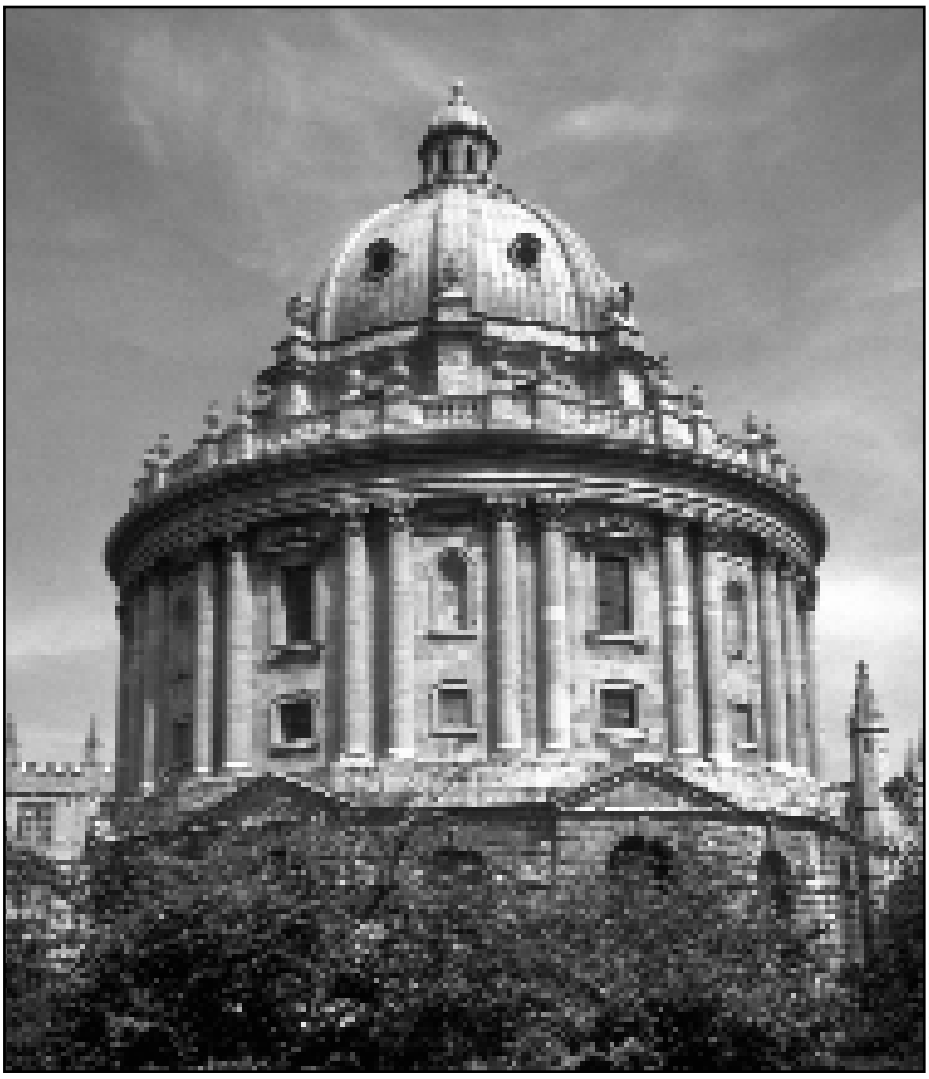
Pathological Society

Understanding Disease



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193rd Scientific Meeting
8–9 January 2008

Hosted by the Department of Cellular Pathology
John Radcliffe Hospital, Oxford

To be held at the University of Oxford
Examination Schools, High Street, Oxford

PROGRAMME

Oxford Radcliffe Hospitals NHS
NHS Trust

CONTENTS

PROGRAMME ACKNOWLEDGEMENTS

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PROGRAMME SYNOPSIS AND TIMETABLE

(Showing times, sessions and venues)

TIME	SESSION	VENUE
TUESDAY 8 JANUARY 2008		
08.00	Registration Coffee	*ENTRANCE HALL* *NORTH SCHOOL*
09.15–09.30	Welcome Address	*SOUTH SCHOOL*
09.30–12.00	Symposium: *Upper Gynaecological Tract Pathology* 10.40–11.10 Coffee Break	*SOUTH SCHOOL* *NORTH SCHOOL*
09.00–17.00	Slide Seminar Competition Case Viewing: *Urological Pathology* (Win a case of champagne!)	*ROOM 8*
12.00–13.00	Trainees Programme: *Meet the Experts* 12.00–12.30 *Giving Evidence in Court* 12.30–13.00 *Mesothelioma*	*SOUTH SCHOOL*
13.00–14.00	Lunch and Trade Exhibition	*NORTH SCHOOL*
14.00–15.00	Poster Viewing and Rounds (Abstracts P1–P52)	*NORTH SCHOOL*
15.00–17.00	Symposium: Proteomics – state of the art? 16.00–16.30 Tea Break	*SOUTH SCHOOL* *NORTH SCHOOL*
17.00–17.45	Pathological Society's 4th Goudie Lecture: *Colorectal cancer: seeing is believing.* Prof JR Jass, Harrow.	*SOUTH SCHOOL*
18.45	Buses depart for Society Dinner.	*OUTSIDE EXAMINATION SCHOOL*
19.30–22.30	Drinks Reception and Society Dinner	*EYNSHAM HALL*
WEDNESDAY 9 JANUARY 2008		
08.00	Registration Coffee	*ENTRANCE HALL* *NORTH SCHOOL*
09.00–09.45	Slide Seminar Competition Review: *Urological Pathology*	*SOUTH SCHOOL*
09.45–12.15	Plenary Oral Presentations (Abstracts PL1–PL8) 10.45–11.15 Coffee Break	*SOUTH SCHOOL* *NORTH SCHOOL*
12.15	Pathological Society Undergradute Essay Prize: Presentation to Miss K Gaitskell, Oxford	*SOUTH SCHOOL*
12.15–13.00	Poster Viewing (Abstracts P53–P97)	*NORTH SCHOOL*
13.00–14.00	Lunch and Trade Exhibition	*NORTH SCHOOL*
13.00–15.00	Renal Pathology EQA Meeting	*ROOM 11*
14.00–17.30	Symposium: *Challenges in Inflammatory Bowel Disease* 16.00–16.30 Tea Break	*SOUTH SCHOOL* *NORTH SCHOOL*
17.30	Meeting Closes	

SCIENTIFIC SESSIONS INFORMATION

PLENARY ORAL SESSION ▸ *South School*

The plenary oral session, in which the 8 highest-ranked submitted oral abstracts will be presented, will be held on: **Wednesday 9 January, 09.45–12.15 hrs**.

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

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

POSTER VIEWING AND ROUNDS ▸ *North School*

Posters will be displayed throughout the meeting but dedicated viewing sessions will be on:
Tuesday 8 January, 14.00–15.00 hrs and **Wednesday 9 January, 12.15–13.00 hrs**.

Poster Rounds: Chairmen will review posters during Tuesday 8 January, 14.00–15.00 hrs and Wednesday 9 January, 12.15–13.00 hrs.

Posters should be **in place by 12.00 hrs on Tuesday 8 January** and **removed by 15.00 hrs on Wednesday 9 January**.

At least one of the contributors must be in attendance during the viewing period, as indicated in the programme synopsis.

Prizes: Prizes are awarded for the three best posters. The Sir Alastair Currie Prize, 2nd and 3rd prizes will be presented at the Society Dinner on **Tuesday 8 January**.

Please note that unfortunately due to shortening of the meeting programme only those posters displayed on Tuesday 8 January will be considered for the Poster Prizes.

TRAINEES' PROGRAMME ▸ *South School*

Tuesday 8 January, 12.00–13.00
Meet The Experts
12.00–12.30 *Giving Evidence in Court*, Dr NCA Hunt, Oxford
12.30–13.00 *Mesothelioma,* Dr CA Clelland, Oxford.

SLIDE SEMINAR – UROLOGICAL PATHOLOGY ▸ *Room 8*

Competition: There will be a slide seminar competition and digital images of all cases will be available for preview during **Tuesday 8 January**.

Prize: A case of champagne will be awarded at the Society Dinner on **Tuesday 8 January**.

Discussion Session: Wednesday 9 January, 09.00–09.45 ▸ *South School*

SOCIETY LECTURE ▸ *South School*

Tuesday 8 January, 17.00–17.45
The Pathological Society of Great Britain & Ireland's 4th Goudie Lecture: *Colorectal cancer: seeing is believing.* To be given by Prof JR Jass, St Mark's Hospital, Harrow, Middlesex.

COMPANION MEETING ▸ *Room 11*

Wednesday 9 January, 13.00–15.00 Renal Pathology EQA

TRADE EXHIBITION ▸ *North School*

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

GENERAL ARRANGEMENTS

REGISTRATION

Registration is via the links on the Society's website: **www.pathsoc.org.uk**
The registration system will issue an automated e-mail acknowledgement.

DISCOUNTED EARLY BIRD FEES (*up to and including 26 November 2007*)

Refreshments and lunch included

Society Members	Whole meeting £120 – OR £80 per day (or part day)
Non-Members	Whole meeting £200 – OR £120 per day (or part day)

Concessions *

Society Members	Whole meeting £40 – OR £25 per day (or part day)
Undergraduates	Whole meeting £40 – OR £25 per day (or part day)
Non-Members	Whole meeting £70 – OR £40 per day (or part day)

FULL FEES (*after 26 November 2007*)

Refreshments and lunch included

Society Members	Whole meeting £200 – OR £120 per day (or part day)
Non-Members	Whole meeting £300 – OR £180 per day (or part day)

Concessions *

Society Members	Whole meeting £70 – OR £40 per day (or part day)
Undergraduates	Whole meeting £70 – OR £40 per day (or part day)
Non-Members	Whole meeting £100 – OR £60 per day (or part day)

CONCESSIONS – QUALIFYING CATEGORIES

Biomedical Scientists / Technicians (all grades)
Honorary or Senior Members of the Society
PhD Students
Postdoctoral Fellows
Trainees
Undergraduates

* Non-Member Concessionary Delegates (including Undergraduates) must provide documentation evidence to qualify for the Concessionary Fees. Please send confirmation of your status, signed by your head of training, stating National Training Numbers, where applicable. This must be e-mailed or faxed.

E-mail: julie@pathsoc.org.uk
Fax: +44 (0)20 7426 0047

SOCIETY DINNER

£50 per ticket.

ADVANCE REGISTRATION CLOSING DATE – MONDAY 17 DECEMBER

Registration will only be accepted on-site at the meeting after this deadline.

CANCELLATIONS

Please note that the Society is unable to refund registration fees for cancellations received **after Monday 11 December**.

GENERAL ARRANGEMENTS

DELEGATE ENROLMENT *(at the Meeting)*

Enrolment at the Delegate Reception Desk will take place in the Entrance Hall from 08.00 hrs each day.

PRESENTATION CHECKING AND PREVIEW

This will be available in Room 8.

ORAL COMMUNICATIONS AND LECTURES

Electronic presentations must be in Microsoft PowerPoint (PC or MAC).
Versions earlier than 2000 are not acceptable.

MESSAGES

During the Meeting, messages for delegates may be left on telephone number: 01865 286357
There will also be a message board located beside the Delegate Reception Desk.

REFRESHMENTS

All refreshments will be served in North School.

BADGES

Delegates are requested to wear their badges at all times.

COAT AND BAGS

Secure facilities will be provided in Room 7.

INTERNET ACCESS

This will be available for all delegates in Room 8.

TRAVEL AND ACCOMMODATION

For travel information a list of local hotels at discounted rates see: **www.pathsoc.org.uk** and follow the links to the meeting information.

SOCIAL ACTIVITIES

Society Dinner: Tuesday 8 January, 19.30 for 20.00, Eynsham Hall, Witney, Oxon. **Buses depart at 18.45 hrs** from outside the Examinations Hall.

Tickets are £50 each. *To reserve your ticket please tick the relevant box when registering.*

LOCAL PLACES OF INTEREST

Please refer to the Internet for information.

SMOKING

Smoking is prohibited at all meetings and social events.

GENERAL ARRANGEMENTS

DISCLAIMER

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

CONTINUING PROFESSIONAL DEVELOPMENT (CPD)

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

Credits: These can be accrued as follows:
For each full day: 7 points
For each half day: 3 points

Certificates: Delegates who are eligible for CPD points should complete the CPD Evaluation Form and Certificate request form which will be provided in their delegate pack at the Meeting. Certificates will be sent by post *after* the meeting.

ENQUIRIES BEFORE THE MEETING

Please contact:

Pathological Society of Great Britain and Ireland
The Warden's Office, Old Medical College Building, Turner Street, London E1 2AD
Tel: +44 (0)20 7976 1260
Fax: +44 (0)20 7426 0047
Email: admin@pathsoc.org.uk

FUTURE MEETINGS

2008

1–4 July Leeds

2009

7–8 January GKT, London

30 June–3 July Cardiff Pathology 2009
5th Joint Meeting of the Pathological Society and the British Division of the IAP

2010

6–8 January Imperial College, London

29 June – 2 July St. Andrews

2011

January Cambridge (to be confirmed)

Ghent Pathology 2011
6th Joint Meeting of the Pathological Society and the British Division of the IAP
(date to be confirmed)

08.00 **Entrance Hall**
REGISTRATION

08.00 **North School**
Coffee

09.00–17.00 **Room 8**
SLIDE SEMINAR COMPETITION CASE VIEWING
Urological Pathology (WIN A CASE OF CHAMPAGNE!)

09.15–09.30 **South School**
WELCOME ADDRESS
Dr S Manek, John Radcliffe Hospital, Oxford

09.30–12.00 **South School**
SYMPOSIUM: *Upper Gynaecological Tract Pathology*
Chair: Dr S Manek, John Radcliffe Hospital, Oxford

09.30–09.50 *Recent Advances in Upper Gynaecological Tract Pathology*
Dr S Dhar, John Radcliffe Hospital, Oxford

09.50–10.05 **[S1]** *The Surgical Management of Endometrial and Ovarian Cancer*
Prof SJ Kehoe, Oxford Gynaecological Cancer Centre, Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford

10.05–10.20 **[S2]** *Medical Management of Endometrial and Ovarian Cancers*
Prof AB Hassan, Cancer Research UK, Oxford

10.20–10.40 **[S3]** *Differential Diagnoses in Common Ovarian Neoplasms*
Prof CS Herrington, University of St Andrews, Fife

10.40–11.10 COFFEE ▸ *NORTH SCHOOL*

11.10–11.30 *Endometrial hyperplasia and carcinoma – recent concepts*
Dr SM Ismail, Wythenshawe Hospital, Manchester

11.30–12.00 **[S4]** *Differential Diagnoses in Uterine Mesenchymal Neoplasms*
Dr R Ganesan, Birmingham Women's Hospital

12.00–13.00 **South School**
TRAINEES' PROGRAMME: ***Meet The Experts***
Chair: Dr BF Warren, John Radcliffe Hospital, Oxford
Dr L Browning, University of Oxford

12.00–12.30 *Giving Evidence in Court*
Dr NCA Hunt, John Radcliffe Hospital, Oxford

12.30–13.00 *Mesothelioma*
Dr CA Clelland, John Radcliffe Hospital, Oxford

13.00–14.00 **North School**
LUNCH and TRADE EXHIBITION

14.00–15.00 **North School**

POSTER PRESENTATIONS and POSTER ROUNDS

CATEGORIES

Autopsy & Forensic **[P1–P4]**
Cellular/Molecular **[P5–P13]**
Education & Audit **[P14–P17]**
Experimental Tumour Pathology **[P18]**
Gastrointestinal **[P19–P31]**
Gynaecological **[P32–P39]**
Head & Neck **[P40–P43]**
Hepatobiliary/Pancreas **[P44–P45]**
Skin **[P46–P48]**
Technical Advances **[P49–P52]**

Poster Round Chairs:

Categories: Gastrointestinal; Head and Neck; Hepatobiliary/Pancreas; Skin
Dr T Helliwell, Liverpool
Dr RFT McMahon, Manchester

Categories: Autopsy/Forensic; Education and Audit; Gynaecological
Dr EJ Soilleux, Oxford
Dr S Manek, Oxford

Categories: Cellular/Molecular; Experimental Tumour Pathology; Technical Advances
Prof CS Herrington, St Andrews
Prof Sir Nicholas A Wright, London

15.00–17.00 **South School**

SYMPOSIUM: *Proteomics – state of the art?*

Chair: Prof P Quirke, University of Leeds
Dr EJ Soilleux, John Radcliffe Hospital, Oxford

15.00–15.20 *Quantitative Proteomics and Its Applications to Study Sub-Cellular Protein Localisation*
Dr KS Lilley, Cambridge Centre for Proteomics, Cambridge Systems Biology Institute, University of Cambridge

15.20–15.40 **[S5]** *Nano-UPLC Improves Sensitivity and Converage for In-depth Proteomic Analysis*
Dr B Kessler, University of Oxford

15.40–16.00 *Glycomics: A potential tool for diagnostics*
Prof A Dell, Division of Molecular Biosciences, Imperial College, London

16.00–16.30 TEA ▸ *North School*

16.30–17.00 *Quantitative Proteomics Analysis of Proteins and Peptides from Tissues and Body Fluids*
Dr M Ward, Proteome Sciences plc, Cobham, Surrey

17.00–17.45 **South School**

PATHOLOGICAL SOCIETY OF GREAT BRITAIN & IRELAND'S 4TH GOUDIE LECTURE

Chair: Prof PA Hall, Queen's University Belfast and General-Secretary of the Pathological Society

[S6] *Colorectal Cancer: Seeing is Believing*
Prof JR Jass, St Mark's Hospital, Harrow, Middlesex

18.45 **Examination Schools (Entrance)**

BUSES DEPART FOR SOCIETY DINNER

19.30–22.30 **Eynsham Hall**

DRINKS RECEPTION and SOCIETY DINNER

08.00 **Entrance Hall**
REGISTRATION

08.00 **North School**
Coffee

09.00–09.45 **South School**
SLIDE SEMINAR FOLLOW UP: *Urological Pathology*
Dr G Turner, John Radcliffe Hospital, Oxford

09.45–12.15 **South School**
PLENARY ORAL SESSION
Chairs: Prof I Ellis, University of Nottingham
Dr EJ Soilleux, John Radcliffe Hospital, Oxford

09.45 **[PL1]** *The clinical and functional significance of de-novo expression of alphavbeta6 integrin by myoepithelial cells in DCIS*
{P} M Allen, K Mulligan, S Clark, IR Hart, J Marshall, L Jones

10.00 **[PL2]** *Characterisation of Novel 'Early Stemness' Gene Events Specific to Highly-Malignant Cancer Stem Cells*
{P} M Gallagher, S Elbaruni, C Heffron, S Guenther, R Henfrey, C Martin, O Sheils, J O'Leary

10.15 **[PL3]** *Hypoxia Inducible Factor Expression and Angiogenesis in Clear Cell Renal Carcinoma*
{P} P Charlesworth, S Biswas, G Turner, R Leek, T Thamboo, H Turley, L Campo, J Crew, A Protheroe, D Cranston, ISD Roberts, KC Gatter, A Harris

10.30 **[PL4]** *Cylindrical Abdominoperineal Excision for Low Rectal Cancer: Proof of its Oncological Superiority*
{P} NP West, P Finan, C Anderin, J Lindholm, T Holm, P Quirke

10.45-11.15 COFFEE ▸ *North School*

11.15 **[PL5]** *Evaluation of HPV DNA and mRNA Detection Technologies for Detecting HPV in Cervical Cytology Specimens*
{P} H Keegan, J McInerney, L Pilkington, P Gronn, I Silva, F Karlsen, N Bolger, J O'Leary, C Martin

11.30 **[PL6]** *Clinical Measurement of Prognostic Immune Signature in Follicular Lymphoma by RT-PCR based Gene Expression Profiling and Immunohistochemistry Demonstrates Favourable T-cell and Unfavourable Macrophage Infiltration*
{P} RJ Byers, E Sakhinia, P Jacob, C Glennie, S McDermott, JA Hoyland, L Menasce, J Radford, T Illidge

11.45 **[PL7]** *Cellular Mechanisms of Tumour Osteolysis in Primary Malignant Bone Tumours {P} R Taylor, F Jones, H Knowles, NA Athanasou*

12.00 **[PL8]** *Diagnosis of amyloidosis by mass-spectrometry: A novel method with wide-ranging potential applications in histopathology*
{P} A Dogan, JA Vrana, JD Gamez, JD Theis, SR Zeldenrust, PJ Kurtin, KL Grogg, HR Bergen

12.15 PRESENTATION:
Pathological Society's Undergraduate Essay Competiton Prize to Miss K Gaitskell, Oxford

12.15–13.00 **North School**
POSTER PRESENTATIONS and POSTER ROUNDS

CATEGORIES:
Breast **[P53–P61]**
Cardiovascular/Pulmonary **[P62–P64]**
Endocrine **[P65–P68]**
Genitourinary/Renal **[P69–P82]**
Lymphoreticular **[P83–P89]**
Neonatal/Paediatric **[P90–P91]**
Neuropathology/Ophthalmic **[P92–P93]**
Osteoarticular/Soft Tissue **[P94–P97]**

Poster Round Chairs:
Categories: Breast; Genitourinary/Renal; Neonatal/Paediatric
Dr G Turner, Oxford
Prof RA Walker, Leicester

Categories: Cardiovascular/Pulmonary; Endocrine; Lymphoreticular; Neuropathology/Ophthalmic; Osteoarticular and Soft Tissue
Prof NA Athanasou, Oxford
Prof AJ Freemont, Manchester,

