remains essential the pre-operative assessment of malignant lesions also increasingly requires the determination of prognostic markers. In most departments this has been developed on core biopsy material but it is possible to provide much of the information on cytological material if it is of a suitable quality and handled appropriately. This allows the benefits of a cytology service to remain available without resorting to multiple biopsy procedures. A constructive dialogue between surgeons, oncologists, histopathologists and cytopathologists is required to ensure all diagnostic modalities are utilised in the best way to provide the most effective service to the patients.

S2

The cytopathologist's role in US-guided transbronchial FNA

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Transbronchial FNA (TBNA) is a minimally invasive procedure for obtaining cytological specimens from mediastinal lymph nodes and tumours but is a 'blind' technique preventing target visualisation with a widely variable yield. Endobronchial ultrasound guided FNA (EBUS-TBNA) allows real-time controlled tissue sampling of lymph nodes as well as centrally located tumours. EBUS guidance may also improve the yield of TBNA (1). Furthermore, the use of rapid on-site assessment significantly improves the diagnostic yield (2).

At Guy's & St Thomas' we have been carrying out on-site evaluation of EBUS-TBNA for the past year and have found that immediate assessment allows the procedure to be interactive and aids decisions about the site and number of aspirates. There are four main diagnostic categories: primary diagnosis and staging of lung cancer and the diagnosis of other metastases, granulomatous disease and lymphomas. These frequently require ancillary tests including cell block for immunohistochemistry, flow cytometry and microbiology which are selected according to immediate assessment. Over 100 cases have been managed in this way with increasing success.

The presence of a pathologist to assess the slides and a biomedical scientist to prepare high-quality direct smears are equally valuable in maximising the value of this technique, which could become the standard of care for mediastinal tissue sampling.

References:
1. Herst FJ et al. Ultrasound-guided transbronchial needle aspiration: an experience in 242 patients. Chest 2003;123:604-607
2. Davenport MD. Rapid on-site evaluation of transbronchial aspirates. Chest 1990;98:59-61

S3

Paediatric cytopathology - a clinical approach to diagnosis

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Since the introduction of chemotherapy as first choice of treatment in small round cell tumours, FNA acquired an important role in providing the morphologic diagnosis. However, cytopathology is not as widely used in paediatric practice as it is in adults. Reasons stem from lack of experience in this field of pathology due to rarity of childhood tumours and from the belief of many paediatricians that only histology can give a definitive diagnosis.

The advantages of cytology over histology are obtaining results with minimal discomfort to children, avoiding unnecessary surgery and potential complications of open biopsy which can delay treatment and compromise outcome. In order to obtain maximal results, cytopathologist, radiologist and paediatrician have to work as a team, sharing all pertinent information.

According to our practice, cytomorphologic picture is characteristic in many childhood tumours and with the aid of immunocytochemistry it is possible to render a definitive diagnosis in approximately 75% of cases. Application of molecular techniques will further improve accuracy. However, ancillary techniques have to be used with care because the results can be misleading. Quality assurance has to be maintained at the technical level for the correct outcome of results, while the cytopathologist has to be aware of the pitfalls in antigen expression within each tumour entity.

Since diagnosing childhood tumours from FNA samples requires experience, it is advisable that it is practiced only in larger centres which can afford ancillary techniques and where rare cases can accumulate, providing a data base for cytopathologists to learn from.

S4

Cervical cancer: a topographic survey of 35 years

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Trends in incidence of invasive cervical cancer (ICC) and carcinoma in-situ (CIS) reflect a balance between risk of disease and effect of screening. Incidence in 5-year age bands from 1971-2005 (www.statistics.gov.uk) has been plotted for birth cohorts as 3-dimensional contoured graphs using hydrographic surveying methodology and Adobe Illustrator software.

Incidence of ICC and CIS/CIN3 in 1915-19, 1930-34, 1950-54 and 1970-74 birth cohorts demonstrate high-risk for young women after World War II and again after reliable contraception became available. Incidence fell in all age bands eligible for screening after the first full round of screening was completed in 1990 (1). CIS/CIN3 incidence is age-specific and now peaks in women aged 25-29 with highest levels recorded in women born since 1970.

The graphs demonstrate the substantial effect of screening during a period of increased risk of disease, supporting the view that screening has prevented an epidemic of cervical cancer (2). Vaccination should now take the story to the next stage and will have the immense advantage of preventing all grades of CIN as well as ICC.

References
1. Bray F et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and effects of screening. Cancer Epidemiol Biomarkers Prev 2005;14:677-86.
2. Peto J et al. The cervical cancer epidemic that screening has prevented in the UK. Lancet 2004;364:249-56.

