GLASGOW PATHOLOGY 2007

Understanding disease

3 – 6 July 2007

Fourth Joint Meeting of the British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland

Hosted by the Department of Pathology University of Glasgow

Venue
The Wolfson Medical School & Boyd Orr Building, University of Glasgow, UK

There will also be Companion Meetings with the Association of Clinical Electron Microscopists, Liver EQA, Renal EQA, and UK NEQAS for Cellular Pathology plus a joint symposium with the British Neuropathological Society

UNIVERSITY of GLASGOW

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PROGRAMME ACKNOWLEDGEMENTS

This Programme is published jointly by the
British Division of the International Academy of Pathology
and the Pathological Society of Great Britain & Ireland

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This Programme was designed, produced and printed in England by
Byte & Type Limited, Birmingham B11 1BL (Tel: 0121 772 3828).

TUESDAY 3 JULY

08.00	**Registration** (Wolfson, The Atrium)
09.00–12.00	**Symposium 1:** *The Importance of Stroma, Blood Vessels & Inflammation in the Development & Progression of Carcinomas.* **Sponsored by Genentech Inc, USA** (Boyd Orr, Lecture Theatre 1)
09.00–12.00	**Symposium 2:** *Forensic Diagnoses and Decisions.* (Boyd Orr, Lecture Theatre 2)
10.30–11.00	**Coffee break** (Wolfson, The Atrium)
09.00–17.00	**Slide Seminar Case Viewing:** *Dermatopathology – Skin Pathology for Ordinary Folk* (Wolfson, Study Landscape, Level 3)
12.00–12.15	**Opening Address:** Prof J Coggins, Vice Principal, Life Science, Medicine & Veterinary Medicine, University of Glasgow (Boyd Orr Lecture Theatre 1)
12.15–13.00	**Keynote Lecture:** Prof F Balkwill, London: *Cancer and plasticity of the inflammatory response in tumour development and progression.* **Sponsored by Cancer Research UK.** (Boyd Orr, Lecture Theatre 1)
13.00–15.00	**Lunch** (Wolfson, The Atrium) **Poster Viewing** (Wolfson, Seminar Rooms 2 & 3; Clinical Skills Area, Level 4) **Trade Exhibition** (Wolfson, The Atrium)
13.30–14.30	**Trainees Session, Meet the Experts:** *Lung Pathology* (Wolfson, Seminar Room 1) Lunch will be provided for participants within the session
14.30–15.30	**Molecular Pathology Group – Update Meeting** (Boyd Orr, Lecture Theatre A)
15.30–17.30	**Oral Presentations** (Boyd Orr, Lecture Theatres 1 & 2)
16.30–17.00	**Tea** (Wolfson, The Atrium)
17.30–18.30	**Public Lecture:** Dr H Burns, Chief Medical Officer for Scotland: *The Biology of Poverty* (Boyd Orr, Lecture Theatre 1)
19.00–20.30	**Civic Reception** (Glasgow City Chambers)

WEDNESDAY 4 JULY

08.00	**Registration** (Wolfson, The Atrium)
09.00–12.00	**Symposium 1:** *Sarcoma / Soft Tissue.* **Sponsored by Novartis Oncology** (Boyd Orr, Lecture Theatre 1)
09.00–12.00	**Symposium 2:** Joint Symposium with the British Neuropathological Society: *Molecular Control of CNS Disease Phenotype, Behaviour and Repair.* **Sponsored by the British Neuropathological Society.** (Boyd Orr, Lecture Theatre 2)
09.00–17.00	**Slide Seminar Case Viewing** (Wolfson, Study Landscape, Level 3)
09.00–15.30	**UK NEQAS for Cellular Pathology Technique** (Boyd Orr, Lecture Theatre A) Lunch will be provided for participants within the session
10.00–11.30	**Coffee breaks** (sessions vary – see detailed programme) (Wolfson, The Atrium)
12.00–12.45	**Pathological Society 28th CL Oakley Lecture**. Dr J Reis-Filho, London: *Basal-like carcinomas: from pathology to mouse-models and beyond* (Boyd Orr, Lecture Theatre 1)
12.45–15.00	**Lunch** (Wolfson, The Atrium) **Poster Viewing** (Wolfson, Seminar Rooms 2 & 3; Clinical Skills Area, Level 4) **Trade Exhibition** (Wolfson, The Atrium)
13.30–15.00	**SHO Trainers' Meeting** (Wolfson, Seminar Room 1)
15.00–17.00	**Plenary Oral Presentations** (Boyd Orr, Lecture Theatre 1)
15.45–16.15	**Tea** (Wolfson, The Atrium)
17.00–17.45	**BDIAP 2nd George Cunningham Lecture** Prof M Wells, Sheffield: *The enigma of trophoblast – a 24 year perspective* (Boyd Orr, Lecture Theatre 1)
17.45–18.15	***Biomarkers in Cancer***, Dr M Kauffman. **Sponsored by Roche**. (Wolfson, Seminar Room 1)
18.15–20.30	**Formal Poster Rounds** (all categories) and Drinks Reception. **Sponsored by Roche**. (Wolfson, Seminar Rooms 2 & 3; Clinical Skills Area, Level 4)