13.00–15.00 **Room 11**
COMPANION MEETING: *Renal Pathology EQA*

13.00–14.00 **North School**
LUNCH and TRADE EXHIBITION

14.00–17.30 **South School**
SYMPOSIUM: *Challenges in Inflammatory Bowel Disease*
Chairs: Prof NA Shepherd, Gloucestershire Royal Hospital, Gloucester
Dr SPL Travis, John Radcliffe Hospital, Oxford

14.00–14.30 **[S7]** *Mimics of Chronic Inflammatory Bowel Disease*
Dr BF Warren, John Radcliffe Hospital, Oxford

14.30–15.00 *Lessons from Animal Models*
Prof F Powrie, University of Oxford

15.00–15.30 **[S8]** *New Genes, New Pathways in IBD Susceptibility*
Dr MJ Parkes, Addenbrooke's Hospital, Cambridge

15.30–16.00 *Operations in IBD and What the Surgeon Needs to Know from the Pathologist*
Prof NJM Mortensen, John Radcliffe Hospital, Oxford

16.00–16.30 TEA ▸ *North School*

16.30–17.00 *New Therapies in IBD. Important and Urgent Questions for the Biopsy Pathologist*
Dr S Keshav, John Radcliffe Hospital, Oxford

17.00–17.30 *Dysplasia in Ulcerative Colitis: Diagnosis and Management*
[S9] Prof NA Shepherd, Gloucestershire Royal Hospital, Gloucester
Dr BP Saunders, St Mark's Hospital at Northwick Park, Harrow, Middlesex

17.30 Meeting Closes

ACKNOWLEDGMENTS

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The Pathological Society of Great Britain & Ireland
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Dr DN Slater, Sheffield

Prof RA Walker, Leicester

Dr BF Warren, Oxford

Dr B Wilkins, Newcastle-upon-Tyne

Abstracts

Plenary

PL1

The clinical and functional significance of de-novo expression of alphavbeta6 integrin by myoepithelial cells in DCIS

{P} M Allen, K Mulligan, S Clark, IR Hart, J Marshall, L Jones
Queen Mary's School of Medicine and Dentistry, London, United Kingdom

Myoepithelial cells (MEC) are essential in the maintenance of normal breast function. Normal MEC exhibit potent tumour suppressor function but it is unclear if this is compromised in Ductal Carcinoma in-situ (DCIS). We have identified de-novo expression of αvβ6 integrin on myoepithelial cells in a subset of DCIS. This study aimed to analyse αvβ6 expression in a large series of DCIS and investigate its effect on MEC tumour suppressor function. Analysis of DCIS (n=>400) demonstrated almost universal induction of αvβ6 in MEC of DCIS associated with invasion compared to ~60% pure DCIS.
A normal-like MEC line was purified from immortalised1089 cell line (N-1089-MEC) and αvβ6 over-expressing MEC generated from this (DCIS-1089-MEC). Both lines exhibited characteristic myoepithelial markers and co-culture assays demonstrated that N-1089-MEC exhibited similar tumour-suppressor effects as primary MEC (reduction in tumour invasion [$p<0.001$] and proliferation [$p<0.001$]). DCIS-1089-MEC bound and migrated to the αvβ6 ligand LAP, and activated a TGF-β reporter demonstrating functional αvβ6. Primary DCIS-MEC showed loss of suppressor function ($p<0.05$), DCIS-1089 MEC exhibit altered behaviour, e.g. more migratory phenotype, however some tumour-suppressor function was maintained.
We have shown that myoepithelial cells exhibit an altered phenotype in DCIS by expressing αvβ6 integrin. We have generated normal-like MEC lines that exhibit all the characteristics of primary MEC including tumour-suppressor function. Primary DCIS-MEC show loss of suppressor function and αvβ6-overexpressing MEC (DCIS-1089-MEC) exhibit altered function but retain some suppressor function. These cell lines provide a useful model to study MEC function in DCIS.

PL2

Characterisation of Novel 'Early Stemness' Gene Events Specific to Highly-Malignant Cancer Stem Cells

{P} M Gallagher[1], S Elbaruni[1], C Heffron[1], S Guenther[2], R Henfrey[2], C Martin[1], O Sheils[1], J O'Leary[1]
[1]Trinity College Dublin, Dublin, Ireland, [2]Applied Biosystems, Foster City, California, United States

Background. Cancer stem cell (CSC) description in brain, breast, prostate, head and neck and ovarian tumours, led to acceptance that CSCs are key to malignancy. Strategies designed to specifically target CSCs, should reduce primary tumourigenesis while reducing metastasis and recurrence. As CSCs clearly mirror normal stem cells (NSCs) of comparable potency, specific clinical inhibition of CSC stemness has not been achieved to date. We believe that identification of CSC-specific events could be developed to achieve targeted removal of CSC stemness in a patient-orientated manner applicable to cancer therapeutics.
Methods. Human teratocarcinoma CSCs were retinoic acid-differentiated over 3 days, whole-genome array analysis performed and profiles further validated through TaqMan real-time PCR analysis. Validated gene expression profiles were bioinformatically compared to published hES data, permitting identification of gene events exclusive to CSCs.
Results. We have generated gene profiles enriched for novel CSC regulators, highlighting genes, specific to highly malignant nullipotent CSCs, from key stemness pathways such as Wnt, Notch, and Shh as well cytokine-cytokine receptor interaction, Jak-Stat, VEGF, TGF-beta and MAPK signalling, the cell cycle and apoptosis.
Conclusion. We have identified novel gene events specific to highly malignant CSCs and postulate that specific CSC-targeting can be achieved by their knockdown.

PL3

Hypoxia Inducible Factor Expression and Angiogenesis in Clear Cell Renal Carcinoma

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Hypoxia Inducible Factors HIF-1 and HIF-2 are over-expressed in many clear cell renal cell carcinomas (CCRCC) due to hypoxia or VHL mutations within the tumour. HIF-1 and HIF-2 have differential functions and target gene expression, although their expression in renal tumours and prognostic implications remain unknown. We analysed 170 CCRCC on tissue microarrays, assessed expression of HIF-1, HIF-2 and their primary target genes BNIP3, CAIX, CyclinD1, GLUT1, LDH5, Oct-4 and VEGF, and correlated these with tumour angiogenesis, stage, grade, tumour diameter and patient survival. On univariate analysis HIF-1 and HIF-2 expression correlated ($p = 0.033$), HIF-2 positively correlated with VEGF, but HIF-1 or HIF-2 had no prognostic association, although nuclear HIF-2 was associated with survival ($p= 0.0136$) when nuclear HIF-1 was highly expressed. High levels of angiogenesis, quantified by CD31 staining, was positively associated with survival ($p= 0.0003$) and negatively correlation with Fuhrman grade ($p=0.0005$) and maximal tumour diameter ($p=0.021$). On multivariate analysis angiogenesis ($p=0.0020$), low grade ($p=0.0317$) and tumour size ($p=0.0421$) were significant prognostic markers of increased cancer specific survival. Expression of HIF isoforms and these six target proteins within CC-RCC did not convey prognostic significance, compared to angiogenesis, which may be important for targeting of novel anti-angiogenic therapies.

PL4

Cylindrical Abdominoperineal Excision for Low Rectal Cancer: Proof of its Oncological Superiority

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Despite the improvements seen following the introduction of TME, low rectal cancer treated by standard abdominoperineal excision (APE) continues to have a poor prognosis due to high rates of CRM positivity and intra-operative perforations. This may be overcome with an extended perineal dissection in the prone position resulting in a more cylindrical specimen.

128 APE's for potentially curable primary rectal adenocarcinoma were identified and subjected to clinicopathological review. This included 27 cylindrical and 101 standard APE's. Additionally, tissue quantitation was performed on the cross sectional photographs from 93 cases using the Leica QWin Image Analyser (1997).

The cylindrical operation removed significantly more tissue within the distal 12 slices and all slices containing tumour (both $p<0.0001$) compared to the standard operation. A greater distance was observed from the internal sphincter/muscularis propria to the anterior, posterior and lateral resection margins (all $p<0.0001$). This was associated with lower CRM positivity (40.6% vs. 14.8%, $p=0.013$) and intra-operative perforation rates (22.8% vs. 3.7%, $p=0.0255$).

Cylindrical APE surgery has the potential to improve patient prognosis by removing more tissue around the tumour. This should reduce CRM positivity and surgical perforations, both of which have been shown to cause local disease recurrence.

PL5

Evaluation of HPV DNA and mRNA Detection Technologies for Detecting HPV in Cervical Cytology Specimens

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HPV infection is the primary agent in the development of CIN and cervical cancer, with screening programmes moving towards the introduction of HPV testing as part of the screening process. In this study we evaluated two HPV detection technologies for detection of HPV in liquid based cytology specimens. These included HPV DNA by Hybrid Capture II (Digene, HCII), which detects 13 high-risk HPV types and E6/E7 mRNA expression by PreTect HPV Proofer (Norchip), which detects HPV 16, 18, 31, 33, and 45.
In summary, 205/299 cytology specimens representing the broad spectrum of the disease (Normal-CIN3) were positive for HPV DNA and 113/299 specimens were positive for E6/E7 mRNA. We report higher concordance rates between both technologies in CIN3 cases (83%) and Normal cases (88%) than in the BNA or CIN1-2 disease categories. The positive predictive value (PPV) and specificity of the HCII DNA test (41% and 43.7% respectively) were lower than that of the PreTect HPV Proofer mRNA test (53.6% and 75.6%) for detection of high-grade disease (CIN2+), indicating that PreTect HPV Proofer may be more useful than HCII for predicting high-grade disease.
This study forms part of the MicroActive Consortium funded under the EU 6th framework *eHealth* Initiative

PL6

Clinical Measurement of Prognostic Immune Signature in Follicular Lymphoma by RT-PCR based Gene Expression Profiling and Immunohistochemistry Demonstrates Favourable T-cell and Unfavourable Macrophage Infiltration

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Gene expression profiling studies have demonstrated immune response gene signatures predictive of outcome in follicular lymphoma (FL) and there is a need for validation of these signatures and for their translation to clinical use. However, measurement of these genes in routine practice remains difficult and to date there have been very few studies validating the hypothesis. In this project we used real-time PCR measurement of gene expression levels in globally amplified polyA cDNA to analyse of immune response signatures in FL. We used real-time PCR to measure expression levels (normalised to the mean of 4 housekeeping genes) of 36 candidate *Indicator* genes, selected from microarray studies, in polyA cDNAs prepared using polyA PCR from 58 archived human frozen lymph nodes, together with immunohistochemistry for CD3, CD4, CD7, CD8, CD10, CD20, CD21 and CD68 in parallel formalin fixed paraffin embedded tissue samples to measure immune response in FL. Immunohistochemical positivity was measured by a semi-automated image analysis method using spectral unmixing to identify areas of immunopositivity. Kaplan-Mier survival analysis was performed against the normalised real-time PCR expression levels of each of the genes and against the percentage immunohistochemical postivity for each of the antibodies except for CD68 survival analysis for which was performed for cases with either 15 or less or more than 15 CD68 positive cells per high power field (hpf). High levels of CCR1, a marker of monocyte actication, were associated with a shorter survival interval ($p<0.02$), whilst immunohistochemistry demonstrated association of high numbers of CD7 positive T-cells with longer survival interval ($p<0.02$) and of high numbers of CD68 positive macrophages with a shorter survival interval ($p<0.032$). The results confirm the role of the host immune response in outcome in FL and identify CCR1 as a prognostic indicator and marker of immune switch between macrophage and T-cell dominant response. The methods used are clinically applicable, whilst the clinical utility of polyA DNA and real-time PCR for measurement of gene signatures and the strength of this approach as a molecular block are confirmed.

PL7

Cellular Mechanisms of Tumour Osteolysis in Primary Malignant Bone Tumours

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Ewing's sarcoma, osteosarcoma and lymphoma are bone tumours that are associated with extensive osteolysis. Whether tumour cells or osteoclasts are responsible for this pathological resorption is uncertain. Tumour-associated macrophages (TAMs) form a major component of the inflammatory infiltrate of bone malignancies. In the presence of RANKL and M-CSF macrophages can differentiate into osteoclasts, multinucleated cells (MNCs) which are specialised to carry out lacunar resorption. To further investigate tumour osteolysis, tissue cultures of Ewing's sarcoma, osteosarcoma and lymphoma were cultured on dentine slices and coverslips for up to two weeks in the presence/absence of RANKL, MCSF and osteolysis inhibitors. TRAP-positive MNC's and lacunar resorption was seen after 7 days of incubation in the presence of MCSF/RANKL. Resorption pits were also seen when Ewing's samples were cultured in the absence of MCSF/RANKL. Zoledronate abolished and calcitonin and osteoprotegerin reduced lacunar resorption. These results suggest that osteolysis in bone sarcomas is effected by osteoclasts and not tumour cells. Osteoclasts are formed by both RANKL dependent and RANKL independent mechanisms from TAMs. The effect of specific osteolysis inhibitors on resorption by these tumours suggests that this tumour tissue culture model may provide a bioassay whereby resorption associated with malignant primary bone tumours can be measured.

PL8

Diagnosis of amyloidosis by mass-spectrometry: A novel method with wide-ranging potential applications in histopathology.

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The management of systemic amyloidosis relies on the treatment of the underlying etiology and differs radically for different amyloid types. Accurate diagnosis remains a problem using conventional methods. In this study, we describe a novel method that can characterize amyloid subtypes using laser microdissection (LMD) and liquid chromatography-mass spectrometry (MS) on formalin fixed paraffin-embedded tissue sections. The study used 60 cases consisting of 16 transthyretin, 9 serum amyloid-associated protein, 20 lambda and 5 kappa immunoglobulin light chain, and 10 negative controls from a variety of tissues. The amyloid type in all cases was previously characterized. Amyloid plaques were captured from paraffin sections using LMD. Proteins were extracted, digested with trypsin and analyzed by LC-MS/MS. Proteins were identified using Mascot database. In Congo red positive plaques, MS correctly identified each of the four types of amyloidosis analyzed with 100% sensitivity and specificity. The use of LMD from paraffin embedded tissue sections and subsequent analysis by MS allows identification of the type of amyloid protein deposited with high specificity and sensitivity. This novel method promises to be a sensitive clinical test for accurate identification of amyloid proteins in routinely processed biopsy specimens and has wide-ranging potential applications in other areas of histopathology.

Abstracts

Posters

P1

Sudden Cardiac Death in Sickle Cell Disease

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We present the case of a 34 year old male, who collapsed suddenly while laughing. On the arrival of paramedics he was in ventricular fibrillation, but could not be resuscitated. He was known to have sickle cell disease and had required a number of transfusions. At autopsy, the gross abnormalities were a very small spleen, pulmonary and cerebral oedema,and biventricular myocardial hypertrophy.
Histologically, the lungs pronounced changes of pulmonary hypertension, while the heart showed moderate left ventricular fibrosis, particularly of the subendocardium and papillary muscles. No sickling was identified in any vessel. The liver showed siderosis and fibrosis with patchy inflammation and extramedullary haematopoiesis, but no cirrhosis. The kidneys showed focal segmental glomerulosclerosis, with tubular atrophy and interstitial fibrosis and inflammation. The residual spleen was calcified, a characteristic relic of 'autosplenectomy' seen in adults with sickle cell disease.
We show examples of the pathological changes in this case and discuss the most frequent changes found at autopsy in cases of sudden death in sickle cell disease.

P2

Adult sudden cardiac death: audit of 5 years of non-hypertensive, non-ischaemic causes and autopsy reports.

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In December 2006, the U.K. sudden adult death syndrome (SADS) network was set up, with the aim of improving diagnosis, genetic analysis and liaison with affected families and their general practitioners in cases of sudden cardiac death due to potentially hereditary causes. In 2007 in Oxford, we implemented a protocol for autopsy investigation of such deaths, including SADS network guidelines. We audited autopsy reporting of non-hypertensive, non-ischaemic sudden cardiac deaths between 2002 and 2006.
Of 29 (27 coronial and 2 consented) cases identified, no report allowed completion of all the questions in the SADS network proforma and no macroscopic findings had been photographed in any case. In 23/29 (79%) cases, a full autopsy was performed, while in the other cases examination of the central nervous system was not deemed relevant. However, heart weight was reported in all cases and the state of the coronary arteries in 28/29 (97%). Cardiac histology was taken in 28/29 (97%) cases, of which 3 (10%) had been referred to a more experienced cardiac centre for a second opinion. The entire heart was not retained in any case. Toxicological analysis was performed in 9 (31%) cases.
3 cases were simply reported as cardiac arrhythmia/ dysrythmia with no underlying cause. In addition to these 3, a further 16 potentially hereditary causes were identified, including cardiomyopathies, muscular dystrophy and myotonic dystrophy. Other causes included forms of myocarditis and pericarditis, amyloidosis and congenital abnormalities. We present our audit findings and our current protocol for tackling SADS autopsies. We also demonstrate the pathology of some of the cases.

P3

Primary Lymphoma of the Heart; Report of a Post-mortem Case

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A 41 year old male was admitted to A&E with sudden onset of palpitation, shortness of breath and nocturnal dyspnea. ECG at admission showed AV flutter with AV dissociation. Imaging showed a widened mediastinum and a mass between the atria and AV node with MRI reported as ?lymphoma. No biopsy was obtained. 10 days later he developed chest pain radiating to the back. ECG showed complete heart block with a pulse rate of 30/min. The following morning he was unresponsive and resuscitation was unsuccessful.
At autopsy there was serous pleural (800mls) and pericardial (100mls) effusion, cardiomegaly (weight 685grams) and atrial enlargement. The atrial wall measured 20mm and LV thickness was 18mm. The coronaries and valves were normal. There was no lymphadenopathy or organomegaly.
Histology of the heart showed a diffuse infiltrate of lymphoid blasts (mainly centroblasts) with frequent mitoses and patchy tumour necrosis. All other organs were unremarkable. The features were in keeping with a primary cardiac diffuse large B-cell lymphoma.
This is a rare condition arising from the atria. Only few cases are reported in the literature. If detected early this responds well to chemotherapy.

P4

Cardiovascular Deaths associated with Stimulant Drug Abuse: a Single Centre Experience

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The cardiovascular complications of recreational drugs are being increasingly recognised as a cause of sudden death in young to middle aged adults. Of 623 Coroner's autopsies performed in our unit during 09/2006-04/2007, we identified 6 sudden deaths attributed to the cardiovascular consequences of stimulant abuse.
The mean age was 40 years (range 35-46 years), 5 males: 1 female. In 5 cases there was a history of cocaine abuse, together with amphetamine and ecstasy in two, and in one case a history of amphetamine abuse alone. The causes of death were accelerated coronary artery disease (4), of which two showed acute myocardial infarction, aortic dissection (1) and subarachnoid haemorrhage (1). Blood and urine were present for analysis in five cases and all demonstrated drug use shortly before death. High levels of amphetamine were present in the blood in 3 cases (0.21-0.4 mg/L), cocaine and metabolites were present in 2, with the additional presence of cocaethylene in one.
Toxicology, performed in view of the history of substance abuse, demonstrated the presence of significant quantities of stimulants in all cases. This would indicate that, in addition to contributing to development of the underlying pathology, the acute effects of stimulants played a role particularly in determining the timing of these deaths. It is essential to obtain a full drug history, even when there is an apparently natural cardiovascular cause of death.

P5

The C-type lectins, DC-SIGN and CLEC-2 play a role in HIV-1 transmission by platelets.

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A substantial quantity of HIV-1 in the blood of infected patients is associated with platelets. It is therefore of interest to identify and characterize the molecules involved in HIV-1 binding to platelets and to determine the consequences of this interaction for HIV-1 spread in infected individuals. We show here that platelets and megakaryocytes express the C-type lectins DC-SIGN and C-type lectin-like receptor 2 (CLEC-2) and that these factors are mainly responsible for HIV-1 capture by platelets. HIV-1 bound to platelets could be transferred to T-cells with high efficiency, suggesting that platelets might promote HIV-1 infection.
We show that CLEC-2, in contrast to DC-SIGN, does not interact directly with the HIV-1 envelope protein gp120, but most probably with a cellular factor, which is incorporated into the viral membrane. Although DC-SIGN and CLEC-2 augmented HIV-1 transfer to T-cells *in trans*, only DC-SIGN enhanced *cis*-infection of target cells by reporter viruses bearing HIV-1 envelope proteins. Finally, incubation of platelet-associated HIV-1 with a DC-SIGN neutralizing antibody abrogated HIV-1 transfer to T-cells, suggesting that virions localized at the platelet surface were transmitted.

P6

LSECtin, DC-SIGN and DC-SIGNR interactions with viruses: Differential pH-dependence, internalization and binding

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The calcium-dependent (C-type) lectins DC-SIGN, DC-SIGNR and LSECtin show tight genetic linkage and share their ability to interact with pathogens. DC-SIGN and DC-SIGNR (DC-SIGN/R) bind to high-mannose carbohydrates on a variety of viruses while, LSECtin does not recognize mannose-rich glycans, but interacts with a more restricted spectrum of viruses. Here, we analyzed whether these lectins differ in their mode of ligand engagement. Generation of an LSECtin-specific monoclonal antibody demonstrated co-expression of DC-SIGNR and LSECtin by liver, lymph node and bone marrow sinusoidal endothelial cells. Treatment with LPS or IFN-γ in combination with TNF-α increased LSECtin expression on isolated human liver sinusoidal endothelial cells, suggesting that LSECtin might be up-regulated under inflammatory conditions. LSECtin and DC-SIGNR exhibited comparable affinities for soluble Ebolavirus glycoprotein (EBOV-GP). DC-SIGN, LSECtin and the Langerhans cell specific lectin Langerin readily bound to soluble human immunodeficiency virus type-1 (HIV-1) GP. However, only DC-SIGN captured HIV-1 particles, indicating that binding to soluble GP is not necessarily predictive of binding to virion-associated GP. Capture of EBOV-GP by LSECtin triggered ligand internalization, suggesting that LSECtin like DC-SIGN might function as an antigen uptake receptor. Thus, exposure to a low pH medium, which mimics the acidic luminal environment in endosomes/lysosomes, released ligand bound to DC-SIGN/R but had no effect on LSECtin interactions with ligand. Our results reveal important differences between expression patterns and pathogen capture by DC-SIGN/R and LSECtin and hint towards different biological functions of these lectins.