S5

Costs and benefits of cervical screening and HPV vaccination

J Peto[1]
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HPV16/18 vaccines are expensive and do not eliminate the need for regular cervical screening. A polyvalent vaccine that protects against all carcinogenic human papillomavirus (HPV) types and is so cheap that it can be offered worldwide irrespective of age will be developed eventually. The delay in developing such a vaccine is a crucial parameter that was omitted in the cost-benefit analyses that have persuaded the UK and governments in many other developed countries to commit enormous resources to purchasing HPV16/18 vaccines for young girls. A reduction of 10 years in this delay could (1) prevent several million cervical cancers, mainly in developing countries; (2) reduce government expenditure on HPV vaccines in developed countries by several billion pounds; and (3) greatly reduce expenditure on cervical screening and treatment. A cost-benefit analysis that took account of this delay would thus lead to the conclusion that very substantial public resources should be devoted to accelerating the development of cheap polyvalent HPV vaccines. Western governments that are already paying for HPV16/18 vaccines should therefore establish collaborative scientific and funding arrangements with this aim. Options might include organising independent international clinical trials of new vaccines, funding the optimisation and scale-up of vaccine manufacture, and buying out some patents to make them generic. Most small and many large companies working on HPV vaccines would welcome a large agreed price or a patent-sharing agreement for a promising development on HPV vaccines or adjuvants that had not yet been tested in a large trial.

S6

Interstitial Lung Disease

AG Nicholson[1]
[1]*Royal Brompton Hospital*

Since initial subdivision of interstitial pneumonias by Liebow and Carrington, subsequent classifications and interpretation of terminology varied as new patterns were included and others excluded. Despite this, several studies in the 1990s showed that recognition of these patterns provided significant prognostic data and a consensus classification system was published in 2002, highlighting the importance of clinical and imaging correlation in relation to accurate diagnosis. The most important of these is usual interstitial pneumonia, the pattern seen in idiopathic pulmonary fibrosis. Subsequent usage has led to further advances in relation to treatment and identifying aetiologies. The same histological patterns may be seen in association with connective tissue disorders, although prevalence and prognoses differ when compared to idiopathic disease. Furthermore, a proposed classification for dealing with diffuse lung disease in children has also been recently published, taking into account recent advances in relation surfactant protein gene mutations as well as recognition of new entities. In practice, many cases of interstitial lung disease are diagnosed without recourse to biopsy, primarily due to advances in HRCT. However, a minor percentage of cases, typically those with non-specific features on imaging, atypical presentation, unexpected longitudinal behaviour or extreme rarity, will still undergo biopsy and this is likely to remain the case for the foreseeable future.

S7

Placental Examination for Non-Paediatric Pathologists

I Moore[1]
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It is recognised that placental examination receives rather scant attention in a busy histopathology department where priority is given to the diagnostic biopsy material.

However, well conducted placental examination will provide the obstetrician with the important information on how to manage the next pregnancy, particularly in cases of poor pregnancy outcome (fetal loss or stillbirth). The results of placental examination may provide information on genetic and recurrent conditions or maternal conditions requiring treatment.

It is not possible in the current climate to examine histologically all the placentas selected by obstetricians or midwives. There is certainly no place for the examination of placentas from uncomplicated pregnancies. A stratified approach is suggested where some categories of the placentas are fully examined while other receive only gross examination. Placentas which are abnormally heavy or abnormally small should have a detailed histological examination.

The guidance will be provided when one should consider the cord appearances and the placental weight as abnormal.

The most frequently, small placentas are an indication of placental malperfusion, which contributes to fetal growth restriction and to intrauterine death in up to 30% of stillbirths. The features of placental malperfusion are, after acute chorioamnionitis, the ones most commonly encountered in every day practice. It is important to be able to identify all the principal changes of placental malperfusion: decidual vasculopathy, infarction, placental abruption, villous maldevelopment and diminished growth. The features of these entities will be illustrated.

S8

Molecular pathology: putting pathologists at the cutting edge of personalised medicine

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The post-genomic era holds the promise of personalised medicine that will be guided by molecular profiles of both the patient and their disease. The pathologist will be a pivotal player in the stratification of patients and the selection of interventions, and it is essential to grasp every opportunity to integrate molecular pathology into high-content clinical trials to guide developments. Targeted therapeutics with linked theranostics and response biomarkers will become increasing available, but ensuring that these are appropriately selected for individual patients is critical to both good medicine and affordable heathcare. Biological therapies for cancer will be highlighted as evidence that molecular pathology can be at the cutting edge of personalised medicine.