THURSDAY 5 JULY

08.00	**Registration** (Wolfson, The Atrium)
09.00–12.00	**Oral Presentations** (Boyd Orr, Lecture Theatres 1 & 2)
09.00–12.00	**Slide Seminar Discussion:** *Dermatopathology, Skin Pathology for Ordinary Folk* (Boyd Orr, Lecture Theatre A)
09.40–17.00	**Companion Meeting: Association of Clinical Electron Microscopists** (Boyd Orr, Lecture Theatre B)
10.15–11.00	**Coffee breaks** (sessions vary – see detailed programme) (Wolfson, The Atrium)
12.00–13.00	**Pathological Society Annual Business Meeting** (Boyd Orr, Lecture Theatre 1)
12.15–13.45	**Renal EQA** (Boyd Orr, Lecture Theatre 2) Lunch will be provided for participants within the session
13.00–15.00	**Lunch** (Wolfson, The Atrium) **Poster Viewing** (Wolfson, Seminar Rooms 2 & 3; Clinical Skills Area, Level 4) **Trade Exhibition** (Wolfson, The Atrium)
14.00–17.00	**Symposium 1:** *Personalised Pathology and Novel Diagnostics: The Way Ahead* (Boyd Orr, Lecture Theatre 1)
14.00–17.00	**Symposium 2:** *Kidney Pathology for the Generalist* (Boyd Orr, Lecture Theatre 2)
15.30–16.00	**Tea** (Wolfson, The Atrium)
17.00–17.45	**Pathological Society's 4th Doniach Lecture.** Prof Sir Nicholas Wright, London: *Pathology: what does it mean to you?* (Boyd Orr, Lecture Theatre 1)
19.30–23.00	**Conference Dinner** (Kelvingrove Art Gallery)

FRIDAY 6 JULY

08.00	**Registration** (Wolfson, The Atrium)
09.00–12.20	**Symposium:** *Current Challenges in Gastrointestinal Pathology* (Boyd Orr, Lecture Theatre 2)
10.25–11.00	**Coffee** (Wolfson, The Atrium)
12.30–14.00	**Liver EQA** (Boyd Orr, Lecture Theatre A) Lunch will be provided for participants within the session

ORAL COMMUNICATIONS

Sessions will be held as follows:

Tuesday 3 July 15.30–17.30 (Boyd Orr, Lecture Theatres 1 & 2)

Thursday 5 July 09.00–12.00 (Boyd Orr, Lecture Theatres 1 & 2)

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.*

PLENARY ORAL SESSION

The six highest-ranked submitted oral abstracts will be presented on:

Wednesday 4 July 15.00–17.00 (Boyd Orr, Lecture Theatre 1)

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

POSTERS (Wolfson, Seminar Rooms 2 & 3; Clinical Skills Area, Level 4)

Viewing: 13.00–15.00 on Tuesday 3, Wednesday 4 and Thursday 5 July.

Formal Poster Viewing, Chairman's Rounds and Drinks Reception (Sponsored by Roche) Wednesday 4 July, 18.15–20.30.