P7

Hypoxia-Inducible Factor is Expressed in GCTB and Mediates Paracrine Effects of Hypoxia on Monocyte-Osteoclast Differentiation

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Hypoxia stimulates osteoclast differentiation from monocytic precursors. Hypoxia-Inducible Factor (HIF) is a key pro-tumourigenic transcription factor regulating hypoxia-inducible gene expression. We describe expression of HIF-1 alpha and HIF-2 alpha in the multi-nucleated, osteoclast-like giant cells and mononuclear stroma of Giant Cell Tumour of Bone (GCTB). Hypoxia (0.1% O_2) and osteoclastogenic cytokines (HGF, M-CSF) induced expression of HIF and downstream genes (BNIP3, Glut-1, VEGF) in osteoblastic MG-63 cells, primary GCTB stromal cells and monocyte-derived osteoclasts. As VEGF can substitute for M-CSF to support osteoclastogenesis, we assessed effects of MG-63 hypoxic conditioned media (CM) on osteoclast differentiation. In the presence of RANKL hypoxic CM induced active osteoclast formation, assessed from numbers of TRAP-positive multi-nucleated cells and area of lacunar bone resorption. This was inhibited with neutralising anti-VEGF antibodies. Targeted siRNA ablated HIF-1 alpha and HIF-2 alpha expression in MG-63 cells and reduced hypoxic VEGF secretion. Hypoxic CM from cells treated with [HIF-1 alpha + HIF-2 alpha] siRNA resulted in significantly reduced osteoclast numbers ($p < 0.005$) and activity ($p < 0.05$). This suggests that local hypoxia could indirectly influence osteoclastogenesis via paracrine, HIF-dependent, secretion of VEGF and is potentially an important mechanism of pathogenesis for GCTB and other osteolytic lesions.

P8

Clinical Significance of Acquired Activated Protein C Resistance Caused by Lupus Anticoagulants

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Background: Lupus anticoagulants (LA) are a risk factor for thrombosis (venous or arterial). Factor V Leiden (FVL) is a risk factor for venous thrombosis. It is not known if patients with a falsely low APCR ratio have an increased risk of thrombosis.
Design: We prospectively identified patients in which LA testing was positive and APCR by DNA testing was performed from 2006-7. We performed a chart review for deep venous thromboses and/or pulmonary emboli. We defined APCR ratio >2 as negative and APCR ratio <2 as positive for acquired APCR. Statistical analysis was performed (Fisher exact test and Chi square tests).
Results: FVL by DNA testing was normal in 27of 29 patients (11 had acquired APCR) and heterozygous for the remaining 2 patients. 7 of 11 patients with a positive APCR ratio had venous thromboses versus 2 of 16 patients with a negative APCR ratio (Fisher p =0 .0084, Chi Square p = 0.0049).
Conclusion: Our study suggests that patients with acquired APCR due to LA have an increased risk for venous thrombosis.

P9

Non-canonical Pathways of Osteoclast Formation

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Osteoclasts are known to form from circulating mononuclear phagocyte precursors in the presence of M-CSF, a survival factor, and RANKL, a key growth factor. We cultured human monocytes in the presence of a number of cytokines and growth factors (VEGF, Flt3, PlGF, HGF, LIGHT, and APRIL) and inhibitors of RANKL (osteoprotegerin) and a neutralising antibody to M-CSF in order to determine if non-canonical (M-CSF/RANKL-independent) pathways existed. We found that VEGF (25ng/ml), Flt3 (10ng/ml), PlGF (25ng/ml) and HGF (25ng/ml) could substitute for M-CSF and that LIGHT (50ng/ml) and APRIL (25ng/ml), both of which are TNF-superfamily members, could substitute for RANKL. Further investigation of RANKL-independent osteoclastogenesis by Western blot analysis revealed that both LIGHT and APRIL activate three key downstream signalling pathways: Akt, NFkappaB, and JNK. The Akt pathway, which is solely activated by TRAF6, is essential for osteoclastogenesis to occur. Analysis of the downstream signalling pathways of RANKL and M-CSF growth factor substitutes will provide insight into the non-canonical pathways of osteoclast formation, which are likely to play a role in the pathological resorption of inflammatory/neoplastic bone lesions, many of which contain cells that produce large amounts of these growth factors.

P10

Early Regulation of 'Early Stemness' Gene Events in Pluripotent Cancer Stem Cells

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Background. Similarities between cancer stem cells (CSCs) and normal stem cells (NSCs) during self-renewal and at 1 week differentiation have facilitated identification of key stemness processes. However, only by identification of key differences between these progenitors can CSC-targeting be developed towards therapeutics. Hypothesising that aberrant regulation of differentiation, rather than of differentiation itself, may characterise CSCs and postulating that early differentiation would be characterised by expression of stemness regulators, we have assessed whether key stemness and cancer processes are detectably regulated during early differentiation.
Methods. Human teratocarcinoma ('classical stem cell' gonadal tumours) CSCs were retinoic acid-differentiated over a period from 3 days up to 4 weeks and expression of key stemness and cancer processes assessed by TaqMan realtime PCR analysis of marker genes.
Results. We have demonstrated that key stemness (Oct-Sox-Nanog, Wnt, Shh) and cancer (PTEN, TGF-beta signalling) processes are co-ordinately regulated from 3 days differentiation implying that regulators of these events are expressed very early in differentiation. Indeed, only Notch and Snail signalling showed no change after 3 days differentiation, being altered only after 1 week differentiation.
Conclusion. We have demonstrated that stemness and cancer processes are regulated from earlier in differentiation that previously observed.

P11

RPL19 is a Promoter of the Malignant Phenotype of Prostate Cancer

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Ribosomal protein L19 (RPL19) is over-expressed in malignant prostate cell lines when compared to their benign counterparts, as shown by quantitative PCR. Preliminary studies by in situ hybridisation revealed the RNA to be differentially expressed in prostate cancers and to discriminate the aggressive form of the disease, hence confirming its value as a reliable indicator of disease outcome. To investigate the role of RPL19 in promoting prostatic malignancy, siRNA was used to suppress expression of the gene in the malignant prostatic epithelial cell line, PC3M. Targets were designed to silence RPL19 variant c, the NM version of the gene (NM_000981). These targets also have the potential to silence 7 of the 8 potential splice variants of RPL19. The most successful target reduced RPL19 expression by 90% and was further investigated following stable siRNA transfection. Effects on cell proliferation and migration were examined. Downstream gene expression profiles of the silenced transfectants were generated and examined using custom DNA oligonucleotide microarrays designed in partnership with Agilent Technologies. These arrays contained individual gene-sequences tailored to our specific field of interest. These profiles now provide a novel insight into the role of ribosomal proteins in the progression of prostatic malignancy.

P12

The unknown primary-use of gene specific RT-PCR for molecular finger printing to identify the primary tumours-an alternative to chip assay

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The expression repertoire of all tissues includes a combination of house keeping and tissue specific genes. Metastatic tumour is identified by conventional H&E stained sections. A further tier in the diagnosis of the tumour and its site of origin is guided by immuno-cytochemistry, although there is a marked shortage of tissue specific antibodies. Patients with advanced cancer have ascites and pleural effusions, where malignant cells are recognised as a second population of cells, but often histogenesis is not readily apparent, even with immunohistochemistry.

Quantitative real time RT-PCR holds out promise of being able to detect multiple tissue specific genes and is applicable to malignant peritoneal and pleural fluid. In this presentation, we demonstrate the use of a Light Cycler, capable of multiplexed PCR reactions for detecting tissue specific gene expression in patients with advanced breast and lung cancer. We have chosen mammo-globulin and TTF1 respectively as candidate genes important for their diagnosis. In the first instance we demonstrate proof of concept by demonstrating expression of tissue specific genes in patients known to have primary tumours in these sites. Next, we investigate the feasibility of the use of real time RT-PCR to identify sites of origin for primary other tumours.

P13

Tissue Profiling of Gastrokine-2/Blottin Expression

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A gastric foveolar protein, Blottin, was found by its binding to TFF2-alkaline phosphatase fusion protein. It is in normal stomach surface and pit cells. Being similar to Gastrokine (GKN)-1 it is renamed Gastrokine-2. It is reduced in gastric adenocarcinoma, up-regulated in gastric metaplasia, duodenal ulcer and Crohn's disease. Here, we assessed Gastrokine-2 in human normal and cancer tissues.
Methods: Gastrokine-2 immunohistochemistry performed on a tissue microarray (42 normal, 50 cancers), was assessed by two pathologists.
Results: Gastrokine-2 was confirmed in normal body and antrum surface and foveolae, but absent from the gastric adenocarcinoma, while a colonic adenocarcinoma was positive. There was weak staining elsewhere, including: normal colon, pancreas, gall bladder, lung, endocervix, skin adnexae, and tumours like appendix goblet cell carcinoid, endometrial adenocarcinoma, ovarian mucinous adenocarcinoma, breast adenocarcinoma and breast phylloides. Other epithelia, connective, melanocytic and neural tissues may lack Gastrokine-2. We found differential nuclear staining in several cases.
Conclusions: GKN-2/Blottin is expressed in colonic adenocarcinoma, upregulated in gastric metaplasias and downregulated in some gastric tumours. It may help in gastrointestinal maintenance and repair alongside TFF peptides and mucins. Its presence elsewhere remains to be understood.

P14

Ki67 Estimation in Neuroendocrine Tumours

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Introduction- The protein Ki67 is a marker of the cell cycle and can distinguish cells within the cell cycle. Therefore an antibody to Ki67 (MIB1) is used as a proliferation marker in neuroendocrine tumours (NETs). In NETs the Ki67 index is important for tumour grading and treatment planning, so accurately estimating the correct percentage is important.
Methodology- Fifty random NET cases were selected and the slides and Ki67 index estimated in the report obtained. The Ki67 index was repeated by counting MIB1 nuclear labelling in approximately 2000 tumour cells per case in areas of highest MIB1 staining. This was done using the Glasgow cell counting graticule. (Going JJ (2006) Counting cells made easier. Histopathology 49:309-311.)
Results- Of the 50 cases selected, 23 had suitable Ki67 stained slides for use in the audit. The range of estimated Ki67 percentage in these 23 cases was 0-40%. The graticule result varied from being the same as the estimate to 31% away. Seven cases changed NET grade after graticule use.
Conclusion- Estimated Ki67 counts are different to Ki67 counts using an eyepiece graticule. The inaccuracies causing cases to change NET grade in seven cases could affect treatment. However, there are limitations to the study.

P15

Workforce Survey Using A Commercial Web Based Survey Instrument

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The shortfall in the histopathology workforce in the UK is well known; an increase in trainee numbers is anticipated to improve the situation. However, it is not known by how much each trainee will contribute to the workforce when qualified. A pilot survey to determine trainees' preferences for posts and their potential headcount / WTE ratio has been previously reported. We have now distributed the survey by email to all trainees registered with the Royal College of Pathologists. There were 239 out of 526 responses to the email request to complete a web-based questionnaire (SurveyMonkey).
Most (70%) intend to work full time or more with an estimated headcount / WTE ratio of 1.0, although many suggested flexibility of hours was likely to be important. Non-consultant career grades were not favoured. The most important factors influencing choice of post were geographical location, partner's career, family ties and type of department. The survey suggests departments of 6 – 15 consultants, with broad subspecialisation and in which they had positive experience as a trainee would be likely to be most attractive. Although teaching and research time would not deter application, they ranked low in ordered priority.

P16

Integrated Training by Online Learning: A Personal Perspective

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Online learning tools have been embraced due to their perceived ease of use and value as a learning resource. With the formation of the Histopathology Training School in a collegiate model and a structured approach to education according to the RCPath year 1 curriculum, could online learning be a valuable resource for trainee pathologists? Also could it open up opportunities for integrated training of medics and scientists?
One of the Histopathology ST1 trainees completed a Biomedical Science MSc online module during the ST1 year. Assessments in the form of online discussions, essays, MCQs and a final PowerPoint presentation resulted in credits towards an MSc.
Guided study of more complex topics was useful and educational, however the module did highlight some potential IT problems with online learning. Some practical aspects of Histopathology training (e.g. handling surgical specimens) proved less suited to this mode of learning. However the integrated nature of the course was stimulating and useful experience. For senior trainees wishing to complement their practical experience with flexible guided study towards an MSc course, online learning could prove to be a useful adjunct.

P17

21st century teaching: Pathology online

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Increased student numbers at Medical Schools across the UK has placed extreme pressure on the delivery of traditional lecture/tutorial based courses within the medical curriculum including pathology.
To combat this problem an e-module in systemic pathology has been developed to replace an entire traditional lecture/tutorial based course. The e-pathology module is centred on audible digitally recorded mini-lectures (restricted to < 20mins) which can be downloaded in different formats making the course portable and instantly accessible irrespective of geographical location. Each mini-lecture is supported by self-assessment 'question and answer' exercises; and complemented by e-based clinical case scenarios. The e-pathology resources are available via the world wide web and on DVD.
With the traditional course the students would have to return to the base teaching hospitals twice weekly for pathology lectures and tutorials irrespective of where their clinical attachments were in Northern Ireland. The flexibility of pathology online removes the need for travelling, reduces student costs and makes more time for self directed study. Students can also access the teaching material that relates best to their clinical practice at that time.
This approach to pathology learning, *using e-technology* engages the student, encourages self directed learning and facilitates student centred pedagogy.

P18

Expression of claudin-4 in poor prognosis carcinomas of the breast and prostate

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Background and Aims: The role of claudins (CLDN) has been suggested in carcinogenesis and cancer therapy. We investigated the expression of CLDN4 in common carcinomas: breast and prostatic cancers. We chose *basal-like breast cancer (BLBC)* (as the worst clinical prognosis group), and a clinically aggressive, *poor prognosis prostate carcinoma (PPPC)* subgroup.
Methods: Using tissue microarrays, 38 BLBCs were compared to 66 grade 1, 2 and 3 non-basal invasive breast carcinomas, further, 13 PPPCs were compared to 10 cases with good prognosis (GPPC) and 14 BPH concerning CLDN4 expression. Immunohistochemistry was evaluated semiquantitatively and morphometrically.
Results: Significant difference was found regarding CLDN4 expression in the BLBC group compared to grade 1, 2 (p=0,001) and 3 (p=0,017) cancers. CLDN4 was significantly up-regulated in PPPCs compared to GPPC (p<0,001) and BPH (p=0,028) group.
Conclusions: Our results suggest that BLBCs and PPPCs are subsets with distinct CLDN4 expression profile. This finding is in accordance with our former observation that CLDN4 is related to cellular differentiation in breast cancer, as might be in other types of adenocarcinomas (e.g. prostatic cancer). Since CLDN4 is the receptor molecule for the Clostridium perfringens enterotoxin, our finding may call attention to a possible therapeutic approach to BLBC and PPPC.

P19

MMR, MCM2, TGFRB and TIMP2 are prognostic for colorectal cancer: results of a TMA analysis of 711 Phase 3 trial patients

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PURPOSE: The expression of genes encoding a number of pathogenetic pathways have the potential to act as prognostic markers in colorectal cancer (CRC). We investigated the relevance of 19 markers within the MMR, cell proliferation and cell cycle, cell signalling and invasion pathways in patients enrolled in a large randomised trial.
METHODS: 711 patients with CRC in a Phase 3 trial of 5-fluorouracil were studied. Tumour tissue microarrays were generated and assessed by immunohistochemistry for MLH1, MSH2, MSH6, PMS2, Ki67, MCM2, cyclin A, p16, bcl-2, bax, VEGF, MMP2, TIMP2, uPA, TGFBRII, SMAD4 and PRL3, and by chromogenic *in situ* hybridisation for EGFR and HER2 amplification. The relationship between overall survival (OS) and marker status was assessed.
RESULTS: MMR, MCM2, TIMP2 and TGFRBII were significantly associated with OS. Despite a higher proliferation rate in MMR deficient tumours (p<0.01), this patient group had a better prognosis (hazard ratio [HR] = 0.55, 95% CI: 0.30-1.00). Elevated MCM2 expression was also associated with a better prognosis (HR = 0.72, 95%CI: 0.50-1.02). Conversely, TGFBRII and TIMP2 overexpression was associated with a poorer prognosis (HR = 2.22, 95% CI: 1.06-4.67; and HR = 1.64, 95%CI: 1.00-2.69, respectively).
CONCLUSION: In addition to confirming the prognostic relevance of MMR status, this study identifies cell proliferation, TGFRBII and TIMP2 expression as all prognostic of patient outcome in colorectal cancer.
This work was supported by grants from Cancer Research UK and the Association for International Cancer Research and a Clinical Research Fellowship grant from St. George's Hospital Charitable Foundation Medical Research Committee.

P20

Gastric cancers of Western European and South African patients show different patterns of genomic instability

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Background: Gastric cancer is the second most common cause of cancer death worldwide, but incidence and mortality rates show large variations across different counties. Previous studies reported environmental and dietary factors influencing gastric cancer risk, but not much is known about the biological differences in gastric cancers in different geographic locations. Therefore, we aimed to compare genomic differences in gastric cancers obtained from patients from Western Europe and South Africa.
Material & Methods: Fifty-eight gastric cancers from 33 Western European and 25 South African patients were included in the study. DNA was isolated and analysed for microsatellite (MIN) and chromosomal (CIN) instability by PCR and microarray comparative genomic hybridisation, respectively.
Results: Tumours from South Africans show significantly more microsatellite instable tumours compared to tumours from West European patients (P<0.0001). In addition, microsatellite stable tumours from both groups could be separated by unsupervised hierarchical cluster analysis (P=0.001). Chromosomal regions 1q31, 3p24-26, 7p21 and 21q21 contributed most to this separation.
Conclusion: Gastric cancers from South African and European patients show differences in their genomic instability patterns, indicating possible different biological mechanisms underlying the disease.

P21

Obstructing giant post-inflammatory polyposis in ulcerative colitis: case report and review of the literature

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Giant post-inflammatory polyps (PIPs) cause great diagnostic confusion in a small number of inflammatory bowel disease (IBD) patients.
PIPs, commonly termed "pseudopolyps", are well-described in IBD. They complicate ulcerative colitis (UC) twice as frequently as colonic Crohn's disease (CD), but may occasionally be seen following episodes of severe inflammation associated with infection or ischaemia. PIPs more than 15mm in diameter or length are termed "giant". can mimic colorectal carcinoma. Giant PIPs present clinically with a variety of symptoms ranging from obstruction to bleeding, but may occasionally be asymptomatic and an incidental radiological or endoscopic finding. Their importance is that this benign and rare sequel of UC or colonic CD is often mistaken clinically and radiologically for carcinoma, in a population of patients who are known to be at increased risk of colonic malignancy, potentially leading to unnecessarily radical surgery.
A case of obstructing giant PIPs of the colon in a patient with apparently well controlled, long-standing UC is presented with a review of the literature. The characteristic clinical, endoscopic and pathological features have to be more widely recognised to ensure appropriate management.

P22

Audit of Lymph Node Yield in Colorectal Cancer (CRC) Resection Specimens

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BACKGROUND: Lymph node involvement is the most important prognostic factor for patients who have undergone radical surgery for colorectal cancer (CRC).
AIMS: To determine the lymph node yield in CRC specimens and match these to the Dukes staging.
METHOD: The reports of 238 patients, underwent surgical resection for CRC in the year 2005, were reviewed for lymph node yield and Dukes stage.
29 patients with rectal cancers had preoperative neoadjuvant chemo-radiotherapy were analyzed separately according to the dose of radiation and the lymph node yield.
RESULTS: The median number of lymph node yield in all cases was 12, ranging between 0-38 nodes. The total number of lymph node negative cases (Dukes stage A and B) were 127, of which 59% had less than 12 nodes retrieved. The node positive cases (Dukes stage C) were 88, of which 50% had less than 12 nodes retrieved.
CONCLUSION: Discussion at the MDT meeting of cases with low LN yield (especially those with less than 8) with a view to improve the surgical and pathological procedures is mandatory. Adjuvant therapy can be offered for selected cases of patients with Dukes stage B and low node yield after clinico-radiological staging and assessment at MDT.

P23

Raf Kinase Inhibitor Protein (RKIP), a potential prognostic marker in Dukes B Colorectal Carcinoma

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Raf Kinase Inhibitor Protein (RKIP) plays a role in a number of cell signalling pathways which are involved in cancer. RKIP expression levels have been shown to be important in a number of human cancers, where it is thought to act as a metastasis suppressor.
In this study we set out to examine the expression levels of RKIP using immunohistochemistry on a tissue microarray consisting of over 200 cases of Dukes B colorectal carcinoma. RKIP expression was scored using a semi-quantitative system combining both the intensity of staining and the percentage area stained. Using this system RKIP expression was divided into 3 groups; negative, weakly positive and strongly positive. Expression was then compared to survival and to pathological parameters such as peritoneal involvement and tumour size.
A significant difference ($p=0.007$) in 5-year disease specific survival was seen between the 3 groups, with high levels of RKIP expression correlating with improved survival. This difference was independent of peritoneal involvement, tumour size and lympho-vascular invasion.
RKIP appears to be a useful prognostic marker in patients with Dukes B colorectal carcinoma and may act as a valuable aid in stratifying these patients for close post-operative monitoring and possible adjuvant therapy.