S9

Pathology of Castleman's Disease and POEMS Syndrome

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Castleman's Disease (CD) is an unusual lymphoid hyperplasia with characteristic morphological features including partially depleted and vascularized follicles with prominent mantle zones and interfollicular fibrosis and, in some cases, marked plasmacytosis. CD is best considered as a morphological syndrome that has a number of etiologies. At least two different histological variants are recognized: Hyaline-vascular and plasma cell variants. Hyaline –vascular variant typically presents as a solitary, central single mass, sometimes with constitutional symptoms and respond to surgical excision. Abnormalities of follicular dendritic cells are implicated in the pathogenesis. The plasma cell variant is heterogeneous with regards to clinical features and morphology, and often presents as a multicentric disease. At least two distinct causes are recognized. So-called plasmablastic variant is associated systemic HHV8 infection, often secondary to systemic immunosuppression, and may transform into plasmablastic lymphomas. Plasma cell variant could also be seen with systemic plasma cell proliferative disorders, in particular, in the context of POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) syndrome.

Bone marrow involvement can be seen in plasma cell variant of CD. In HHV8-associated cases , the marrow may contain characteristic CD lymphoid follicles and scattered interstitial HHV8+ plasmablasts can be detected in most cases. In CD associated with POEMS syndrome marrow contains lymphoplasmacytic aggregates and, typically, the plasma cells within the lymphoplasmacytic aggregates show light chain restriction. The myeloid and megakaryocytic haematopoiesis may be hyperplastic mimicking a myeloproliferative disease.

S10

Molecular Techniques In Bone Marrow Trephine Biopsy Diagnosis

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The trephine bone marrow (BM) biopsy plays a central role in diagnosis and staging of haematological neoplasms and other disorders affecting haematopoiesis. Haematopathology has advanced significantly due the inclusion of molecular genetic techniques in its diagnostic repertoire. Many molecular tests can nowadays be successfully performed on paraffin-embedded tissues, but their application to trephine BM biopsies has lagged behind for several reasons. If the technical aspects specific to this template source such as various fixation and decalcification procedures (acid-based vs. EDTA) are taken into consideration, both DNA- and RNA-based tests can be modified successfully for BM biopsies. Since the cellular composition of the BM trephine is not subject to the same bias as that of aspirates, which are commonly strongly hemodilute or may underrepresent marrow elements due to fibrosis, molecular examination of the BM trephine can yield additional valuable information. The current indications for molecular BM diagnostics range from the demonstration of lymphoma involvement by gene rearrangement analysis, identification of tumour-specific translocations or point mutations, such as the JAK2 V617F, in lymphoid and chronic myeloproliferative disorders along to the detection of microorganisms or marrow involvement by soft tissue sarcomas. Quantitative PCR techniques for the investigation of allelic imbalances and gene expression levels, as well as the use of laser-assisted microdissection, open new avenues for research and advanced diagnostics. The molecular detection of minimal residual disease in haematological neoplasms, especially in the context of new treatment strategies, will provide future challenges.

S11

Molecular Pathogenesis of the Myeloproliferative Disorders

A Green[1]
[1]*University of Cambridge*

The human myeloproliferative disorders represent a spectrum of clonal haematological malignancies, with three main members: polycythaemia vera (PV), essential thrombocythaemia (ET) and idiopathic myelofibrosis (IMF). Surprisingly a single acquired gain-of-function V617F mutation in JAK2 is present in virtually all patients with PV and in approximately half those with either ET or IMF. Our subsequent results suggest that V617F-positive ET and PV form a phenotypic continuum, that homozygosity for this mutation plays a key role in the PV phenotype and that V617F-negative ET and V617F-positive ET represent distinct disorders. More recently we have made the unexpected discovery that leukaemic transformation is associated with loss of the JAK2 V617F mutation and we have identified a cluster of new JAK2 mutations which define a previously unrecognised myeloproliferative syndrome. These data are laying the foundation for new approaches to the diagnosis, classification and therapy of the myeloproliferative disorders.

S12

Infectious Disease Pathology: Diagnosing Emerging and Exotic Infections as well as Potential Bioterrorist Events

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Contrary to predictions made earlier in the last century, infectious diseases remain the leading cause of death worldwide. Many complex factors contribute to this growing threat and to the broader array of recognized pathogens. Pathologists are characteristically among the first health care workers involved in recognizing infectious disease outbreaks and hence are in an excellent position to discover new zoonotic diseases and other emerging infectious disease syndromes as well as recognizing potential bioterrorist events.

A syndrome based approach to pathologic diagnosis of emerging infectious disease and other unexplained illness relies on the combined use of tissue culture, serology, histopathologic examination, immunohistochemistry, ultrastructural evaluation, PCR, and in situ hybridization to reach a specific diagnosis. The systematic approach serves as a good model for investigation of unexplained death caused by infections. Examination of tissues using this approach can significantly narrow the focus and help achieve a diagnosis.