Note to presenters: *Ideally, posters should be in place by 09.00 hrs on Tuesday 3 July and removed by 17.00 hrs on Thursday 5 July. At least one of the contributors must be in attendance during the formal viewing period, as indicated in the programme synopsis. The Pathological Society Sir Alastair Currie Prize and second and third poster prizes will be presented at the Conference Dinner.*

SYMPOSIA

Tuesday 3 July, 09.00–12.00

Symposium 1 *The Importance of Stroma, Blood Vessels & Inflammation in the Development & Progression of Carcinomas.* **Sponsored by Genentech Inc.** (Boyd Orr, Lecture Theatre 1)

Symposium 2 *Forensic Diagnoses and Decisions.* (Boyd Orr, Lecture Theatre 2)

Wednesday 4 July, 09.00–12.00

Symposium 1 *Sarcoma / Soft Tissue.* **Sponsored by Novartis Oncology.** (Boyd Orr, Lecture Theatre 1)

Symposium 2 Joint Symposium with the British Neuropathological Society (BNS): *Molecular Controls of CNS Disease Phenotype, Behaviour and Repair*. **Sponsored by the BNS.** (Boyd Orr, Lecture Theatre 2)

Thursday 5 July, 14.00–17.00

Symposium 1 *Personalised Pathology and Novel Diagnostics: The Way Ahead.* (Boyd Orr, Lecture Theatre 1)

Symposium 2 *Kidney Pathology for the Generalist.* (Boyd Orr, Lecture Theatre 2)

Friday 6 July, 09.00–12.20

Symposium *Current Challenges in Gastrointestinal Pathology.* **Sponsored by Novartis Oncology.** (Boyd Orr, Lecture Theatre 2)

TRAINEES SESSION

Tuesday 3 July, 13.30–14.30, *Meet the Experts – Lung Pathology* (Wolfson, Seminar Room 1).

SPECIAL INTEREST GROUPS

Tuesday 3 July, 14.30–15.30, Molecular Pathology Group – Update (Boyd Orr, Lecture Theatre A).
All welcome.

Wednesday 4 July, 13.30–15.00, SHO Trainers' Meeting (Wolfson, Seminar Room 1).
All welcome.

SLIDE COMPETITION & SEMINAR

Dermatopathology: Skin Pathology for Ordinary Folk

Competition: There will be a slide competition using digital slide images, which will be available for viewing on Tuesday 3 July and Wednesday 4 July (Wolfson, Study Landscape, Level 3).

Follow-up Discussion Session: Thursday 5 July from 09.00–12.00 (Boyd Orr, Lecture Theatre A).

KEYNOTE AND NAMED LECTURES

Tuesday 3 July

12.15–13.00 **Keynote Lecture:** *Cancer and plasticity of the inflammatory response in tumour development and progression.* Prof F Balkwill, London.
Sponsored by Cancer Research UK (Boyd Orr, Lecture Theatre 1).

Wednesday 4 July

09.00–09.30 **Symposium: *Sarcoma / Soft Tissue***
Keynote Lecture: *New entities and new twists on old entities.*
Prof J Meis-Kindblom, Birmingham (Boyd Orr, Lecture Theatre 1).

09.00–10.00 **Symposium: *Molecular Controls of CNS Disease Phenotype, Behaviour and Repair***
Keynote Lecture: *The clinicopathological significance of molecular abnormalities in medulloblastoma – a paradigm for the diagnosis and management of childhood brain tumours.* Prof D Ellison, Memphis, USA (Boyd Orr, Lecture Theatre 2).

12.00–12.45 **CL Oakley Lecture:** *Basal-like carcinomas: from pathology to mouse-models and beyond.* Dr JS Reis-Filho, London (Boyd Orr, Lecture Theatre 1).

17.00–17.45 **George Cunningham Lecture:** *The enigma of trophoblast – a 24 year perspective.* Prof M Wells, Sheffield (Boyd Orr, Lecture Theatre 1).

Thursday 5 July

17.00–17.45 **Doniach Lecture:** *Pathology: what does it mean to you?* Prof Sir Nicholas Wright, London (Boyd Orr, Lecture Theatre 1).