P24

Diaphragm Disease of the Large Bowel – A Rare Mimic of Carcinoma

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Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) is a well-known cause of diaphragm disease of the small bowel where it often leads to intestinal obstruction. We report a classical case of diaphragm disease of the large bowel in a fifty-one year old woman who presented with a painful right-sided abdominal mass. She has been on long- term use of Diclofenac for the treatment of rheumatoid arthritis. CT of the abdomen revealed a stricture of the ascending colon and carcinoma was suspected. Right hemicolectomy showed diaphragm formation and multiple ulcers in the ascending colon. Histology showed intact mucosa over the diaphragm, thickened muscularis mucosae, diffuse submucosal fibrosis and, in other areas of the large bowel, multiple non-fissuring ulcers compatible with long term use of NSAIDs. Diaphragm disease associated with prolonged use of NSAIDs is usually seen in the small bowel. Our case report represents an unusual presentation in large bowel.

P25

Mitochondrial DNA mutations give an insight into clonal and lineage relationships in the human small intestine

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Introduction: Mitochondrial DNA mutations can be acquired by random genetic drift over the lifetime of an individual. The mitochondrial genome encodes enzymes involved in oxidative phosphorylation, such as cytochrome c oxidase (COX). The pattern of spread of cells carrying a high proportion of mutated mitochondrial encoded COX can be followed using enzyme histochemistry and immunohistochemical techniques, thus permitting morphological identification of stem cells and their progeny.

Aims: 1)To establish the presence of mitochondrial DNA mutations in small intestinal crypts and 2) To use mitochondrial DNA mutations to study stem cell architecture, clonality, lineage relationships and patch size in the small intestine.

Materials and Methods: Enzyme histochemistry for COX and nuclear encoded succinic dehydrogenase and immunohistochemistry for COX was performed on frozen and formalin fixed paraffin small intestinal mucosa.

Results: Mitochondrial DNA mutations are present within small intestinal crypts. Partially and wholly COX negative crypts were seen. Lineage analysis showed that a single stem cell produces all lineages within an intestinal crypt. Patches of COX negative crypts upto 9 crypts in size were identified.

Conclusions: Mitochondrial DNA mutations are established in human small intestine. More than one stem cell exists per crypt. A single stem cell is able to undergo niche succession followed by repopulation of the crypt with its progeny. A large patch size is present, and this may be increased in patients with FAP as a consequence of increased crypt fission.

P26

More than just an evolutionary relic – an unusual cause of small bowel obstruction?

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Appendiceal adenocarcinoma is rare and a very unusual cause of small bowel obstruction. Primary appendiceal adenocarcinomas represent less than 0.5% of all gastrointestinal neoplasms and only 0.1% of 'routine' appendicectomies are found to contain a primary carcinoma of the appendix. The peak incidence of presentation is typically in the fifth to seventh decade.

We present a case of an 89-year old female who presented with the clinical features of bowel obstruction. An abdominal radiograph demonstrated features suggestive of distal small bowel obstruction but no free sub-diaphragmatic gas was identified on chest radiograph. Conservative therapy was commenced, but failure of symptomatic improvement led to computerised tomography scanning of the abdomen being performed. This suggested an abnormal soft tissue thickening in the right iliac fossa. A subsequent laparotomy revealed a mass centred on the appendix. Histological examination of the resection specimen revealed a primary adenocarcinoma of the appendix. This case illustrates a rare cause of small bowel obstruction, in which the diagnosis was not suspected until laparotomy and not clearly made until histological examination of the resection specimen.

Patients with primary adenocarcinoma of the appendix are at risk of intra-abdominal involvement in particular pseudomyxoma peritonei. Tumours identified histologically as colonic rather than mucinous type possess a worse clinical outcome. Currently, the long-term prognosis of appendiceal carcinoma is not clearly defined, due to the small number of published studies, but one series of 94 cases quoted a 55% five-year survival.

P27

Colorectal cancer associated genes: a feature selection approach comprising small regions of DNA copy number alteration, gene expression profiles and somatic mutations

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The instability of colorectal cancer genomes results in abnormal chromosome numbers per cell and a variety of structural chromosomal abnormalities including deletion, duplication, amplification, inversion and translocation. The large size and complexity of many of these abnormal regions makes definitive identification of the key cancer-associated genes presumed to lie within them a laborious and in many cases still unfinished task. Here we provide new data on small (<20Mb) regions of copy number gain and loss detected in a series of 109 primary cancers studied using genomic microarrays with resolution of 1-2Mb. These were combined with published data on tumour-associated gene expression (Notterman et al. (2001) Cancer Res 61: 3124 – 3130) and point mutation (Sjoblom et al. Science (2006) 314: 268 – 274) to derive refined sets of cancer-associated genes.

Linear discriminant analysis (LDA), combining data that related to copy number gain or loss, gene expression and the presence of point mutation identified 10 genes that consistently permitted distinction between normal mucosa and cancer. These genes include suspected oncogenes and putative tumour suppressor genes, together with several genes so far not designated as cancer-related.

This study illustrates the power of functional genomics and genome informatics in refining parameters that discriminate cancer tissue from normal.

P28

Vascular Malformation Presenting as Intussusception

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We report the case of a vascular malformation presenting as intussusception in a boy.

A previously fit and well fifteen year old boy presented with a three week history of abdominal pain, vomiting and weight loss. On a few occasions he had loose stools with blood. He underwent an elective colonoscopy which showed the presence of a possible intussusception. An ultrasound confirmed the diagnosis and on the same day he was operated. A limited ileocolic resection with end to end anastomosis was performed. He made a good post-operative recovery and was on full feeds on discharge.

The right hemicolectomy received showed an area of caecal ulceration which measured 20mm and on slicing appeared to be limited to the submucosa. Histology showed ulceration with granulation tissue which had a somewhat lobular architecture. Also, there was a transmural proliferation of vessels of varying calibre which also extended into extramural adipose tissue. Regional lymph nodes had features of early vascular transformation. The features were in keeping with a vascular malformation an uncommon but well-known cause of intussusception. There were no features of malignancy. Complete resection is curative.

P29

The clonal beginnings of intestinal metaplasia in the human stomach: Fission is an important mechanism of spread

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Introduction: The clonal origins and mechanisms of spread of intestinal metaplasia (IM) are poorly understood. Mihara et al., (2006 Am. J. Path. 169(5):1643) suggested that IM is a polyconal disorder with distinct glands having different methylation patterns. Our data, using mitochondrial DNA (mtDNA) mutations as a marker of clonal expansion, has shown that normal gastric glands are clonal: all cells containing the same mtDNA mutation. We showed that clonal patches occur with multiple glands each containing the same mutation. Here we investigate the clonal makeup of IM and how it spreads.
Materials and Methods: Enzyme histochemistry (for cytochrome *c* oxidase and succinate dehydrogenase) was performed on sections of human gastric IM. Laser-capture microdissection was used to isolate CCO-ve metaplastic glands and PCR sequencing on the entire mtDNA genome was performed. Immunohistochemistry for CD10, MUC2 and serotonin was used as markers of differentiated epithelial cells.
Results: Entirely CCO-ve IM glands were observed indicating that such glands are clonal. Immunohistochemistry revealed that all the major differentiated lineages were present in such glands. Interestingly, mixed glands were also present suggesting that multiple stem cells reside in these glands. We observed regular patches of CCO-ve glands which all contain the same mtDNA mutation suggesting that there is one founder crypt which has expanded by fission.
Discussion: These data suggest that IM has its origins as a clonal disorder and that fission is a method by which it spreads through the stomach. When compared to methylation studies there is conflict. We would suggest therefore that as mtDNA mutations take many years to accrue to detectable levels this provides an earlier lineage of IM whereas methylation is far more rapid and diverges quicker.

P30

Usefulness of AMACR in distinguishing dysplastic epithelium in patients with barretts oesophagus

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Introduction: There is substantial inter-observer variability in diagnosing dysplasia (especially low-grade dysplasia and Indefinite for dysplasia) in Barrett's oesophagus, hence need to find adjunct means of doing so. A recent study(ref) evaluated the expression of Alpha-Methylacyl-CoA-racemase (AMACR), a mitochondrial and peroxisomal enzyme, in diagnostically difficult lesions in BO with a reasonably high degree of sensitivity and specificity. We investigated if these results are reproducible in a larger cohort with better follow up data.
Material & Methods: 86 oesophageal biopsies (14BO, 38indefinite, 11LGD, 10HGD and 15adenocarcinomas) were stained using a monoclonal anti-AMACR antibody. The slides were evaluated by two pathologists in a blinded fashion for perinulcear granular staining. Discordant cases were re-evaluated to arrive at the final diagnosis.
Results:

	No of Positive cases(%)
Barrett's. no dysplasia	0/14 (0)
Indefinite for dysplasia	10/36 (28)
Low-grade Dysplasia	2/11 (18)
High- Grade dysplasia	4/10 (40)
Adenocarcinoma	10/15 (67)

Conclusions: Of the positive cases in the study group 5/10(50%) subsequently developed at least low-grade dysplaisa. Our results indicate that AMACR is a useful marker for detecting IND which progressed to a worse category and has as sensitivity and specificity of 62.5% and 82% respectively.
Ref : Dorer, R. and R.D. Odze, *AMACR immunostaining is useful in detecting dysplastic epithelium in Barrett's esophagus, ulcerative colitis, and Crohn's disease.* Am J Surg Pathol, 2006. **30**(7): p. 871-7

P31

Variation in the Histopathological Analysis of Gastrointestinal Dysmotility: an International Study

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Surgical resection or full thickness bowel biopsy is often an 'end-of-line' procedure for the relief of symptoms or the diagnosis of gastrointestinal neuromuscular disorders. Such disorders include idiopathic slow transit constipation and intestinal pseudo-obstruction, conditions associated with considerable morbidity, and for those at the severe end of the intestinal failure spectrum, a high mortality.
We have investigated the approaches taken in histology laboratories in the interpretation of samples from patients with these disorders, testing the hypothesis that there is little in the way of common practice.
We approached laboratories throughout Europe and the United States, asking them to complete a web based questionnaire about what stains they undertake on such samples, and have collated the responses.
Of the 130 laboratories who responded (50% response rate to initial contact), 86 processed gastrointestinal motility disorder samples. 34 different techniques were used. Of these 86 laboratories the only stain that all laboratories performed was a haematoxylin and eosin stain, with 54 doing levels. The next most commonly performed stains were CD117 (33), S100 (32), SMA (19), PAS (16), Desmin (12), NSE (11), HVG/EVG (10), Masson trichrome (9), CD45 and ACE (6), PGP9.5 (3) CD34, NF (2). Only one laboratory in the cohort performed each of the remaining 18 stains.
The means number of stains performed was 2.7 and the range 1-12.
No correlation was found between the location of the laboratories or the number of specimens received and the number of stains done.
Vast variation exists in the practice.

P32

Has the ThinPrep method of cervical screening maintained its improvement over conventional smears in terms of specimen adequacy?

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Background: Liquid based cytology (LBC) has replaced conventional smear assessment in many centres over recent years. In our laboratory this transfer happened in 1999. At that time we performed a split sample study comparing the conventional method of cervical smear evaluation with the ThinPrep system. This split sample study identified a dramatic improvement in specimen adequacy with LBC. While 11% of conventional preparations were reported as unsatisfactory and almost 9% were reported as sub-optimal, evaluation of the same cases using LBC saw this combined figure reduced to 2.3%.
Aim: To evaluate whether this dramatic fall in unsatisfactory smears has been maintained with the use of LBC.
Materials and Methods: The database for all smears reported for 2005 (100% LBC) was interrogated. The number of unsatisfactory reports was calculated. The reason for an unsatisfactory report was recorded for each case. The overall unsatisfactory rate was compared with that reported in the 1999 split sample study.
Results: A total of 41,312 smear tests were reported in 2005. 1,342 (3.25%) were reported as unsatisfactory.
Discussion: Our findings support the ongoing value of LBC in a routine cervical screening laboratory in terms of continuing to maintain a low rate of unsatisfactory smears.

P33

Villoglandular Adenocarcinoma of the Cervix: High Risk HPV Infection is Associated with Disruption of DNA Licensing and Replisome Proteins

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Villoglandular Adenocarcinoma (VGA) of the cervix is reported to have a good prognosis with a limited metastatic potential. Recently, it is recognised that VGA may have an aggressive biological behaviour. Identification of significantly dysregulated DNA replication licensing genes was achieved using gene expression profiling analysis. Their dysregulation generally indicates presence of high risk HPV. The objective was to assess expression patterns of these protein markers in VGA in relation to HPV status. Protein expression of the following markers was assessed: p16(INK4A), bcl-2, MIB-1, mcm 2,3,5,7 cdc 6, geminin, Topoisomerase IIα, survivin and nuf, in 8 cases of histologically confirmed VGA. HPV status was determined using an in house developed quantitative real time TaqMan PCR for HPV 16 and 18. All cases showed > 60% cellular positivity for mcm2, mcm3, Topoisomerase II, survivin, nuf, and geminin. 7/8 cases showed > 60% cellular positivity for p16(INK4A), mcm5, Cdc6. 5/8 cases showed > 60% cellular positivity for mcm7, and 6/8 cases were bcl2 negative. HPV typing revealed HPV 16 in 6/8 cases while HPV 18 was detected in 7/8 cases and 5 cases demonstrated dual infection. This study describes HPV status in VGA may be associated with dysregulation of DNA replication licensing proteins.

P34

An Integrative Transcriptome Map of Recurrence in Ovarian Cancer

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Background: The majority of ovarian cancers present in advanced stages. Despite an initial 80% response rate, most patients relapse and fewer than 15% become long-term survivors. The aim of this study was to identify novel markers of recurrent/chemoresistant disease.
Design: The study consisted of 2 cohorts: (1) 5 primary and 5 recurrent serous papillary adenocarcinomas (2) 3 paired ovarian cancers of different histology; papillary serous, mixed mullerian and clear cell. Gene expression analysis was performed using the Applied Biosystems array 1700. Independent validation was performed on 10 primary and 3 recurrent serous papillary adenocarcinomas.
Results: Upregulated genes in the recurrent tumours in both cohorts segregated in the same gene families: S100B and S100A8 (S100 calcium binding proteins), TJP3 and Claudin 16 (tight junction proteins), BTC and NRG2 (EGFR ligands), and interleukin receptors IL1R2 and IL27RA.
Conclusion: We propose an integrative model for ovarian cancer recurrence, in which tumour cells during relapse produce adhesion molecules to mediate attachment, cytokines and inflammatory mediators to stimulate survival and a variety of growth factors bound to their receptors to fully proliferate in order to confront and modulate their immediate environment. Some of the mechanisms involved in recurrence could be specific to the drugs used.

P35

Altered Expression of miR-223 and miR-9 in Recurrent Ovarian Cancers may Target the FGF Family

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Background: Our transcriptome profiling has previously identified a gene signature which may be representative of recurrent/chemoresistant ovarian cancer. Our recent profiling of 180 miRNAs in the same cohort of recurrent versus primary serous papillary adenocarcinomas identified miR-223 and miR-9 as the top up and downregulated miRNAs respectively.
Methods: Independent validation of miR-223 and miR-9 was carried out by extracting total RNA from 12 primary and 8 recurrent fresh frozen ovarian tumours using the Ambion mirVana™ miRNA isolation kit. miRNA expression levels were examined using the Applied Biosystems stemloop RT/PCR kit (ABI). Quantification of recurrent samples was carried out relative to primary using the ΔΔCt method. Let-7a was used as an endogenous control.
Results: miR-223 was upregulated in recurrent versus primary fresh frozen tumours and miR-9 downregulated by more than two fold change.
Conclusions: miR-223 and mir-9 are predicted to target members of the Fibroblast Growth Factor family which was identified as a target in our transcriptome study. This gene family may be associated with the acquired metastatic capacity or recurrence pattern of advanced epithelial ovarian cancers and warrants further investigation.

P36

Giant Leiomyoma of the Uterus in an Adolescent Girl

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Uterine leiomyoma are rare in children and adolescents. Here we present a case of giant uterine leiomyoma (GUL) in a 14 year old female who presented with abdominal pain and a mass.

The well circumscribed lesion weighed 2880 grams and measured up to 23cm in size. The cut surface was cream coloured and whorled with small foci of haemorrhage and myxoid areas.

The tumour was composed of interweaving fascicles of bland spindle-shaped cells with variable cellularity. Mitoses were present at 5 per 10 high power fields with no abnormal forms noted. Focal hydropic degeneration, haemorrhage and infarct-type necrosis was seen. Immunohistochemistry showed the cells to be strongly positive for desmin, caldesmon and smooth muscle actin but negative for CD10.

Cytogenetic studies revealed an abnormal karyotype with multiple abnormalities including a t(1;12) translocation, a probable variant of the t(12;14) associated with uterine leiomyoma.

A diagnosis of GUL was made of which there are only three other case reports in the paediatric literature. These lesions all had a variable presentation and without careful investigation might be clinically confused with ovarian malignancy. Conservative management to preserve fertility is the preferred option. Histological features favouring a malignant diagnosis must be interpreted with caution.

P37

Potentially Important microRNA Cluster at Chromosome 17p13.1 in Papillary Serous Carcinoma of the Peritoneum

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Background: The pathogenesis of ovarian cancer is complex, but chromosome 17 has been implicated as a potential location important in the pathogenesis of papillary serous carcinoma of the peritoneum (PSCP) as well as ovarian serous carcinoma (PSOC). High frequencies of LOH have been described at locus 17p13.1 (the genomic locus for p53 and the microRNA cluster miR-195 and miR-497) in both tumour types.
Methods: Total RNA was extracted from 20 PSOC and 20 PSCP FFPE high grade advanced cases using Ambion RecoverAll™ Total Nucleic Acid Extraction Kit. Stemloop RT/PCR kit was used for miRNA expression profiling (ABI). Analysis of relative miRNA expression data was performed using the ΔΔCt method with Let-7f as normaliser. miRGen was used to analyse predicted targets. p53 mutations were detected by protein overexpression on a TMA containing 73 PSCP/PSOC tumours.
Results: miR-195 and miR-497 showed significant downregulation in PSCP and PSOC. Over-representation of potential pathways ($p<0.05$) affected included angiogenesis, FGF, T-cell activation and WNT signalling pathways. p53 overexpression was detected in 79% (23/29) of PSCP tumours versus 93% (41/44) of PSOC tumours (93%).
Conclusion: It appears that miR-195 and miR-497 may have a role as tumour suppressor genes in ovarian and primary peritoneal serous carcinoma pathogenesis.

P38

Unusual Uterine Tumour in a Gap Year Student

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Leiomyosarcoma represents one -third of uterine sarcomas. The median age of patients is 50-55 years. Approximately 15% of patients are younger than 40 years. Amongst these younger patients, most have germ line mutations of fumarate hydratase (FH) gene(1). Leiomyosarcoma is reported in some premenopausal women as a second neoplasm following radiotherapy for childhood solid tumour(2).
We report here an unusual case of de novo uterine leiomyosarcoma in a 19 year old gap year student from South Africa. The patient was admitted as an emergency for severe and repeated menorrhagia. Diagnostic endometrial currettings showed sheets of poorly differentiated tumour in keeping with a smooth muscle tumour. The hysterectomy revealed a fleshy 11 cm tumour within the endometrial cavity .On histology the endometrium and myometrium were infiltrated by a high grade malignant tumour with epithelioid and spindle cell morphology. The tumour had a mitotic index of 47/10 mitosis per high power field. Coagulative tumour cell necrosis was also seen. There was lymphovascular space invasion together with cervical stromal and lymph node metastasis. Immunohistochemistry showed strong and diffuse positivity for caldesmon .Focal positive staining was seen with SMA, desmin and CD34.Very focal staining was seen with AE1/3.The tumour was negative for myogenin, CD45, HMB45,S-100,ALK-1,CD 10 ,CAM5.2.,CD117,nestin and DOG1.
To the best of our knowledge this is the youngest patient diagnosed with de novo uterine epithelioid leiomyosarcoma.
1.H J Lehtonen et al .,Increased risk of cancer in patients with fumarate hydrate germline mutation.J .Med Genet.2006 Jun;43(6):523-6
2.Pauline AC,Flower BZ. Secondary neoplasms after radiotherapy for a childhood solid tumour. Pediatr Hematol Oncol.2005 Mar;22(2):89-101.