Discussion will include examples of unexplained illnesses or death suspected to be of possible infectious causes and various outbreaks of emerging and re-emerging diseases which CDC investigated during recent years and the benefits of syndrome based approach in aiding in the differentiation and diagnosis. Specific syndrome based approaches will be discussed including: pneumonia (e.g. SARS, influenza); encephalitis (e.g. West Nile, Nipah); hemorrhagic fevers (e.g. Hantavirus, anthrax, Ebola); cutaneous rash illnesses (e.g. monkeypox, rickettsial pox); and infections in immunosuppressed individuals (e.g. West Nile, LCMV, Rabies).

S13

HIV, the Brain and the Final Common Pathway to Dementia

J Bell[1], IC Anthony[1]
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The efficacy of combination antiretroviral therapy (HAART) has led to HIV/AIDS becoming a chronic rather than inevitably fatal disease. HIV associated dementia (HAD) emerged as a complication of untreated AIDS in 30-40% of subjects. Opportunistic conditions such as Progressive Multifocal Leucoencephalopathy and primary central nervous system lymphoma could also give rise to severe cognitive impairment. Since the advent of HAART, the incidence of HAD has fallen significantly but paradoxically the prevalence of cognitive disorders is rising as long term survival improves.
What is the cause of this CNS disorder in chronic HIV/AIDS?
HIV is capable of infecting the brain directly through its affinity for microglia. These resident brain macrophages carry CD4 and chemokine receptors that are required for HIV attachment and entry. The resulting inflammatory HIV encephalitis, characterised by infected microglia and giant cells, may be mild or florid but the presence of activated microglia that release pro-inflammatory cytokines leads to neuronal damage and death.
Recent investigations have shown that although the brain may not show overt pathology, persistent neuroinflammation is present in HAART treated individuals. In addition these brains display a higher level than normal for age of insoluble Tau and beta amyloid, proteins which also accumulate in Alzheimer's disease (AD). This is paralleled by similar changes in cerebrospinal fluid, suggesting that affected individuals may develop early onset AD-like illnesses in future. Co-factors contributing to neurodegeneration include hepatitis C, drugs of abuse, ApoE genotype and possibly HAART itself.

S14

Immune reconstitution disease associated with tuberculosis

S Lawn[1]
[1]*University of Cape Town*

Tuberculosis-associated immune reconstitution disease (TB IRD) in HIV-infected patients is an adverse consequence of the restoration of mycobacterium-specific immune responses during the initial months of antiretroviral treatment (ART). This may manifest as either the clinical deterioration of TB that was initially responding to TB treatment ('paradoxical' TB IRD) or as the clinical presentation of previously occult disease ('unmasking' TB IRD). Paradoxical TB IRD is reported to occur in between 8 and 43% of TB patients initiating ART. Clinical manifestations are diverse and, although most cases are self-limiting, a minority are life-threatening and deaths have been reported. Although development of disease has been found to be associated with large expansions of mycobacterium-specific CD4 T cells in peripheral blood, the immunopathological mechanisms at the actual site of disease have yet to be defined. It has been hypothesized that immunoregulatory T cell sub-sets are deficient while others have suggested that rapid restoration of innate immune mechanisms in macrophages plays a key role. Much remains to be elucidated and ongoing studies of this phenomenon may provide important insights into the immunopathogenesis of TB.

S15

HIV-related pathology: what you are missing

S Lucas[1]
[1]*KCL School of Medicine*

Since HIV/AIDS became known from 1981, the 'standard' list of HIV-associated clinical pathology has become familiar to pathologists. These include viral, bacterial, mycobacterial, fungal, protozal, helminthic infections; some cancers (particularly B-cell lymphomas), dementia and wasting syndrome. The original case-definition surveillance list of opportunistic diseases (CDC 1987, revised 1992) includes the majority of conditions encountered regularly. But a variety of additional conditions and infections has become evidently associated with HIV as time passes. These include:
Drug toxicity: toxic reactions (skin, liver) to antibiotics (eg co-trimoxazole). Reactions to anti-HIV therapy: steatosis, lactic acidosis, hepatic necrosis, muscle degeneration. IRIS (immune reconstitution inflammatory syndrome) occurs when cell-mediated immunity improves, with presentation and/or worsening of infective lesions due to florid oedema, inflammation and necrosis. Skin lesions: sarcoidosis, leprosy first presentation, HPV eruptions, acne. Vascular disease: vasculitis, accelerated atheroma, pulmonary hypertension, HIV-related cardiomyopathy. CNS lesions: CD8 encephalitis, Guillain-Barre syndrome, tau-'opathies. Liver: non-cirrhotic portal hypertension, focal nodular hyperplasia. Other cancers: lung adenocarcinoma, seminoma, T-cell and Hodgkin lymphoma. Osteopaenia, non-pathogen-assocciated inflammatory bowel disease (IBD), non-HIVAN glomerular disease. These and the 'new' infections will be illustrated and discussed.
Message: HIV disease can present with a very wide range of pathologies. Think HIV!

PRESENTERS' INDEX

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