Friday 6 July

09.00–09.45 **Symposium: *Current Challenges in Gastrointestinal Pathology***
Keynote Lecture: *Diagnostic pitfalls in inflammatory bowel disease.*
Prof RH Riddell, Toronto, Canada (Boyd Orr, Lecture Theatre 2).

PUBLIC LECTURE

Tuesday 3 July, 17.30–18.30, *The Biology of Poverty*, Dr H Burns, Chief Medical Officer for Scotland (Boyd Orr, Lecture Theatre 1).

COMPANION MEETINGS

Wednesday 4 July

09.00–15.30 UK NEQAS for Cellular Pathology Technique (Boyd Orr, Lecture Theatre A).

Thursday 5 July

09.40–17.00 Association of Clinical Electron Microscopists 10th Annual Scientific Meeting (Boyd Orr, Lecture Theatre B).

12.15–13.45 Renal EQA (Boyd Orr, Lecture Theatre 2).

Friday 6 July

12.30–14.00 Liver EQA (Boyd Orr, Lecture Theatre A).

TRADE EXHIBITION (Wolfson, The Atrium)

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

CONTINUING PROFESSIONAL DEVELOPMENT (CPD)

This Meeting has been approved by the **Royal College of Pathologists** for the purposes of Continuing Professional Development. Credits 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 Certificate Request Form which will be provided in delegate bags at the Meeting.

REGISTRATION

Registration is **only** available via:
http://pathsoc.conference-services.net/registration.asp?conferenceID=1059&language=en-uk

Advance Registration Closing Date
Advance registration will close on **Monday 25 June 2007**. After this deadline registration will only be accepted on-site in Glasgow.

FEES Fees include all refreshments and lunch

EARLY BIRD FEES (Before 9 June 2007)

BDIAP and Pathological Society Members
£210 for the whole meeting, or £85 per day (or part day)

Non-Members
£300 for the whole meeting, or £145 per day (or part day)

CONCESSIONS

BDIAP and Pathological Society Members who are:
Biomedical Scientists (all grades), Honorary or Senior Members, PhD Students, Post-doctoral Fellows, Technicians (all grades), Trainees

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

Undergraduate Students*
£50 for the whole meeting, or £25 per day (or part day)

Non-Members* who are:
Biomedical Scientists (all grades), PhD Students, Post-doctoral Fellows, Technicians (all grades), Trainees

£75 for the whole meeting, or £40 per day (or part day)

FEES (On or after 9 June 2007)

BDIAP and Pathological Society Members
£300 for the whole meeting, or £125 per day (or part day)

Non-Members
£435 for the whole meeting, or £205 per day (or part day)

CONCESSIONS

BDIAP and Pathological Society Members who are:
Biomedical Scientists (all grades), Honorary or Senior Members, PhD Students, Post-doctoral Fellows, Technicians (all grades), Trainees

£75 for the whole meeting, or £40 per day (or part day)

Undergraduate Students*
£75 for the whole meeting, or £40 per day (or part day)

Non-Members* who are:
Biomedical Scientists (all grades), PhD Students, Post-doctoral Fellows, Technicians (all grades), Trainees

£105 for the whole meeting, or £60 per day (or part day)

* Delegates from categories 'Undergraduates' and 'Non-Member Concessions' must provide identification documents as proof of their student or trainee status, including NTN's where applicable. Proof must be by way of a statement from the Head of Department and should be sent to: julie@pathsoc.org.uk or faxed to: +44 (0)20 7976 1267

CONFERENCE DINNER

The charge for the Conference Dinner is £50 per person.

CANCELLATIONS

Please note that we are **unable** to refund registration fees / dinner tickets for cancellations received after **Friday 22 June 2007**.

DELEGATE ENROLMENT

Enrolment will take place from **08.00 hrs** on each day in the Wolfson Medical School Building, the Atrium area.

ENQUIRIES

Enquiries before the Meeting regarding administration should be directed to:

British Division of the IAP
PO Box 73, Westbury-on-Trym, Bristol BS9 1RY
Tel: +44(0)117 907 7940
Fax: +44(0)117 907 7941
E-mail: bdiap@blueyonder.co.uk

OR:

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

PRESENTATIONS

Presentation Checking & Preview

Presentation checking and preview will be available in the Wolfson, Study Landscape Area, Level 3.