P39

Nuclear Thyroid Transcription Factor (TTF-1) Expression in Endometrial Carcinoma

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A 51 year old female presented with nausea, vomiting and weight loss. She had past history of total abdominal hysterectomy and bilateral salpingooophorectomy elsewhere in January 2005 for a grade 3 endometrial carcinoma with lymphovascular space invasion, FIGO stage 1b at least. Currently she was found to have widespread disease with pelvic mass and multiple liver and lung metastasis on CT scan. The tumour markers were elevated with CA 19.9=1325, CA 125=691 and CEA=81.The liver mass was biopsied and showed a poorly differentiated carcinoma with focal glandular differentiation. Immunohistochemistry showed positive staining with CK7 and vimentin, which was consistent with endometrial origin. The tumour was negative for CK20, CDX2, CEA, ER and PR. However the tumour showed nuclear positivity for TTF-1 immunostain. A primary tumour in the lung/thyroid was ruled out radiologically.
TTF-1 is a nuclear transcription protein which is expressed in thyroid and lung epithelial cells. Nuclear immunolocalization is commonly used as a marker for adenocarcinomas of the thyroid and lung. It is also reported in pulmonary and extrapulmonary neuroendocrine tumours. A D Graham et al (1) recently reported nuclear TTF-1 staining in primary ovarian epithelial tumours .Our present case highlights the importance that although TTF-1 should be regarded as a sensitive marker for lung and thyroid primary, other epithelial tumours may also express nuclear TTF1.
1.Histopathology ,48,764-778;2006

P40

Expression of Cell Cycle Regulatory Proteins in Head and Neck Squamous Cell Carcinoma – a Tissue Microarray Study

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To determine whether the expression of proteins controlling proliferation and progression has a value in predicting patient prognosis; epidermal growth factor receptor (EGFR), phosphorylated-EGFR, Her-2/neu, cyclin D1, p16 and Ki-67 were evaluated by immunohistochemistry on tissue microarrays of 200 cases of squamous cell carcinoma (45 oral cavity, 72 pharynx and 83 larynx). Nodal metastasis was present in 83 cases and 17 cases received preoperative radiotherapy. The median survival time was 14 months. Three cores or more were scored in 83% of cases. Expression of EGFR was observed in 86%, p-EGFR in 80%, Her-2/neu in 37%, cyclin D1 in 94%, and Ki-67 in 93% of cases, and p16 was lost in 76%. Median values were used to study the associations between these proteins and clinico–pathological parameters. High EGFR and cyclin D1 expression were associated with low tumour grade ($p< 0.037$; <0.001 respectively); high cyclin D1 expression was associated with pharyngeal site ($p<0.001$) and absent nodal metastasis ($p<0.013$). Overall survival was longer in cases without nodal metastasis (log-rank, $p=0.011$) and who received radiotherapy (log-rank, $p=0.024$) but not associated with any of the proteins studied. Cyclin D1 expression has potential prognostic value in patients with head and neck squamous carcinomas.

P41

Differential Expression of Cell Cycle Control Proteins in Primary Head and Neck Squamous Cell Carcinomas and Nodal Metastases

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To provide information on cell cycle biomarkers and tumour progression, epidermal growth factor receptor (EGFR), phosphorylated-EGFR, Her-2/neu, Ki-67, cyclin-D1 and p16 were examined by immunohistochemistry on tissue microarrays of 76 cases of primary squamous carcinoma and their nodal metastases. The expression of EGFR, p-EGFR and Ki-67 was similar in groups of primary tumours and metastases, while expression of Her-2/neu and cyclin-D1 was higher in primary tumours than metastases ($p<0.006$; <0.018 respectively). Loss of p16 was more frequent in primary tumours ($p<0.000$). The group values conceal variations in expression in individual cases. Using a 20% difference in labelling index compared with the primary carcinoma, cyclin-D1 was increased in 8.9% and decreased in 38.8% metastases; EGFR was increased in 13.4% and decreased in 32.8% metastases, and Ki-67 was increased in 32.3% and decreased in 7.7% metastases. Using a 5% difference in labelling index, nuclear p-EGFR was increased in 12.1% and decreased in 40.9% metastases; Her-2 was increased in 10.6% and decreased in 16.6% metastases and p16 was increased in 9% and decreased in 9% metastases. Although microarrays may not be ideal for studying tumour progression, the results indicate that tumour biomarker expression in primary carcinomas may not reflect expression in metastases.

P42

Rhabdomyosarcoma of the Head and Neck Region in Adults

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Rhabdomyosarcomas of the head and neck region are predominantly found in children with a peak age of incidence at five years, and are a rare tumour of adults. We present two cases of rhabdomyosarcoma in adult patients.

Case1 was of a 30 year old male who presented with a warty lesion on his tonsil that was gradually increasing in size. After biopsy, the tonsil was resected. Each specimen showed oedematous mucosal tissue with normal epithelium and an infiltrate of the subepithelial tissue by sheets of rounded and spindle cells with eosinophilic cytoplasm. Immunocytochemical labelling was positive for vimentin, desmin, myoglobin and myogenin. A diagnosis of embryonal rhabdomyosarcoma of botryoid type was made.

Case 2 was an 84 year old female with an ulcerated nodule of the laryngeal mucosa. A diagnostic biopsy shows pleomorphic spindle cells with many mitoses and eosinophilic cytoplasm with cross-striations. Immunocytochemical labelling was positive for desmin, myogenin and smooth muscle actin in the spindle cells. A diagnosis of spindle cell rhabdomyosarcoma was made.

The management strategies for rhabdomyosarcoma in adults are not clearly defined. These patients had no evidence of metastatic disease and were treated with primary surgical excision and radiotherapy.

P43

Differential expression of HOX genes in oral keratinocytes and oral cancer cell lines

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HOX proteins control proliferation, differentiation and apoptosis during embryonic morphogenesis. HOX genes are expressed in adult tissues but often distinct from those found in their embryonic precursors. Aberrant expression of HOX genes has been reported during malignant transformation of many solid cancer types but the role of these genes in cancer of the oral cavity has not been investigated. The present study aims to compare the HOX gene expression profiles of normal oral keratinocytes with oral cancer cell lines.
The HOX gene expression profiles of normal oral keratinocytes and four oral carcinoma cell lines were determined by real-time quantitative-PCR. Comparison of these profiles identified 22 HOX genes expressed in all four carcinoma cell lines, but absent in all of the normal keratinocytes studied. Comparison of the results obtained from the oral cancer cell lines with a subset of leukaemia cell lines resulted in selection of a subset of HOXD genes for further investigation. Preliminary western blots and immunocytochemistry for the HOXD8-D11 proteins showed good correlation with the real-time quantitative-PCR results.
It is concluded that the HOXD genes may have an important role in oral cancer. The functional significance of these genes are currently under laboratory investigation.

P44

Acinar Cell Cystadenoma of the Pancreas: Role of Electron Microscopy

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Background: Acinar cell cystadenoma of the pancreas (ACA) is a cystic neoplasm characterized by a lining showing acinar cell differentiation. This study investigates the role of ultrastructural evaluation in the diagnosis of ACA.
Design: Benign unclassified pancreatic cysts were retrieved from the files of the Massachusetts General Hospital. Electron microscopy (EM) was performed on tissue retrieved from paraffin and immunohistochemistry performed on selected cases.
Result: We identified 6 pancreatic cysts that could not be definitively classified (all women with an age range of 31 to 63 years). They were all cystic radiographically and grossly with a size range of 0.3 to 7.5 cm (mean 3.5 cm), did not communicate with the pancreatic ductal system, and lined by a single layer of non-specific cuboidal epithelium. On EM, electron dense zymogen granules were identified in case 1; stacked rough endoplasmic reticulum was identified in case 1 ⁄ 2. The lining epithelium of these two cases were positive for trypsin, cytokeratin, but negative for chromogranin and synaptophysin. The other four cases lacked ultrastructural evidence of acinar cell differentiation.
Conclusion: EM uncovered evidence of acinar cell differentiation in two cases which was corroborated by immunohistochemistry. This study suggests that ultrastructural evaluation could assist in the classification of otherwise "unclassified" benign pancreatic cysts.

P45

Lessons learned from 5 year survivors of pancreatic adenocarcinoma: A critical look at the AJCC staging system

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Background: 5-year survival for pancreatic adenocarcinoma (PDAC) following surgical resection is 12-19%. The AJCC Cancer Staging Manual 6th Edition is used to stratify stage-specific survival. Conflicting results regarding the predictive value of the T-classification have been noted. We evaluated the prognostic impact of the T-classification utilizing our PDAC 5-year survivors.
Design: PDAC patients surviving 5 or more years post curative surgical resection were identified. Grade, stage, nodal and margin status, and tumour site and size were recorded. Involvement of adjacent structures, features of pT3 lesions was noted.
Results: All data was available for 21 of 56 5-year survivors with PDAC, 9 males and 12 females (median age 67years). The bile duct was involved in 5, and the duodenum in 8 of 19 Whipple specimens. Peripancreatic tissue was involved in 14 of 21 resections. Six patients had stage I, and 15 had stage II disease. Seven patients with T3 lesions had positive nodes. The median survival was 75.6 months.
Conclusion: The current T-classification of the AJCC staging system does not accurately predict 5 year survival in PDAC patients following curative surgical resection. Additional studies are required to refine the staging system to more accurately reflect the clinical behavior of these tumours.

P46

Cutaneous Mastocytosis Localised To A Radiotherapy Field: Case report and review of the literature.

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We report the case of a 62 year old lady who developed a localised, asymptomatic, erythematous, macular and telangiectatic rash localised to a radiotherapy field, 2 years after surgical and radiation treatment of breast carcinoma. A biopsy demonstrated cutaneous mastocytosis. There were no features of systemic mastocytosis. The clinical features were those of telangiectasia macularis eruptiva perstans (TMEP) or urticaria pigmentosa, depending on the exact criteria used in the subtyping of cutaneous mastocytosis. Localisation of cutaneous mastocytosis to a radiotherapy field has only been reported twice previously. We discuss possible reasons for this striking localisation.

P47

Cutaneous Mastocytosis in HIV: An Unfortunate Co-incidence?

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Mastocytosis refers to a spectrum of mast cell proliferations, ranging from those with cutaneous involvement only (urticaria pigmentosa) to aggressive systemic conditions that may be associated with myelodysplasia or myeloproliferative disorders or leukaemias[1]. Cutaneous mastocytosis (CM) is a proliferative disorder of mast cells apparently confined to the skin that may be reactive rather than neoplastic and is often self-limiting, particularly in children. As far as we are aware, an association between Human Immunodeficiency Virus (HIV) and mastocytosis has not previously been reported. We report the case of a young male, who developed cutaneous mastocytosis on his trunk and limbs, following an episode of severe sunburn. He was diagnosed with Human Immunodeficiency Virus (HIV) shortly afterwards. We discuss this interesting and previously unreported temporal relationship between the development of mastocytosis and recent HIV infection, speculating on potential pathogenetic mechanisms of association.

P48

Eccrine Angiomatous Hamartoma

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Eccrine angiomatous hamartoma (EAH) is a rare, benign cutaneous hamartomatous proliferation. Patients typically present with a solitary nodule of the extremities usually appearing at birth or during the prepubertal years. The clinical presentation ranges from simple angiomatous nodule to erythematous – purpuric plaque. EAH is generally asymptomatic but can occasionally present with pain and hyperhidrosis. On histopathology, EAH is characterized by a dermal proliferation of well differentiated eccrine secretory and ductal elements closely associated with thin walled angiomatous channels.
We report a case of multiple EAH in a 13 year old girl present since birth. Clinically, this condition must be differentiated from other neonatal angiomatoses and a definitive diagnosis is based upon histology. The natural history of EAH is benign and typically slow growing. It is important to recognize this condition because it is a benign lesion for which aggressive treatment is not indicated, simple excision is reserved for painful or cosmetically disfiguring lesions.

P49

miRNA expression analysis in formalin-fixed paraffin-embedded (FFPE) material.

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Introduction: Archival formalin-fixed paraffin-embedded (FFPE) tissues have limited utility in applications involving analysis of gene expression due to mRNA degradation and modification during fixation and processing. miRNAs are a small class of RNA recently described as playing important roles in gene regulation, yet their robustness in FFPE is largely unknown.This study analyzed 160 miRNAs in paired snap frozen and FFPE cells to investigate if miRNAs may be successfully detected in archival specimens.
Methods: N-thy-ori cells were grown to confluence and aliquots with equal cell numbers were (a) snap frozen and (b) formalin fixed and paraffin embedded into a cell block. Total RNA was extracted using Ambion mirVana miRNA Isolation kit for snap frozen cells, and Ambion RecoverAll Total Nucleic Acid Isolation Kit for FFPE cells. The quality and quantity of RNA yields was measured with Nanodrop and TaqMan® microRNA assays, Human Panel-Early Access Kit.
Results: miRNA extracted from FFPE blocks was successfully amplified using Q-RT-PCR. TaqMan® analysis showed a good correlation of miRNA expression pattern between FFPE and snap frozen cells, with R^2>0.95.
Conclusion: We conclude that methylol cross-links between RNA and protein which occur during tissue processing inhibit the yield of total RNA. However, small RNA molecules appear to be less affected by this process and are recovered more easily in the extraction process. In general miRNAs demonstrated reliable expression levels in FFPE compared with snap frozen paired samples, suggesting these molecules might prove to be robust targets amenable to detection in archival material.

P50

Modified Extraction Protocol and Incorporation of Pre-Amplification TaqMan improve Gene Expression detection in archival samples.

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Introduction: Although formalin-fixed paraffin-embedded (FFPE) tissues represent an abundant archive their use is limited in applications involving analysis of gene expression because of RNA degradation and modification during fixation and processing. This study aimed to improve the quality of RNA extracted from FFPE by modification of selected extraction protocols. Further, it evaluated a novel pre-amplification system (PreAmp) designed to enhance expression analysis from tissue samples.
Methods: N-thy-ori cells were used for (a) snap frozen and (b) FFPE (cell block) processing using equal numbers of cells. RNA was extracted in parallel using: Stratagene Absolutely RNA FFPE Kit, Gentra Purescript RNA Purification Kit, Ambion RecoverAll Total Nucleic Acid Isolation Kit, and Invitrogen Trizol Reagent, in addition to modified Stratagene and Ambion protocols. The quality and quantity of RNA yields was measured with Bioanalyzer, Nanodrop and TaqMan® assays with and without pre-amplification using a panel of assays with a range of amplicon size (62-164 bp).
Results: RNA quality in FFPE samples was improved when the modification step was incorporated. This step disrupted cross-links while not compromising RNA integrity. TaqMan® detection was influenced by variables including: master mix, amplicon size and the incorporation of a pre-amplification step. TaqMan® PreAmp consistently achieved decreased C_T values in both snap frozen and FFPE aliquots compared with no pre-amplification.
Conclusion: Modification to extraction protocols has facilitated procurement of RNA that may be successfully amplified using Q-RT-PCR. TaqMan® PreAmp system is a robust and practical solution to limited quantities of RNA from FFPE extracts.

P51

Physical Basis of Colours Seen in Congo Red-Stained Amyloid in Polarised Light

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Amyloid stained by Congo red, examined between crossed polariser and analyser, is usually said to show apple-green birefringence, although various colours are seen, not just green. Previously, there has been no satisfactory explanation of these properties. The birefringence of orientated Congo red varied with wavelength and was maximal near the absorption peak, changing from negative (slow axis perpendicular to smears or fibrils) on the shortwave side of the peak to positive (slow axis parallel) on the longwave side. This was explained by anomalous dispersion of the refractive index. Negative birefringence gave transmission of blue, positive gave yellow, and the mixture was perceived as green. Additional or strain birefringence in the optical system partly or completely compensated blue or yellow, giving yellow/green or yellow, and blue/green or blue. With uncrossing of polariser or analyser, birefringent effects declined and dichroic effects appeared, giving progressive changes from green to red as the plane of polarisation approached the absorbing axis, and from green to colourless the opposite way. Other mechanisms previously suggested to explain the colours had negligible effects. Congo red-stained amyloid between crossed polariser and analyser, rather than showing apple-green birefringence, should more accurately be said to show anomalous colours.

P52

Same day pathology - a reality or myth? Evaluation of the Peloris™ and Bond-max™

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Cancer waiting time initiatives have focused pathologists minds on the importance of rapid turnaround of critical diagnostic biopsies. In this study we describe the evaluation of a new xylene- free processing machine for routine diagnosis, in conjunction with an automated immunostainer for routine, rapid reporting of cancer pathological specimens.
Preliminary analysis of a series of liver biopsies for cancer indicates 1 hour processing schedule after 1 hour fixation of small core biopsies provides rapid histological diagnosis. Furthermore in conjunction with the Bond-max automated immuno-stainer we have achieved same day reporting of needle biopsies with the added advantage of immuno-phenotype.
Similar preparation of bloody, fresh colectomy specimens using an 8 hour processing
schedule has enabled the rapid processing and reporting of larger colorectal resection specimens. This strategy indicates the obviation of processing time lags, indicating that even the larger cancer specimens can be reported in a 24 hour time frame. Hence if clinically indicated, even larger specimen can be processed rapidly without compromising diagnosis. Detailed evaluation of this technology specifically to evaluate the possibility of same-day pathology of needle biopsy specimens for cancer is evaluated critically.

P53

Hormone Receptor Status on Breast Core Biopsy, Resection or Both ? – Report on an Internal Audit

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Introduction
Core biopsy for the diagnosis of breast cancer is an acceptable and accurate method of diagnosis. Immunohistochemical studies to determine hormone receptor status is routinely carried out on core biopsies. However, whether a biopsy is an accurate representation of the entire tumour is debatable, as discordant rates between core and resection specimens vary.
Methods
We reviewed 100 breast core biopsies and subsequent resections over a four-year period in which immunohistochemistry for hormone receptors (oestrogen receptor, progesterone receptor and Her2-neu) had been carried out on both specimens. The reports for this cohort of breast cores and resections were reviewed and immunohistochemistry results compared. Cases with discordant results were re-evaluated.
Results
Twenty-four cases had discordant results (Five cases had two discordant results); ER 4%, PR 18% and Her-2 7%. On re-evaluation only nine cases had truly discordant results; PR 8% and ER 1%. Reasons for falsely discordant results included; incorrect reporting, interpretative errors and failure of immunohistochemical staining.
Conclusion
Discordance between breast core and resection immunohistochemistry in our centre is low supporting those who advocate immunohistochemistry on breast core biopsy only. However uncertainty remains as to which is the better specimen to evaluate as highlighted by errors encountered in this audit.

P54

HER 2/neu Oncogene Amplification in Node Negative Breast Cancer Egyptian Patients

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Background: HER 2/neu oncogene alterations have been recently used as a prognostic factor to define a subgroup of high risk node negative breast cancer (NNBC) patients.
Objective: Assessment of HER-2/neu oncogene amplification in NNBC Egyptian patients in relation to hormone receptor (ER and PR) status and histopathological features of prognostic significance.
Material and methods: Formalin fixed paraffin embedded tissues from 50 NNBC, including: 6 cases of ductal carcinoma in situ (DCIS), 34 invasive ductal carcinomas, 6 invasive lobular carcinomas, 2 stromal sarcomas and 2 undifferentiated carcinomas. were tested. PCR amplification of HER-2/neu and ER/PR immunohistochemically were assessed.
Results: HER-2/neu oncogene amplification was demonstrated in 30% (15/50) of NNBC and was more prevalent in young patients, and mostly in ductal carcinomas (14/15). HER-2/neu gene amplification correlated significant with clinical tumour stage, size and histologic grade. HER-2/neu gene amplification was more frequently detected in DCIS , comedo type and significantly correlated with clinical tumour stage, size and grade. No significant correlation was found between HER-2/neu gene amplification and the hormonal receptors (ER & PR).
Conclusion: Her2/neu amplification in NNBC Egyptian patients with advanced clinical stage, size and poor histological differentiation denotes its association with more aggressive phenotypes and probably worse prognosis.

P55

Atypical Pregnancy-Like Hyperplasia with Subsequent Invasive Disease – A Case Report

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Pregnancy-like (pseudolactional) hyperplasia (PLH) is a relatively new nomenclature with a well described benign histological appearance. However the presence of atypia is rare, making management decisions difficult. Here, we present a case of atypical PLH with subsequent development of invasive disease.
A 53 year-old postmenopausal patient presented with an impalpable screen-detected hypoechoic nodule within an area of microcalcifications. Core biopsies showed prominent lactational changes associated with high-grade cytological atypia. An open diagnostic biopsy demonstrated columnar cell change with microcysts containing calcifications. A minute focus of lactational change with minimal atypia was present but no high-grade cytological atypia.
At 6 month follow up, a palpable abnormality was detected that was radiologically indeterminate. Core biopsies confirmed invasive disease requiring a wide local excision and sentinel lymph node biopsy (patient's choice). Histopathology demonstrated a 21mm invasive ductal carcinoma NST, grade 3, lymph node negative, ER and PR positive and HER-2 negative. Interestingly, this was associated with further areas of atypical PLH and DCIS.
In conclusion, it was difficult to ascertain whether atypical PLH was a precursor for invasive disease or simply a coexisting pathology. In view of the above diagnostic challenges we recommend excisional biopsies of such lesions with frequent review.

P56

Unusual metachronous malignancy in a male with initial primary breast carcinoma

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We present a case of a 72 year old male patient diagnosed with invasive ductal carcinoma, of no special type, grade II, ER and PR positive in July 2002. He was treated by mastectomy and axillary node clearance with subsequent tamoxifen. No radiotherapy or chemotherapy was administered. He then presented in January 2007 with abdominal complaints and was shown to have an almost 4 cm depth large omental cake over most of the anterior abdomen. Biopsy of the lesion showed a papillary tumour positive for calretinin, WT-1, CK5/6 with strong membranous positivity for EMA in keeping with a peritoneal mesothelioma. Strong positive occupational history of asbestos exposure was retrospectively confirmed.
Second primary cancers are well documented following primary male breast cancer. Documented sites of secondary cancers include prostate, contralateral breast, colorectal, lung and bronchus, bladder, melanoma and stomach. Various risk factors implicated include host factors (genetic abnormality, immune function and hormonal imbalances), environmental and/or occupational exposures, lifestyle factors, effects of treatment for first cancer, hereditary cancer syndromes or even gene-environment interactions.
To the best of our knowledge such an association has not been reported previously.

P57

The rising incidence of male breast cancer

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Male breast cancer (MBC) is rare, accounting <1% of all cancers in men however the incidence is increasing worldwide. Figures from CRUK indicate that around 300 cases are diagnosed in the UK annually. Here we present the number of cases of MBC from 6 UK cancer registries in England, Wales and Scotland from 1981-2004 and compare them with SEER data from the USA between 1973 and 1998.
Result: From 1981 to 2004, the number of MBC cases doubled from 70 to142 in the East of England. Meanwhile, number of cases increased noticeably form 33 to 88 in Merseyside, while in Scotland and Wales the cases increased from 85 to 103 and 55 to 87 respectively. Data on Northern and Yorkshire showed a similar trend during 1995-2004, when the numbers rose from 68 to 140. This paralleled data from USA which showed the incidence of breast carcinoma in men has significantly increased over the 26 years(Giordano, Cohen et al. 2004).
Conclusion: Based on the data available we conclude that the incidence of male breast cancer is rising in the UK and US. Possible reasons for this will be discussed.
Giordano, S. H., D. S. Cohen, et al. (2004). "Breast carcinoma in men: A population-based study." Cancer 101(1): 51-57.

P58

Validation of a new technology for the assessment of HER-2 status in breast cancer

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Background: Inconsistency in the generation of HER-2 results has been recognised when using well established tests such as IHC followed by FISH on 2+cases. (Rabiya S. Tuma, inconsistency of HER2 test raises questions, JNCI, 31/08/07). Alternative techniques have been proposed such as front line Fluorescent orChromogenic in situ hybridization (FISH or CISH) .
Recently a variation of CISH called silver in situ hybridization (SISH) has been released on a fully automated system. The same system can also be used for HER2 IHC using a rabbit monoclonal antibody known as 4B5. SISH represents an evolution towards in situ hybridization tests (ISH) where light microscopy is favoured for the pathological assessment of the HER2 status. Currently there are only a few studies comparing SISH with previous validated gene based techniques such as FISH or CISH.
Aim: The aim of the study is to evaluate the reliability of HER-2 assessment performed using SISH.
Design: Tissue microarry from 300 breast cancer cases with known HER-2 status as detected by FISH and IHC have been stained using SISH and IHC on a fully automated systems. The slides were assessed by two pathologists independently and the results compared to those obtained previously
Result: There was an extremely high concordance between SISH and FISH. There were only 5 discrepant cases 3 of which were due to heterogeneity within the tumour sample in which some areas had amplified tumour cells and others did not. The other 2 discrepant cases were in the border/line low level of amplification category in which SISH and FISH have slightly different cut-off values for amplified/not amplified cases.
A score of 3+ IHC staining for 4B5 protein was seen in the vast majority of the cases with high level amplification f the HER2 gene, but cases with borderline/low level of amplification were scored 2+. The detailed analysis of the protein is still ongoing at the time of writing but will be available for discussion soon.

P59

FISH for Her-2 amplification in breast cancer; the Harlow experience

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We have established FISH for Her2 within the Essex pathology network, delivering a service at a very cost effective level. In this presentation we present an audit of our first 200 cases form 6 different centres in Essex. Of 205 cases 44 cases (21%) were reported to have Her2 amplification by FISH and 8 (4%) cases reported to be in the borderline category. Of greater interest we report haploidy for chromosome 17 in 21 of 205 cases (10%) diploidy 105 of 205 cases (51%) for chromosome 17 in and polyploidy in the remaining cases. We discuss the correlation of the Her2 status and ploidy (chromosome17 numbers) with the pathological parameters in these subset of patients.
We are grateful to QUEST for funding the establishment of FISH as a service within our laboratory.

P60

The prognostic significance of intramammary lymph node metastases

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The reported prevalence of intramammary nodes is between 1% and 28%. They are a possible site for metastatic spread of breast cancer. However the clinical significance of intramammary lymph node metastases is still unclear. The aim of this retrospective study was to ascertain the relation between intramammary lymph node metastases and survival outcome in breast cancer patients. One hundred and twelve intramammary lymph node specimens were identified from the pathology database over a 13 year period. One hundred were associated with a primary breast malignancy. Mean follow up was 34 months (Range 0–151 months). Statistical analysis indicated that patients with intramammary lymph node metastases have a significantly poorer outcome both on univartiate and multivariate analysis. This was found in patients with isolated intramammary lymph node involvement and those with associated axillary node involvement. The greater the number of involved intramammary nodes the poorer the prognosis. The presence of intramammary lymph node metastases is an independent predictor of poor outcome in patients with breast cancer. Identifying intramammary lymph node metastases is important for the accurate staging of breast cancer patients and to ensure optimization of adjuvant treatment.

P61

The relationship between Matrix Metalloproteinase Single Nucleotide Polymorphisms, genotype and breast cancer progression in Caucasian and British-Black women

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Matrix Metalloproteinases (MMPs) have been implicated in tumour cell invasion and spread, moreover, polymorphisms within the promoter of several MMPs have been shown to have allelotypic effects on levels of gene transcription. Of particular interest is the prior observation that African American women with breast cancer (BCa) have higher MMP expression when compared to Caucasian women. In this study we have evaluated the association between promoter polymorphisms in MMP-1, 3, 7, 8, 9, 12, 13 and clinicopathological factors of BCa in Caucasian and British-Black (BB) women. Associations between genotype and lymph node (LN) status were estimated by logistic regression, whilst association between genotype and overall survival (OS) were investigated using the method of Kaplan-Meier and estimated using log-rank test. Our data demonstrate a significant association of the C/T genotype for MMP-9 and the 2G/2G genotype for MMP-1 with LN positive disease in Caucasian women, but not in BB women. In addition, there is a trend for decreased OS in Caucasian women with the MMP-1 2G/2G that is not observed in BB women. However, in both ethnic groups the MMP-1 2G/2G genotype is associated with increased tumour size. These findings indicate that MMP genotype is associated with distinct patterns of BCa behaviour, but there are inherent genetic differences between Caucasian and BB women which may, in part, reflect the distinct clinical behaviour of BCa in different ethnic groups.

P62

Cytological outcome of conventional transbronchial Fine-Needle Aspiration of lymph nodes

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Transbronchial needle aspiration (TBNA) is a minimally invasive bronchoscopic technique that allows pathological examination of mediastinal and hilar lymph nodes. *Objectives:* The aim of this study is to assess the cytopathological outcome of TBNA of lymph nodes. *Methods:* One hundred and seventy eight patients who underwent TBNA of mediastinal and hilar lesions from May 2000 to June 2007 were reviewed. *Results and conclusion:* Final diagnoses were available in 172 cases. TBNA results were considered to be adequate if the cytological material revealed a malignant lesion or sufficient number of benign lymphoid cells. In addition, we found that anthracotic pigment-laden macrophages to be a reliable criteria of specimen adequacy. Forty one cases (24%) were reported as inadequate. The overall sensitivity, adequacy, negative and positive predictive values of TBNA in the diagnosis of malignant lesions were 83.5%, 87%, 63% and 100% respectively. Our results confirm that TBNA is a sensitive and useful technique when results are properly analysed. We also recommend liquid-based preparation of TBNA cytological material to reduce the cost and work-load per case and to enable ancillary techniques to be performed.

P63

Metals and lung disease

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Two autopsy cases and seven referrals were investigated for pulmonary disease linkage to occupational metal exposure.
The first case (76 M), with documented cadmium exposure 35 years prior to his death, was found at autopsy to have widespread emphysema (centri- and pan-acinar) with no cancer/fibrosis. Mass spectroscopy confirmed presence of significant cadmium overload.
The second case (79/F) provided history of beryllium toxicity, 30 years before her death. The autopsy lung findings were of end-stage honeycomb lung fibrosis with scattered granulomas and scars. Elevated beryllium levels were found.
The series of seven patients (all M, age 57-79) provided occupational history of exposure in a single non-ferrous smelting unit. These had lung fibrosis (mainly UIP type) and six had various bronchogenic neoplasia. The cases showed elevated metal levels of lead, cadmium, antimony, tin and arsenic, using mass spectroscopy
Control samples were taken from fixed lung from patients (lacking history of industrial working) with macroscopically normal lung from concurrent surgical cases.
Metal fume and dust related lung disease is an under recognised area in pathology requiring careful clinical/occupational history, augmented by detailed macroscopic and histological examination with mass spectroscopy.

P64

Quantitative sputum cytology to detect lung cancer

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Background: Improved early detection remains the most promising method of improving patient's survival from lung cancer and is a realistic goal in the short term. This study reports the findings of a large scale trial evaluating a novel, fully automated, method of DNA cytometry on sputum, to detect lung cancer.
Methods: Over a period of a period of 24 months of 1235 patients, clinically suspicious of having lung cancer, were recruited into a multinational validation trial, using the LungSign sputum cytology test. Induced sputum was collected at the time of initial presentation, fixed and treated with dithiothreitol (DTT). Papanicolaou stained smears were prepared and analysed by conventional cytology, alongside monolayer cytospin preparations, stained using the feulgen-thionin method. These slides were analysed using the LungSign test, a fully automated computerised DNA cytometry system.
Results: Of the 1123 patients analysed, 370 proved to have lung cancer (prevalence 33%). The LungSign test provided an ROC "area under curve" value of 0.692, and for a specificity of 90 detected 40 % of all lung cancers. Results were similar for all lung cancer types, as well as early (up to 1b) and later (stage 2a and above) stages. Conventional cytology detected 16% of cancers, specificity 99%. The inadequacy rate was 12% compared with 43% for conventional cytology.
Conclusions: In a high risk population the LungSign test provides an effective means of detecting those patients most likely to have lung cancer. It measures a continuing variable, that allows for different cut points to be set; making the test useful both in screening patients for lung cancer, as well as in evaluating suspicious lesions detected on CT, thereby directing efficient use of other, more expensive and invasive diagnostic modalities.

P65

Osteopontin promotes invasiveness in adrenocortical carcinoma cells but is not associated with altered survival in patients with adrenocortical cancer (ACC)

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Osteopontin (OPN) is a glycoprotein of the extracellular matrix and interacts with its receptor integrin $\alpha v\beta_3$, which we previously found to be expressed in benign and malignant endocrine tissues, and which were shown to contribute to tumourigenesis in several types of cancers. Recently, expression profiling of adrenal neoplasms revealed OPN mRNA to be expressed in these tumours. To characterize OPN and integrin $\alpha v\beta_3$ expression in normal, benign and neoplastic adrenocortical tissues, IHC of conventional tissue slides and tissue arrays (n=163 samples) were performed. To investigate an association of OPN expression with prognosis in ACC survival analysis in 109 patients were performed. Invasion and proliferation assays were used to study the functional role of OPN *in vitro*. In normal adrenal tissue, OPN and integrin $\alpha v\beta_3$ were found to be expressed strictly in the cortex. Expression of OPN and integrin $\alpha v\beta_3$ was more heterogenous in adrenocortical adenomas and in ACC with staining intensity being more accentuated in single tumour cells or nests. These results were confirmed by Western blot analysis. Due to patients survival no association between OPN and disease prognosis could be found. Treatment of OPN expressing adrenocortical cell line NCI259R with human OPN increased invasiveness dramatically, supporting the idea that OPN acts to facilitate tumour development and metastases. Cell proliferation was not altered. In this study we show for the first time, that OPN is expressed in the human adrenal gland and is strictly confined to the cortex, making it, thus, a potential diagnostic marker to distinguish between adrenal cortex and medulla. The level of OPN expression does not correlate with survival in patients with ACC. OPN stimulates invasiveness but not proliferation *in vitro*. Our ongoing studies aim to clarify the role of OPN in adrenal tumourigenesis.

P66

Osteopontin and CEACAM1 as diagnostic and prognostic markers of thyroid carcinoma

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Osteopontin (OPN) and its putative interacting partner CEA-cell adhesion molecular (CEACAM1) mediate diverse but similar biological functions. OPN is a glycoprotein of the extracellular matrix that has been implicated in cell migration and invasion and is expressed in several types of human carcinoma. We have previously demonstrated that CEACAM1 limits thyroid tumour size but promotes lymph node metastasis. Here we examined the expression and localization of OPN in normal, benign, and malignant thyroid tumours and correlated our findings with clinical data and with the expression of CEACAM1. A series of 297 human thyroid samples were collected in a tissue array and immunohistochemistry was performed for osteopontin and CEACAM1. Frozen tissue obtained from a subset of these tumours was used for western blotting to confirm the specificity of the reaction for osteopontin. OPN was expressed by 22% of normal thyroid glands and 78% showed no OPN immunoreactivity; this is in comparison to CEACAM1 which was negative in all normal samples ($P<0.001$). OPN expression was increased in thyroiditis and thyroid adenomas. More than 50% of adenomas were OPN positive whereas 100% were negative for CEACAM1 ($P<0.001$). OPN was overexpressed in 81% of papillary carcinoma samples in comparison to CEACAM1, which was positive in 14% of cases ($P<0.001$). OPN was also expressed in 75% of medullary carcinomas and all anaplastic carcinomas ($P< 0.001$ vs. normal tissue). OPN staining intensity was significantly higher than that for CEACAM1 in all groups ($P<0.001$). With respect to lymph node metastases, 25/35 of papillary, all medullary (n=4/4) and all anaplastic (n=4/4) carcinoma metastases were positive for OPN. In contrast to CEACAM1, which was preferentially expressed in metastatic papillary carcinomas, no associations were found between OPN expression and patient age, gender, tumour size, or the presence of lymph nodal or distant metastases. Western blot analysis of 30 papillary and follicular thyroid carcinomas confirmed our immunohistochemistry data ($P<0.001$).
Statistical modeling confirms OPN as a better diagnostic marker in distinguishing benign from malignant thyroid tumours than CEACAM1, however, CEACAM remains a better prognostic marker for metastatic disease in papillary thyroid carcinoma.

P67

Geographical mapping using ret/PTC and BRAF V600E mutations in papillary thyroid carcinoma.

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INTRODUCTION:
Papillary thyroid carcinoma (PTC) frequently presents as multiple tumour-foci within a single thyroid gland. In addition, a significant proportion of PTC are also pluriform, with synchronous tumours comprising different histological variants. This raises the question of the clonal origin of PTC. Among genetic aberrations described in PTC BRAF V600E mutation and ret/PTC activation occur most commonly. It has been suggested that the underlying genetic anomaly present in PTC correlates with the morphology present.
The objective of this study was to examine disparate geographical and morphological areas from a single PTC for the presence of ret/PTC or BRAF mutations.
RESULTS:
Laser Capture Microdissection was used to harvest cells from areas of classic PTC, insular, and anaplastic carcinoma in addition to tumour cells adjacent to vascular invasion and lymphocytic infiltrate. DNA and RNA were co-extracted and analysed using TaqMan based PCR/RT-PCR. All of the tumour areas proved negative for ret/PTC 1 rearrangement. Two distinct foci with classic morphology harboured the BRAF mutation. All other tumour areas, including the insular and anaplastic were negative for the mutation.
CONCLUSION:
This result suggests that pluriform PTC do not necessarily evolve from classic PTC progenitor foci and is also in keeping with previous reports of association between the BRAF V600E mutation and classic morphology.

P68

ret/PTC-1 Expression Alters the Immunoprofile of Thyroid Follicular Cells

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ret/PTC-1 has been described in autoimmune thyroid disease (AITD) and thyroid neoplasia . A common morphologic feature in each is the presence of a florid lymphocytic infiltrate. It is unclear if the presence of ret/PTC-1 facilitates cross-talk between the infiltrate and thyrocytes. Moreover the extent to which ret/PTC-1 may be involved with molecular pathobiology and disease progression remains to be uncovered.
RNA from ret/PTC-1 positive and negative thyrocytes was analysed over a time course to identify variations in immunoprofile following co-culture with activated T cell lymphocyte supernatant from Hashimoto Thyroiditis (H.T.) and normal donors. Expression analysis was performed using TaqMan® Immune profiling Low-Density Arrays (Applied Biosystems, CA, USA) comprising gene expression markers for 93 immune related targets plus 3 endogenous controls. Stimulation of normal thyrocytes with activated T cell supernatant from the H.T. donor yielded global up-regulation of immune targets compared with base line expression. In particular, targets associated with cytotoxic cell death, TCR and T cell signaling were up-regulated in normal thyrocytes. These targets were significantly down-regulated in corresponding ret/PTC-1 harboring thyrocytes exposed to the same stimulus.
Activation of the c-ret oncogene down-regulates a subset of immune targets which could compromise immunogenicity in the thyroid and facilitate papillary thyroid carcinoma development.

P69

Comparative Study of C4d Staining in Frozen and Paraffin Sections of Renal Allograft Biopsies.

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Background
Positive C4d staining in the diagnosis of acute antibody mediated rejection (AMR) in renal allograft biopsies is defined as bright linear staining of >50% of peritubular capillaries (PTCs) on immunofluorescence. The criteria for a positive result in paraffin sections are however less well defined. Similarly, the comparative sensitivities and specificities of the two techniques have not been widely studied.
Methods
Frozen sections of 55 unselected renal allograft biopsies taken for graft dysfunction between March 05 and April 07 were stained with a monoclonal C4d antibody and a two stage immunofluorescence technique. A positive result was defined as above. Paraffin sections were stained using a polyclonal C4d antibody and an ABC technique. A positive result was defined as linear staining of all or almost all PTCs.
Results
46 cases were negative and 5 positive using both techniques. 1 case was negative on frozen section but positive on paraffin section and 3 were positive on frozen section but negative on paraffin. All the positive cases were diagnostic or suspicious of AMR using Banff criteria.
Conclusions
This study indicates that the two techniques are broadly comparable in terms of sensitivity and specificity in the diagnosis of AMR in renal allograft biopsies.

P70

Persistent Müllerian Duct Syndrome Associated With Irreducible Inguinal Hernia : A Case Report

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Persistent müllerian duct syndrome is a rare form of male pseudohermaphroditism. A case is reported of normal male appearance and a right irreducible inguinal hernia. On exploration, an uterus with two fallopian tubes were found in the hernia sac. The uterus and fallopian tubes were en bloc removed. Hernia repair were performed. This patient´s karyotype was 46,XY and he was fertile. As a 55 years old man,he did not have any external genital anomalies. In conclusion, Persistent müllerian duct syndrome can be discovered accidentally in a fertile adult patient without any external genital abnormality in hernia surgery.So,this possibility should be always considered in old patients with irreducible inguinal hernia.

P71

An Autopsy Study of P.falciparum Malaria Associated Renal Disease in Southeast Asian Adults

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An autopsy based study of the renal pathology of P.falciparum associated severe malaria was performed in 63 southeast Asian adults. Histopathology, electron microscopy and immunoperoxidase staining was used to examine the pathological changes in kidneys and correlated with the premortem clinical incidence of malaria associated acute renal failure (MARF); quantitation of parasite sequestration and immunophenotyping of leukocyte subsets. MARF is common in this group (57%) and associated with acute tubular damage, sequestration of parasitized red blood cells (PRBC) and pigment, and host leukocyte responses within both glomerular and interstitial capillaries. No evidence for a membranous or immune complex mediated glomerulonephritis was found. Mesangial hypercellularity in some cases was due to significantly increased numbers of CD68+ve monocytes. Statistically, sequestration of knob positive (K+) PRBC and the sequestration index were significantly higher in the kidneys of patients suffering from premortem acute renal failure ($p<0.02$). However levels of sequestration were much lower than in brain tissues from the same patients. Minimal immunostaining for the pro-inflammatory cytokines TNF-α, IL-1 and IL-10 or HIF-1 was found. These findings suggest falciparum malaria associated acute renal failure in adults is linked to parasite sequestration but multifactorial in origin, and is not an acute immune complex mediated glomerulonephritis.

P72

Auditing Testicular Germ Cell Tumour Diagnoses – Is there A Need for Supraregional Pathology Review?

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An audit was performed of a recently established supraregional pathology review service for testicular germ cell tumours. This dual reports all tumours across a region of seven district hospitals, reporting to specialist clinicians at 2 cancer centres. 206 cases were seen in three years, of which 120 were referred. Breakdowns of demographic data, types of tumour seen and staging are broadly in accordance with published figures. The resulting histology database is a valuable resource for future research and clinicopathological correlation, but correlated poorly with those from the local cancer network generated from surgical throughput figures. Problem areas in diagnosis included differentiation of yolk sac tumour from embryonal carcinoma, recognition of vascular invasion; and staging of cord invasive tumours. Tumour size and rete invasion were not clearly recorded, arguing for a proforma based approach to be introduced regionwide. Although staging was altered in 9/120 (7.5%) referred cases there were no diagnostic disparities (0%). These results indicate that local pathologists are extremely reliable in their diagnosis of testicular germ cell tumours. Supraregional review has value in double reporting, checking staging and prognostic criteria and in providing an opinion in difficult (usually metastatic) cases, and establishing a resource for future research.

P73

Is the use of voided urine cytology (VUC) an unnecessary test in adult haematuria?