Presentation Format

Powerpoint® only, must be PC compatible, must be on memory sticks only.

Presenters

Presenters must attend their nominated lecture theatre 30 minutes before their presentation time.

Slide Seminar

PCs for Slide Seminar Viewing will be located in the Wolfson, Study Landscape Area, Level 3.

Posters

Poster boards will be A0 (landscape). Please do not exceed these dimensions. Velcro will be provided.

INTERNET ACCESS

Each delegate will be allocated a secure login to the University computing services at registration. Delegates will be able to access web-mail using PCs in the Wolfson, Study Landscape Area, Levels 3 & 4.

MESSAGES

During the Meeting, messages for delegates may be left at the following telephone number:

+44 (0)141 330 3043

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

REFRESHMENTS

All refreshments will be served in the Wolfson, the Atrium, unless stated otherwise in the detailed programme.

BADGES

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

COATS & BAGS

Secure facilities will be provided for coats and bags in Interview Room 1 (Rm 231) and Interview Room 2 (Rm 232), both are located on the ground floor of the Wolfson. These rooms will be kept locked during the day and the key will be available at the Registration Desk which will be manned throughout the Conference opening hours.

TRAVEL & ACCOMMODATION

See website for information.

MAPS

Detailed maps are located on the inside front and both covers of this Programme.

SMOKING

From 26 March 2006 it is illegal to smoke in all indoor public places in Scotland, including workplaces, public venues, restaurants, bars, cafes and hotels.

DISCLAIMER

The British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland cannot be held responsible for any injury or loss sustained during the Meeting.

SOCIAL ACTIVITIES

Tuesday 3 July, 19.00–20.00/20.30

Civic Reception (City Chambers, Glasgow).
Please reserve your free ticket when registering – places are limited.

Wednesday 4 July, 18.15–20.30

Evening Poster Rounds and Drinks Reception (Wolfson, the Atrium).
Sponsored by Roche.

Thursday 5 July, 19.30 for 20.00–23.00

Conference Dinner (Kelvingrove Art Gallery).
Please reserve your ticket (cost £50) when registering – places are limited.

Local Places of Interest

Please see: http://www.cvso.co.uk/links.htm. Information will also be available in delegate bags.

FUTURE MEETINGS

British Division of the IAP

2007
November 23–24
Urological Pathology, London

2008
Spring
Gynaecological Pathology, Dublin

April 8
First Trainees' Meeting, London

Autumn
IAP International Congress, Athens

November 28–29
Hepatic and Pancreato-Biliary Pathology, London

2009

2010
Autumn
IAP International Congress, Sao Paolo

2012
Autumn
IAP International Congress, Cape Town

Pathological Society of Great Britain & Ireland

2007
July 1–2
First Summer School, Glasgow

2008
January
Winter School, Newcastle Pathology Course

January 8–9
Winter Meeting including Trainees' Programme, Oxford

July 1–4
Summer Meeting, Leeds

2009
January 7–9
Winter Meeting including Trainees' Programme, Kings College, London

2010
January 6–8
Winter Meeting including Trainees' Programme, Imperial College, Kensington Campus

June 29 – July 2
Summer Meeting, St. Andrews

JOINT MEETINGS
of the British Division of the IAP and the Pathological Society of Great Britain & Ireland

2009
June 30 – July 3
Cardiff Pathology

2011
Summer (date to be confirmed)
Ghent Pathology 2011

Trade Exhibition and Supporting Organisations

The British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland wishes to acknowledge the support of the following companies participating in the Trade Exhibition:

AGENDIA

CARL ZEISS

DAKO UK LTD

As pathology enters a new paradigm integrating even more technology and modern laboratory workflow, Dako is aiming to be a key driver in improving our customers' laboratories. Advancing cancer diagnostics takes a united approach, Dako is dedicated to bringing the pathology lab together, through an innovative approach to workflow with unified solutions that link instruments, connect to the LIS/LAN and virtually eliminates potential sources of error.

Dako builds upon our 40-year heritage of quality and innovation in antibodies and reagents, which remain the foundation for the pathology lab of tomorrow.