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Introduction Patients referred with macroscopic /microscopic haematuria are investigated with renal ultrasound scan, cystoscopy and urine cytology. Whilst imaging of the upper urinary tracts and cystoscopy is useful in confirming diagnosis, the usefulness of urine cytology is debated.
Aim To determine the diagnostic yield of VUC in patients with haematuria and/or cancer in comparison to imaging and cystoscopy
Materials and methods Results of 6060 urine samples were reviewed and were categorised; 1: benign. 2: repeat required (insufficient sample). 3: suspicious, of malignancy and 4: diagnostic of malignancy. The results of upper tract imaging and cystoscopy were analysed to ascertain if the urothelial carcinoma was confirmed.
Results 5893/6060 (97.2%) were negative and 167 (2.75%) were required further follow-up. 69/167 were excluded (poor records). 98/167 results required further analysis (see table)

CYTOLOGY CATEGORIES	URINE CYTOLOGY	DIAGNOSIS CONFIRMED BY IMAGING AND CYSTOSCOPY
REPEAT	34	6
SUSPICIOUS	44	18
MALIGNANT	20	17
TOTAL	98	41

RESULTS OF ANALYSIS OF 98 CASES

Discussion Urine cytology is used as a routine test for all patients being investigated for haematuria. The patients also undergo upper tract imaging and cystoscopy. The results show that urine cytology is an unreliable test for finding bladder cancers and it has an unnecessary cost burden. The advantages of one stop clinic will be discussed.

P74

A Rare Case of Isolated Renal Rosai Dorfman Disease

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Rosai Dorfman disease (Sinus histiocytosis with massive lymphadenopathy) was initially described as an idiopathic non-neoplastic disorder in lymph nodes. A number of cases have been reported involving extranodal sites including the respiratory tract, skin, meninges, orbit and bone. Extranodal Rosai Dorfman disease is usually a part of the typical disease with nodal involvement.
We present a case of an 81-year-old female with a history of anemia and episodes of bleeding per rectum. An abdominal ultrasound and CT scan showed a left renal mass. Histopathological examination of the nephrectomy showed a well-demarcated lesion composed of sheets of histiocytes in a background of mixed inflammatory cell infiltrate. Some of the histiocytes showed characteristic emperopolesis with numerous intracellular lymphocytes.
Renal Rosai Dorfman disease is a rare extranodal form of Sinus histiocytosis with massive lymphadenopathy. It may occur as part of typical nodal disease or in isolation. In the latter event it may mimic a malignant renal neoplasm on clinical and radiological investigation.

P75

Hybrid Oncocytic Renal neoplasm

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The most common renal tumours are clear cell, papillary, chromophobe and collecting duct renal cell carcinomas (RCCs), and benign oncocytomas and angiomyolipomas. Hybrid Renal Cell neoplasm's (HRCNs) containing areas of tumour cells displaying cytological features of chromophone renal cell carcinoma (CHRCC) and renal oncocytoma (RO) have been recently described in patients with renal oncocytosis and Birt- Hogg-Dube(BHD) syndrome. The association of renal oncocytoma with renal cell carcinoma has been reported. There is growing evidence that RO and CHRCC may be related entities with RO representing the benign end of a spectrum and CHRCC residing at the malignant end. Specifically, both may arise from the tubular intercalated cell, they share common histological features that can make it challenging to distinguish one from the other.
We report two unusual presentation of sporadic HRCN. Both the patients were females in late 60s and presented with abdominal pain. One of them had liver metastasis, and other had an associated conventional RCC.
The presence of BHD should be investigated in patients with multiple bilateral tumours and especially if tumour is hybrid oncocytic tumour.

P76

Peritubular Capillaritis in Renal Allografts: Prevalence, Scoring System, Reproducibility and Clinicopathological Correlates

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The accumulation of inflammatory cells in glomerular and peritubular capillaries (PTC) of renal allografts is a recognised histological feature of rejection, particularly antibody-mediated rejection (ABMR). While glomerulitis is graded according to the established Banff classification, no criteria for scoring peritubular capillaritis (ptc score) have been established.
We retrospectively applied ptc-scoring criteria to 688 renal allograft (46 pre-implantation, 461 protocol, 181 indication) biopsies. 26.3% of all analyzed biopsies had peritubular capillaritis (implant 0%, protocol 17.6%, indication 45.5%; $p<0.0001$). The most common capillaritis pattern was of moderate severity (5-10 luminal cells), focal in extent (10-50% of PTC), with a minority of neutrophils. 24.3% of C4d- compared with 78% of C4d+ biopsies showed capillaritis ($p<0.0001$). >80% of biopsies with glomerulitis had peritubular capillaritis. 50.4% of biopsies with borderline or T-cell mediated rejection (TCMR) and 14.1% of biopsies without TCMR or ABMR showed capillaritis ($p<0.0001$). The inter-observer reproducibility of the PTC-scoring features was fair to moderate.
Indication biopsies show a significantly higher prevalence of capillaritis than protocol biopsies. Capillaritis is more frequent and pronounced in ABMR, but can be observed in borderline and TCMR cases. Scoring of peritubular capillaritis is feasible, and facilitates assessment of PTC pathology in renal allograft biopsies.

P77

Polyoma Virus Infection and Urothelial Carcinoma of the Bladder: is there a Link?

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The polyoma virus BKV is implicated in the pathogenesis of bladder carcinoma, both in renal transplant recipients and immunocompetent individuals. We investigate a possible oncogenic role of BKV by staining tumour tissue for PV T-Ag.
PV T-Ag was negative in 20 consecutive urothelial carcinomas from non-transplant patients. Tumour tissue was available from 8/10 local renal transplant recipients (1990-2007) who have developed urothelial carcinoma. Six patients were transplanted before our first case of BKV nephropathy, diagnosed in 2000; their tumour tissue was negative for PV T-Ag. Two patients were transplanted since 2000. Both had prior BKV re-activation, one diagnosed on urine cytology at 6 months, the other on renal biopsy at 2 years post-transplantation. One developed invasive urothelial carcinoma 4 years post-transplantation; this demonstrated tumour cell positivity for PV T-Ag, with no staining of non-neoplastic urothelium. The other patient developed urothelial carcinoma-in-situ 3 years post-transplantation that was negative for PV T-Ag. Urine cytology 2-3 months prior to the biopsy diagnosis demonstrated large numbers of atypical cells, initially misinterpreted as BKV-infected decoy cells.
PV infection is not associated with urothelial carcinoma in non-transplant patients, and is uncommon in transplant-associated tumours. PV T-Ag positivity in one tumour may reflect a role in tumourigenesis, or alternatively be a secondary phenomenon, resulting from early infection of replicating neoplastic urothelium. Morphological similarities between neoplastic and BKV-infected urothelial cells in the urine raise doubt about previous cytological evidence suggesting a pathogenetic link.

P78

Lipid Cell Variant of Urothelial Carcinoma – An Uncommon Entity

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Urothelial carcinoma may present with many morphological variants. The lipid cell variant of invasive urothelial carcinoma is a rare entity associated with an aggressive behaviour and poor prognosis. Only 6 cases have been described in the English literature.
We report two cases of lipid cell variant of urothelial carcinoma. In both cases usual type urothelial carcinoma was associated with lipid-cell variant cells, confirmed on both occasions with a positive reaction for cytokeratin staining.
Case 1. A 73 year old male had predominantly typical grade 2 papillary urothelial carcinoma, but there were lipocyte-like cells within some papillary cores.
Case 2. A 79 year old male had a grade 3 urothelial carcinoma with a variety of histological patterns including some plasmacytoid differentiation and there were also cells with a very strong similarity to lipoblasts. This case came to cystectomy and similar histology was seen in metastatic nodal disease.
These cases illustrate the potentially subtle presence of lipid cell differentiation and also its aggressive behaviour.

P79

Differential Phosphorylation of HSP-27 Determines the Malignant Phenotype of Human Prostate Cancer Cells

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The protein HSP-27 is a reliable biomarker of metastatic prostate cancer, strong expression predicting poor clinical outcome. This study tested the hypothesis that site-specific phosphorylation of HSP-27 directly modulates the invasive phenotype of human prostate cancer cells by a mechanism that results in down-regulation of apoptosis while enhancing cell motility. In human prostate cancer cell lines, phosphorylation of HSP-27 was stimulated with heregulin (HRG-1) through the intermediary HER2/*neu*. Selective inhibitors SB203580 and KRIBB3 blocked site-specific phosphorylation of HSP-27 at serines Ser^{78} and Ser^{82}, interrupting the regulated pathways. Conversely, phosphorylation of Ser^{15} was unaffected by either heregulin or by the inhibitors. Using immunohistochemistry, the distribution of phosphorylated HSP-27 was identified in tissue sections. Only the isoforms phosphorylated at Ser^{15} occurred within the nuclei of prostatic epithelial cells while those isoforms phosphorylated at Ser^{78} and Ser^{82} were restricted to the cytoplasm. Phosphorylation at Ser^{82} was abolished in the malignant cells. Thus, this study has confirmed differential intracellular processing of HSP-27 in prostatic epithelial cells. The data strongly suggest the presence of a novel protein kinase that phosphorylates HSP-27 at Ser^{15} and is responsible, in part, for the action of this protein in promoting prostate cancer invasion and metastasis.

P80

Peripheral Primitive Neuroectodermal Tumour of the Kidney with Invasion of the Inferior Vena Cava

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Peripheral primitive neuroectodermal tumours are a rare group of primary malignant tumours which arise uncommonly in the kidneys.

The case presentation is of a nephrectomy specimen and material from inferior vena cava removed from a 21 year old female. Imaging prior to surgery had shown that the tumour extended into the inferior vena cava. On macroscopic examination most of the kidney had been replaced by a friable, grey/white, lobulated mass. The tumour was growing along the renal vein and also infiltrated the ureter. Microscopy revealed sheets of small, uniform, primitive, blastema-like malignant cells separated by fibrous bands. Perivascular rosetting was present and the malignant cells had scanty cytoplasm. Similar neoplastic material was removed from the vena cava. Immunohistochemical labelling showed widespread, strong membranous positivity for CD99 and CD56 but no labelling for WT1. The morphology and immunophenotype favoured a diagnosis of a peripheral primitive neuroectodermal tumour. FISH analysis using a break-apart probe showed rearrangement of the EWS gene on 22q12, confirming the diagnosis. The patient subsequently received chemotherapy.

This case illustrates an uncommon primary renal neoplasm with the rare manifestation of continuous growth along the inferior vena cava.

P81

Spironolactone treatment reduces cell number in renal cell carcinoma

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We investigated the effects of spironolactone treatment on cell number and protein expression in RCC4 cells. Currently Spironolactone can be used in the management of hypertension in conjunction with other diuretics. Experimental data suggests that KiRas4a is a mineralocorticoid responsive protein in the kidney and is activated to produce downstream signalling. Spironolactone works by blocking the action of aldosterone in the kidney. Consequently the mineralocorticoid receptor is not activated and the localisation of KiRas to the plasma membrane does not promote the same level of downstream signalling therefore inhibiting activation of transcription factors that promote cell proliferation and the expression of proteins required for salt reabsorption.
We have examined the effects of spironolactone on RCC4 cells by following the trend in cell number 24, 48 and 72 hours post treatment in order to examine effects on cell growth. Additionally protein expression in the Ras-Raf-MAPK cascade has been observed following western blotting techniques. These studies have confirmed that spironolactone reduces expression of KiRas, phospho Raf, phospho MAPK and phospho S6 in RCC4 cells and furthermore reduces cell number. We hypothesise that KiRas4A has a growth promoting role possibly mediating responses in renal cell carcinoma and that spironolactone may have the ability to slow tumour growth by reducing the expression of the Ras-Raf-MAPK cascade.

P82

Co-Expression of AKT and Caveolin-1 is a Prognostic Marker in Renal Cell Carcinoma

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Surgically treated localised renal cell carcinomas (RCC) commonly recur as distant metastasis. Both caveolin-1 and the components of the mTOR pathway are implicated in the RCC progression. .We postulate interaction between caveolin-1 and the MTOR pathway.
A tissue microarray was constructed from 174 consecutvtive localised RCCs from patients followed up for disease free survival . Immunohistochemistry for caveolin–1 and AKT –an important mTOR effector- was performed by conventional techniques. Caveolin-1 and AKT immunohistochemical reaction was scored as positive or negative.
Thirty seven tumours were positive for AKT and 28 for caveolin-1. Only caveolin-1 was associated with poor outcome on univariate (Kaplan Meier) analysis; p=0.001; neither were influential on multivariate analysis if tumour grade, vascular invasion and capsular invasion are included. Twenty three tumours were positive for both AKT and caveolin-1, this combined marker was a highly significant influential covariate in Cox regression multivariate analysis: hazard ratio: 2.1, p= 0.017 (95%CIs: 1.1 to 3.9)
The co-expression of AKT and caveolin-1 identifies a group of patients at high risk of progression and suggests synergy between the pathways. This offers important prognostic information and has the potential to predict response to targeted therapeutic strategies.

P83

An Interesting Case of Primary Effusion Lymphoma (PEL) in an Elderly Patient

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Primary effusion lymphoma (PEL) is an unusual type of B cell lymphoma. The majority of cases occur in Human Immunodeficiency Virus (HIV) infected individuals. This neoplasm is associated with human herpes virus 8 (HHV8) or Kaposi sarcoma herpes virus (KSHV). Most cases are also co-infected with Epstein-Barr virus (EBV).

We report a rare case of primary effusion lymphoma (PEL) with no obvious cause of immunosuppression in an elderly patient. A 73 year old married Caucasian lady presented with left sided pleuritic chest pain and shortness of breath. Left sided pleural effusion was diagnosed and tapped. No lymphadenopathy was identified on clinical examination or on CT scan. Cytology of the pleural fluid revealed a diffuse B cell lymphoma which was supported by cytogenetics- t (3:22) (q27:q11). As the disease was involving the pleural cavity alone, a diagnosis of primary effusion lymphoma (PEL) was made. She was HIV negative, HHV8 negative, EBV negative and Hepatitis C negative. She was treated with R-CHOP and DXT. She is alive and well 17 months after the diagnosis in spite of poor prognosis associated with this lymphoma.

P84

Flow Cytometric Immunophenotyping (FCI) of Lymphoma in Egyptian Patients Correlation with Histopathology and Conventional Immunophenotyping

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Objective: To evaluate the role of FCI in diagnosis and characterization of lymphoma tissue specimens from Egyptian patients.
Methods: FCI using 2 and 3 - colour staining approaches, was performed on 50 fresh lymph nodes specimens from Cairo NCI patients with suspected lymphoma and correlated withimmunohistochemistry (IHC)].
Results: By FCI, cases were diagnosed as follows: 9 (18%) reactive hyperplasia (RH), 32 (64%) B - cell non - Hodgkin's Lymphoma (B-NHL) [24 diffuse large (DLBCL), 2 follicular, 3 small lymphocytic, 2 mantle cell lymphoma and a case of T cell rich B cell lymphoma], 3 (6%) T cell NHL, 2 (4%) Hodgkin's Lymphoma (HL) while 4 (8%) were non – lymphomatous tumours (NLT). Light chain restriction (LCR) was detected in the 32 FCI diagnosed B-NHL. The overall concordance between FCI versus histopathology and IHC was 88%. The sensitivity and specificity of FCI in diagnosis of NHL was 94.9 % and 100% respectively; in HL they were 40% and 100% respectively and in NLT, both sensitivity and specificity were 100% while for RH were 100% and 89.1% respectively.
Conclusions: FCI is a successful method in diagnosis and classification of lymphoma as well as in detection of monoclonality.

P85

A retrospective review of classical cytogenetic practice in lymphoma diagnosis

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This retrospective observational study describes our experience of classical cytogenetic investigation of lymphomas. We were unable to find recognised standards against which to audit our practice.
We reviewed cytogenetics reports from all cases of biopsy-proven lymphoma submitted for classical cytogenetic analysis over one year (2006) and correlated them with biopsy findings. All fresh material was considered for cytogenetic analysis, tissue being sent if there was sufficient for this as well as histological diagnosis. The biopsy diagnoses were peer reviewed as is standard practice in the north and east of Scotland.
In 50 cases material was sent. Of these, 26 samples produced results, the remainder failing to grow. Of the 26, 16 yielded data with specific diagnostic information, eg t(14;18), and 10 cases provided cytogenetic abnormalities consistent with lymphoma. In 2 cases, cytogenetic findings refined diagnosis. No cases were found where the biopsy and cytologenetic results conflicted. Samples that failed to grow included classical Hodgkin lymphoma.
This study demonstrates that, in our hands, 52% of classical cytogenetic investigations yield information that corroborates or enhances the histological diagnosis. In Hodgkin lymphoma (6%) failure to show an abnormality indirectly supports the diagnosis. We consider cytogenetics is a valuable adjunct in lymphoma diagnosis.

P86

Primary central nervous system lymphoma: a retrospective study of immunophenotype

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Primary lymphomas of the central nervous system (PCNSLs) are recognised as being mostly "high grade" and B-cell lineage. Published attempts to sub-classify these into follicle centre and activated B-cell types are few.
We reviewed sections from our archive of PCNSLs(1991-2006), finding 20 cases. One had insufficient material to allow further study and was excluded. Eleven cases arose in brain, 6 in spine, 2 in meninges/extradural space. We carried out immunocytochemistry on 19 cases for CD20, CD79a, CD10, BCL2, BCL6, MUM-1, Cyclin D1, CD 21, CD23, CD30 and pan-T markers (CD3, CD4, CD5). Staining was scored and agreed by two of us using a multi-headed microscope.
Results indicate all the cases were non-Hodgkin lymphoma, 18 being classified as diffuse large B-cell lymphoma. One meningeal case was difficult to classify. The immunohistochemical profile is illustrated in the table:

ICC	CD20	Cd79a	Bcl2	Bcl6	CD10	MUM1
No +ve	18	19	14	12	5	14

Most cases of PCNSLs stained positively with MUM-1 (14) whilst only 5 were CD10 positive. Three were MUM-1/CD10 positive. Only two were CD10 positive MUM-1 negative. BCL6 positivity was in CD10 and MUM-1 positive cases. This suggests that most PCNSLs show activated B cell or late germinal centre phenotype.

P87

A Rare Case of T-Cell Non-Hodgkins Lymphoma in a Patient With Common Variable Immunodeficiency

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Common variable immunodeficiency (CVID) is a heterogenous group of genetically determined primary immunodeficiencies with an associated increased risk of autoimmune diseases, gastric cancers and lymphoid malignancy. According to the literature up to 50% of patients have some T-lymphocyte dysfunction and the risk of Non-Hodgkin's Lymphoma (NHL) in CVID is 1.4% - 7%, with reported cases of NHL in CVID mostly comprising of B-cell lymphomas.
We report the case of a 23 year old male with known CVID who presented with chronic refractory anaemia, pruritis, night sweats and deteriorating renal and liver function, with renomegaly, hepatosplenomegaly and abdominal lymphadenopathy on CT scan. Lymph node biopsy showed effacement of native architecture by T-cells, mainly of cytotoxic profile (CD8 positive T-cells expressing TIA-1), sparse B cells and scanty IgA plasma cells. Splenic histology was similar, but with less T-cells. PCR for TCR gene rearrangement analysis identified one to two dominant amplifications within an intense polyclonal background. The patient was diagnosed with Peripheral T-Cell Lymphoma (with a Cytotoxic phenotype). He received CHOP chemotherapy and gradually improved.
We will discuss in detail the clinical, morphological, immunohistochemical and molecular findings of this rare case of T cell NHL in this patient with CVID

P88

Langerhan Cell Rich Mycosis Fungoides

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We present two cases of mycosis fungoides (MF) infiltrated by large numbers of dermal Langerhans cells (LCs). Each followed an unusually aggressive course with progression to high grade T-cell lymphoma. Large numbers of LCs simulating Langerhans cell histiocytosis may be associated with various malignancies and are likely to represent a reactive phenomenon. The role of tumour infiltrating dendritic cells (DCs) in stimulating an immune response and mechanisms of tumour evasion are of increasing interest. Studies show that the function of tumour infiltrating dendritic cells may be defective with failure in maturation, migration to regional nodes and expression of costimulatory molecules required to activate naive T lymphocytes. These defects may result from factors produced by the tumours themselves. We believe that LCs have a unique interdependent relationship with cutaneous T-cell lymphoma (CTCL). T cell interaction is required for prolonged dendritic cell survival and mature CD4+ cells are dependent on MHCII expressing dendritic cells. CTCLs may produce factors which prevent LC maturation and nodal migration. It is likely that the immature DCs retain antigen presenting capabilities presenting tumour antigen back to the CTCL, stimulating growth but failing to migrate and elicit an anti-tumour immune response.

P89

Del(6)(q22) and BCL6 rearrangements in primary central nervous system lymphoma are indicators of an aggressive clinical course

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Despite therapeutic advancements, biological markers that predict the natural history of primary central nervous system lymphoma (PCNSL) are lacking. *BCL6* rearrangements and deletions involving 6q22 are thought to be common genetic abnormalities but their prognostic significance is unknown. Our aim was to determine the prevalence and survival impact of del(6q22), and *BCL6* gene rearrangements in PCNSL.

Seventy-six specimens from 76 patients with PCNSL were studied. Interphase FISH was performed using probes for BCL6, IGH-BCL6, and del(6q22) on paraffin sections. Survival data were analyzed for patients diagnosed after 1997 (n=53), corresponding to the change to high dose methotrexate as the standard of care.

Thirty-four (45%) cases showed del(6q22), 6 of which also contained a *BCL6* rearrangement. Seventeen (22%) cases had a *BCL6* rearrangement. Of the 53 patients analysed for survival, 23 lacked del(6q22) or *BCL6* rearrangement and had a median overall survival (MS) of 731 days. The 17 patients with an isolated del(6q22) had a MS of 90 days and the 13 patients with a *BCL6* rearrangement had a MS of 442 days (p=0.0016).

Del(6q22) and *BCL6* rearrangements are common in PCNSL and are associated with decreased survival, particularly del(6q22) seemingly independent of patient age and treatment time trends.

P90

Aberrant Expression of β-HCG in Anaplastic Large Cell Lymphoma

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Expression of β subunit of human chorionic gonadotrophin (β-HCG) is usually encountered in germ cell tumours with trophoblastic differentiation. Its occurrence has been reported in carcinomas and a few cases of lymphomas.

We describe the first case of anaplastic large cell lymphoma (ALCL) in paediatric age group with aberrant expression of β-HCG on immunohistochemistry and associated with a raised serum level of β-HCG.

A 14-year old boy presented with a right inguinal mass and a raised serum β-HCG level. Biopsy of the mass revealed a malignant neoplasm composed of large, pleomorphic cells with prominent nucleoli. Immunohistochemistry showed reactivity to CD30, EMA, β-HCG, ALK, granzyme B and T-cell intracellular antigen-1. Chromosomal analysis showed t(2;5)(p23;q35) translocation and polymerase chain reaction demonstrated T-cell receptor gene rearrangement.

The patient did not respond well to chemotherapy and he died eight months after the diagnosis. Failure to achieve remission is unusual in ALK+ ALCL which usually has a favourable outcome following chemotherapy. This questions the association of β-HCG expression by tumour cells and a more aggressive disease.

We report this case to highlight a possible diagnostic pitfall and raise the speculation regarding the prognostic implication of this unusual phenotype.

P91

Tailgut Cyst – A Rare Sacrococcygeal Mass in Childhood

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Tailgut cyst is a rare, congenital developmental lesion assumed to arise from the remnants of the embryonic postanal gut. Most cases are seen in the retrorectal region in adult women.

A 12-year-old boy with known deletion of chromosome 6q presented with a sacrococcygeal mass. MRI revealed a 3 cm cystic lesion, dorsal to the sacrum and coccyx, showing no communication with the spinal canal and a normal lumbosacral spine.

Macroscopic examination revealed a multiloculated subcutaneous cyst containing viscid, yellowish-brown material. This lesion was lined by a variety of epithelia found in adult and fetal gastrointestinal tract including stratified squamous epithelium, ciliated columnar epithelium with scattered mucin secreting cells and transitional epithelium. Disorganised bundles of smooth muscle were noted within the cyst wall. No neuroglial tissue, heterologous mesenchymal derivatives or skin adnexal structures were identified. The appearances were those of a tailgut cyst.

The main differential diagnosis of sacrococcygeal lesions in children includes epidermoid cyst, dermoid cyst, teratoma, hindgut cyst, meningomyelocoele and ependymoma.

Complete surgical resection is the treatment of choice to prevent recurrence, infections and rare malignant transformation.

We report an unusual case of this rare entity at an atypical site in the paediatric age group.

P92

Molecular Diagnostic Approaches Invasive Fungal Infection in Immunocompromised Hosts

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The diagnosis of invasive fungal infection in histological material plays a crucial role in accurate treatment of these potentially life threatening conditions. The provision of biopsy material, particularly from the CNS, is undertaken only reluctantly in patients who are already seriously ill, but can make an important contribution to patient management. Routine microbiological culture may confirm the presence of a specific fungal species but histologically confirmed invasive fungal infection is often associated with negative fungal cultures. Immunohistochemical reagents for demonstrating specific fungi are limited and do not allow species differentiation. Empirical prophylactic antifungal treatment regimes used in immunosuppressed patients may be unsuccessful due to the changing epidemiology of invasive fungal infection. Making a rapid and accurate diagnosis is thus important. We present two cases of invasive fungal infection in immunocompromised hosts in which ancillary molecular pathological techniques, including in situ hybridisation and fungal specific PCR on paraffin-embedded tissues, aided the diagnosis of uncommon zygomycoses, including cerebral aspergillosis and pulmonary Cunninghamella bertholletiae infection. In one case this directed a change to appropriate anti-fungal therapy, and in another explained the failure of premortem treatment. Molecular diagnostics represent a valuable adjunct to routine histopathology to reduce the mortality of these diagnostically challenging conditions.

P93

MRI compared to histopathology in X-linked adrenoleukodystrophy

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Quantitative MRI techniques, like diffusion tensor imaging (DTI), magnetization transfer imaging (MTI) and magnetic resonance spectroscopy (MRS) can provide information on pathologic processes occurring in white matter disorders. We compared histopathologic parameters with quantitative MR parameters in X-linked adrenoleukodystrophy (ALD) brains to determine the correlation between the two. We performed MRI in 5 ALD patients, including MTI and DTI to obtain magnetization transfer ratio (MTR), apparent diffusion coefficient (ADC) and fractional anisotropy (FA) maps, in most cases with MRS. In two of the patients autopsy was performed with a postmortem MR study of fresh 1-cm-thick brain slices directly after removal, using the same techniques except for MRS. This postmortem MR study was repeated after at least 5 weeks of formalin fixation, together with formalin-fixed brain slices from 20 ALD patients and 15 controls obtained from other centres. After imaging, the coronal brain-slices were embedded in paraffin, and whole-mount sections were made to obtain a precise MR-histopathologic correlation. Routine neuropathologic staining techniques as well as immunostains were applied to quantify density of myelin and axons and the amount of astrogliosis using morphometric techniques. Per region-of-interest, these histopathologic parameters were correlated with ADC, FA, MTR and metabolites measured by in vivo MRS.
Preliminary findings show severe reductions in MTR and FA and increased ADC corresponding to severe axonal and myelin loss in burnt-out gliotic areas, whereas only mild decreases in MTR and FA correlated with severe myelin loss but only a mild degree of axonal loss in areas of ongoing demyelination. Additionally, MRS findings differed between these areas

P94

Infantile Cartilaginous Hamartoma of the Rib Cage

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Infantile cartilaginous hamartoma of the ribs is a rare lesion of infancy and early childhood with an incidence of 1 in 3,000 (0.03%) among all primary bone tumours. Most cases present at less than 1 year of age and may be congenital. It arises in the rib cage and is characterised by a varying admixture of cartilaginous, vascular and primitive-appearing stromal and mesenchymal elements with no zoning and no purposeful architecture. The primitive nature of the mesenchymal stroma and the haphazard arrangements of the tissue may result in the erroneous diagnosis of malignancy, hence the old literature referred to this entity as "osteochondrosarcoma". The tumour may present as a deforming chest wall mass, with respiratory symptoms or may even be an incidental finding.
–The present case is of a chest wall mass in a 4 month old Asian male infant who presented with rapidly worsening dyspnoea. Biopsy from this mass was diagnosed as osteosarcoma in his native country. However, review of the case was requested and it was sent to an experienced musculo-skeletal histopathologist. This resulted in a diagnosis of an infantile cartilaginous hamartoma (benign mesenchymoma of rib).
–Infantile cartilaginous hamartoma behaves in an entirely benign fashion and is curable with local resection.

P95

Absence of Lymphatics is a Useful Diagnostic Marker in Distinguishing Soft Tissue Sarcomas from Reactive and Locally Aggressive Myofibroblastic Lesions

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Soft tissue sarcomas do not generally metastasise via lymphatics and the presence or absence of lymphatic vessels within sarcomas and pseudosarcomatous benign or locally aggressive proliferative/reactive myofibroblastic tumours is not known. In this study we analysed by immunohistochemistry, the expression of the lymphatic endothelial cell markers LYVE-1 and podoplanin on cases of benign and malignant soft tissue tumours, including nodular fasciitis (2), proliferative fasciitis (2), ischemic fasciitis (1), deep fibromatosis (14), leiomyosarcoma (7), fibrosarcoma /MFH (9), low-grade fibromyxoid sarcoma (4) and synovial sarcoma (5). All cases of nodular, proliferative and ischemic fasciitis contained LYVE-1 / podoplanin-positive lymphatic vessels as did 10 of 14 cases of deep fibromatosis. In all the sarcomas studied, LYVE-1/podoplanin-positive lymphatic vessels were only identified in reactive soft tissues around the tumour and not within the tumour. Our findings indicate that identification of lymphatic vessels may be of diagnostic utility in distinguishing reactive and proliferative myofibroblastic lesions from soft tissue sarcomas. They also indicate that lymphangiogenesis does not occur to any great extent within soft tissue sarcomas, providing an explanation for the infrequent finding of lymph node metastasis associated with these tumours.

P96

Dendritic cell infiltration and DC SIGN expression by tumour cells in bone sarcomas.

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Dendritic cells (DCs) are antigen presenting cells that have been implicated in the pathogenesis and progression of carcinomas but their role in the immune response to primary bone sarcomas is not known. In this study we looked for the presence of DCs and other immune cells in bone sarcomas. We used a panel of monoclonal antibodies to identify DCs (DC SIGN, S100, CD 11c), T cells (CD3, CD4, CD8), B cells (CD20) and macrophages (CD14, CD68) in cases of osteosarcoma (4), giant cell tumour of bone (3), Ewing's sarcoma (2) and chondrosarcoma (17 including 6 mesenchymal chondrosarcomas) and found that apart from Ewing's sarcoma there was a significant DC infiltrate in these tumours. In chondrosarcoma DC SIGN expression was noted not only on reactive inflammatory DCs but also on the cartilage tumour cells. It was also noted in the spindle-cell component of mesenchymal chondrosarcomas.
Our findings show that the DCs are likely to play a role in the immune response to bone sarcomas. Expression of DC SIGN may be a useful diagnostic marker to identify mesenchymal chondrosarcomas.

P97

Myofibroblasts in Giant Cell Tumour and Other Giant Cell-Rich Lesions of Bone: Relation to Tumour Recurrence and Grade

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Myofibroblasts exhibit morphological and immunophenotypic features of both fibroblasts and smooth muscle cells. The presence of these cells in giant cell tumour of bone (GCTB) and other giant cell rich lesions has not been fully characterized. In this study we determined by immunohistochemistry, the expression of smooth muscle actin (SMA) and other smooth muscle / myofibroblast markers on mononuclear stromal cells in GCTB, non ossifying fibroma (NOF), aneurysmal bone cyst (ABC), chondromyxoid fibroma (CMF) and chondroblastoma (CB). We found that mononuclear cells expressing SMA but not desmin, calponin, caldesmon were present in GCTB, NOF, ABC, CMF and CB. Cultures of mononuclear stromal cells isolated from GCTB also expressed SMA. In GCTB, NOF, ABC, CMF and CB, SMA expressing cells were often found at the growing edge of the lesion. Almost all cells in NOF strongly expressed a myofibroblastic phenotype, confirming the reactive nature of this lesion. SMA expression was prominent in recurrent GCTB and appeared to show a stronger correlation with aggressive behaviour of GCTB than expression of the proliferation markers Ki-67 and PCNA, indicating that identification of SMA expression may be a useful marker in the grading of GCTB.

Abstracts

Speakers

S1

The Surgical Management of Endometrial and Ovarian Cancer

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During the least decade the surgical interventions in both endometrial and ovarian cancer have undergone scrutiny within the context of prospective randomised trials. In endometrial cancer, whereby surgery is deemed the optimum intervention, with localised disease, the value of lympadenectomy in such early disease was assessed in the largest RCT, called ASTEC. This study , now completed, has been reported and preliminary results will be discussed. In ovarian cancer, which in 90% of cases, are epithelial in origin, the surgical approach in advanced disease, is to attempt to achieve what is termed 'optimum debulking' . This is whereby any residual tumour after surgery, is less than 1cm in any measurement. Such patients seem to have the best survival prospects – though whether due to the skill of the surgeon, or the inherent tumour biology remains debatable. Two RCTs, EORTC 55971 and CHORUS [MRC based] are trying to answer this question , though the complete answer may be within a trial containing a non-surgical arm.

S2

Medical management of endometrial and ovarian cancers

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The stage and the bulk of disease in ovarian and endometrial cancers define the subsequent outcome for patients. The histological subtype also defines aggressiveness of disease, and all of these factors frame the medical management of these patients. Whilst surgical debulking in the presence of metastases has some role, the eventual outcome for patients now depends on the combination of multimodality therapy. Traditionally these have encompassed chemotherapy, radiotherapy and surgery. Chemotherapy for ovarian and endometrial cancer has been developed entirely empirically. Out of this work, platinum based chemotherapy appears to have the highest activity in reducing the size of metastatic lesions. In the context of microscopic disease after early stage resections, with the treatment given within the adjuvant setting, then there evidence of improvement in overall survival. Molecular genotyping of cancers, particularly ovarian and endometrial cancers is likely to result in some tailoring of the current therapeutic approaches. Early evidence from the use of bevazucimab, a VEGF inhibitor, has shown single agent activity in advanced ovarian cancer. Subsequent agents that target signaling pathways may impact on the molecular classification of tumours as part of diagnostic pathology processes.

S3

Differential Diagnoses in Common Ovarian Neoplasms

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The majority of ovarian tumours are epithelial in origin but there is tremendous heterogeneity in their appearance, which may mimic non-epithelial tumours. Moreover, epithelial tumours from other body sites frequently metastasise to the ovary and accurate identification of these tumours is of clear clinical importance. In addition, recent clinico-pathological studies and molecular pathological data suggest that the traditional classification of primary epithelial tumours of the ovary requires some modification, with delineation of distinct categories, some of which cross traditional morphological boundaries. High-grade serous and endometrioid tumours, and undifferentiated carcinomas, have a common association with *p53* mutation and loss of BRCA1/2 function. Low-grade serous carcinomas are associated with serous borderline tumours and mutations in the *BRAF/KRAS* genes. Similarly, mucinous carcinomas are associated with borderline mucinous tumours and *KRAS* mutation. Low-grade endometrioid tumours are associated with ovarian endometriosis and mutation of the *beta-catenin* and *PTEN* genes. The situation for clear cell and transitional cell carcinomas is less clear, although there is some evidence that different sub-types of these tumours may also exist. The refinement of classification of primary epithelial ovarian tumours not only aids our understanding of these tumours but also provides further tools for their accurate identification and distinction from mimics: this has clear potential clinical benefit.

S4

Differential diagnoses in uterine mesenchymal neoplasms

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Uterine mesenchymal tumours are frequently encountered in routine surgical pathology. The commonest is the typical leiomyoma, which is present in about 25% of women of reproductive age. A number of leiomyoma variants can be misinterpreted because of their unusual macroscopic or microscopic appearance. There are a number of features that will assist separation of leiomyoma variants (with their implied benign outcome) from malignant tumours. Smooth muscle tumours of uncertain malignant potential (STUMP) are a further area of diagnostic difficulty. Endometrial stromal tumours (EST) are the second most common category of uterine mesenchymal tumours. They are typically composed of cells that resemble the endometrial stromal cells of the proliferative endometrium. The areas of differential diagnosis include endometrial stromal nodule vs. endometrial stromal sarcoma (ESS), EST vs. cellular endometrial polyp, EST vs. highly cellular leiomyoma and ESS vs. intravenous leiomyomatosis. Unusual entities like EST with smooth muscle differentiation, uterine tumour resembling sex-cord tumour and PEComas are entities presenting as tumours of the uterine mesenchymal tissue. Immunohistochemistry can be used in the diagnosis of uterine mesenchymal tumours but the limitations of the various antibodies used must be understood in the context of differential diagnosis.

S5

Nano-UPLC Improves Sensitivity and Coverage for In-Depth Proteomic Analysis

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Nano-liquid chromatography mass spectrometry (LC-MS) represents an indispensable method for the analysis of biomolecules in modern biomedical sciences. Challenges include the availability of biological material (low to sub-femtomol levels) and their complexity (>1000 molecules), from which as much structural information is desired to be obtained. An effort to achieve this goal includes advances in mass spectrometer performance, but also in separation technologies, such as nano-HPLC. More recently, ultra performance liquid chromatography (UPLC), first developed for more rapid separation solutions to reduce costs and increase throughput, has been introduced to nano-LC-based methods for proteomics. Elevated chromatography performance by nano-UPLC coupled to fast MS/MS significantly increases sensitivity and in-depth analysis of peptides and proteins. Moreover, more precise quantitative information can be obtained based on superior reproducibility and stability of total ion and base peak intensity chromatograms. UPLC-based advantages for quantitative and comparative proteomics based applications are discussed.

S6

Colorectal cancer: Seeing is believing

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Over the past decade colorectal cancer has come to be viewed as a multi-pathway disease in which only a subset is explained by the linear stepwise model known as the adenoma-carcinoma sequence. An important starting point for this paradigm shift was the development of molecular classifications of colorectal cancer based on mechanisms that could target multiple genes simultaneously. One of these mechanisms is a particular type of genetic instability known as DNA microsatellite instability (MSI) due to silencing of a DNA mismatch repair gene such as *MLH1*. Another mechanism is the state of DNA hypermethylation known as the CpG island methylator phenotype (CIMP). *MLH1* is one of many genes silenced by CIMP. The pathologist was particularly well placed to observe an alternative pathway to colorectal cancer by applying the technique of immunohistochemistry to hyperplastic polyps, lesions that were once considered to be completely innocent. The direct observation of dysplastic subclones within hyperplastic polyps showing loss of nuclear expression of MLH1 not only established the precancerous potential of these lesions, but linked them to a specific 'serrated pathway' of colorectal tumourigenesis. Similar approaches using antibodies to the DNA repair gene MGMT highlighted alternative serrated pathways. In reviewing these changes to our understanding of the evolution of one of the most important types of human malignancy, particular emphasis will be placed on the instructive importance of the microscopic image: to see is to believe.

S7

Mimics of Chronic inflammatory bowel disease.

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This talk is based entirely on a chapter written by Neil Shepherd and myself in: *Jewell DP,.Mortensen N, Pemberton J, Steinhart H, Warren BF. Challenges in Inflammatory Bowel Disease Blackwell Oxford 2006*.

The talk will uncover some pathological confusion in inflammatory bowel disease which relates entirely to pathology being pursued in isolation without concern for clinical context. Context in gastrointestinal pathology is crucial for the production of adequate pathology reports which will actually help to guide patient management. Cancer MDT meetings are excellent for the standardisation of cancer care and involve pathologists in new found levels of communication. The downside of this evolution in medicine is the lack of remaining time for the discussion of management of chronic benign diseases such as chronic inflammatory bowel disease. The decisions for surgery and major new drug therapy are not without consequence, and if incorrect may stay with the patient for a long time.

The talk will cover initial diagnosis from infective colitis, the problems of assessing the role of granulomas and the involvement of pathology in all aspects of IBD surgery in particular pouch surgery.

S8

New genes, new pathways in IBD susceptibility

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The last 12 months has seen sensational progress in characterizing the genetic determinants of inflammatory bowel disease (IBD). The breakthrough has been achieved as a consequence of the new technology of genome-wide association (GWA) scanning. This technique is demanding of cutting-edge genotyping and bioinformatic technologies, and requires robust statistical analysis, but has already proven itself capable of delivering highly resolved, highly replicated data in the select group of diseases to which it has so far been applied. One of the most dramatically successful of these has been Crohn's disease. Until recently NOD2 was the only confirmed CD susceptibility gene. GWA scanning has added no fewer than 6 more genes, with 6 other confirmed loci identified requiring additional fine-mapping to pinpoint the causative gene or regulatory domain. Most of the genes were previously unsuspected and, intriguingly, some of the strongest hits map to gene deserts, hinting at novel mechanisms of complex disease susceptibility. IL23 and autophagy pathways have been highlighted by multiple hits in separate genes, flagging these as key mechanisms in chronic intestinal inflammation. The strength of the association ($p<10^{-9}$ - 10^{-35}) at these and other loci gives clear direction for downstream functional and immunological work focused on pathways of clear relevance to IBD pathogenesis. A number of the genes identified also represent potential targets for drug therapy. Genetic analysis in complex disease truly has come of age, and IBD genetics is helping to lead the charge.

S9

Dysplasia in ulcerative colitis: diagnosis and management

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Surveillance for ulcerative colitis (UC) is a recommendation of (inter)national guidelines: pathologists spend considerable time in the assessment of biopsies. Neoplasia risk is largely determined by the extent and longevity of disease. The risk for neoplasia in colonic Crohn's disease (CD) may be as high but there are few data on surveillance and practicalities of demonstrating dysplasia in CD. We know much more about dysplasia in UC.

Helpful information on surveillance in UC comes from BSG IBD Management Guidelines (www.bsg.org.uk). Riddell-type classification should be used for neoplasia in UC and pathologists are encouraged to use the indefinite category. There is good inter-observer agreement for high grade dysplasia (HGD) but less good for low grade dysplasia (LGD) and indefinite for dysplasia. In the UK, lower levels of inter-observer agreement and poor predictability of LGD mean that colectomy is not usually indicated. The differentiation of DALM from sporadic adenoma is of continuing controversy and there is much literature on this. As ever, clinical context is critical.

'Indefinite for dysplasia' is an indication for repeat colonoscopy, especially after treatment, and a full biopsy protocol to confirm or refute dysplasia. Currently, for HGD, colectomy is considered appropriate, age and co-morbidity allowing. The current management of LGD depends on context. In flat mucosa, surveillance/expert colonoscopy and local excision is appropriate. If there is LGD in a DALM, then either local excision or, if associated with dysplasia in flat mucosa, colectomy may be appropriate.

Great changes are afoot. There is now good evidence that chromo-endoscopy can detect most dysplastic lesions in UC. Pathology is more reliable with double reporting, expert reporting and subspecialisation whereas fancy pathological techniques, in an attempt to diagnose dysplasia and the type of dysplasia, add little. Most polypoid dysplastic lesions in ulcerative colitis can be treated by local excision at endoscopy. The future of the management of dysplasia in UC is in the introduction of endoscopic techniques which are able to diagnose and effectively treat neoplastic lesions at the time of endoscopy.

PRESENTER'S INDEX