The future is close. Let's connect.

HAMAMATSU PHOTONICS UK

Hamamatsu Photonics is the world's largest, independent manufacturer of custom opto-electronic components and is particularly noted for the quality of products.

The featured product at this meeting is the NanoZoomer Digital Pathology system, which can digitise a pathology slide (brightfield or fluorescence mode in single or multi-level planes) quickly and at high resolution to produce a digital slide of outstanding image quality, which can be viewed on a local workstation or network.

Uses for digital slides include:

Computer Aided Diagnoses in the Pathology laboratory
Telepathology Applications
Education & Training of Medical Staff
Image Distribution, Duplication, Archiving & Retrieval
Research Applications

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NOVARTIS ONCOLOGY
Commitment to improving the outcome and quality of life of patients with cancer – the driving force for Novartis Oncology in developing new and novel compounds.

Focus by Novartis Oncology on bringing real benefits for patients has resulted in significant breakthroughs, enabling the launch of highly potent, specific treatments for use by the Oncology community.

Targeted therapies for advanced breast cancer, tumour-induced hypercalcaemia, skeletal-related events from malignancies involving bone, chronic myeloid leukaemia, gastrointestinal stromal tumours and other cancers are changing disease management.

Working in collaboration with clinicians, support groups, patients and families, efforts have been synchronized to reduce the burden of cancer.

ROCHE PRODUCTS
Roche has been a world leader in Oncology for over 40 years, discovering, researching and developing innovative treatments for cancer. Now world number 1 in oncology, the Roche oncology portfolio includes several innovative targeted treatments for breast, colorectal, lung and haematological cancers Roche was the first company to introduce monoclonal antibodies in the treatment of cancer – novel drugs which, unlike chemotherapy target the cancer cells directly. Further information is available from the Roche Products stand.

Roche Products Limited, Hexagon Place, 6 Falcon Way, Shire Park,
Welwyn Garden City AL7 1TW. Tel: 01707 366000.
Roche Products Medical Information: 0800 328 1629.

SURGIPATH EUROPE
Surgipath Europe Ltd can offer a complete range of consumables, reagents and equipment to cellular pathology laboratories throughout the UK. Surgipath Europe will be exhibiting the RHS-1 Rapid Histoprocessor, the MacroPath Gross Digital Imaging System and our range of Tissue Marking Dyes. Visit our stand to learn more about the Pathos Automated Rapid Histoprocessor, FineFIX Formalin Substitute, our range of high quality stains & reagents and our excellent customer service – 95% of consummable orders are despatched within 24-hours.

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Trade Exhibition and Supporting Organisations

The British Division of the International Academy of Pathology and the Pathological Society of Great Britain & Ireland would also like to thank the following companies and organisations for their support:

BREAKTHROUGH BREAST CANCER
Breakthrough Breast Cancer is the UK's leading charity committed to fighting breast cancer through research, campaigning and education. Breakthrough's research programme is aimed at bringing scientific expertise together to develop better diagnostic and prognostic techniques, safe and targeted treatments for people with breast cancer and to find new ways of presenting the disease. In addition to funding high quality research, Breakthrough campaigns for policies that support breast cancer research and better services, as well as promoting breast cancer education and awareness. Breakthrough's vision is a future free from the fear of breast cancer. www.breakthrough.org.uk

BRITISH NEUROPATHOLOGICAL SOCIETY

CANCER RESEARCH UK

GENENTECH INC
Founded more than 30 years ago, Genentech is a leading biotechnology company that discovers, develops, manufactures and commercializes biotherapeutics for significant unmet medical needs. A considerable number of the currently approved biotechnology products originated from or are based on Genentech science.

Genentech manufactures and commercializes multiple biotechnology products and licenses several additional products to other companies. The company has headquarters in South San Francisco, California and is listed on the New York Stock Exchange under the symbol DNA. For additional information about the company, please visit: http://www.gene.com

NHS GREATER GLASGOW & CLYDE

NOVARTIS ONCOLOGY See page 13 for more information

ROCHE PRODUCTS See page 13 for more information

UNIVERSITY OF GLASGOW

NOVARTIS
ONCOLOGY

A commitment to improve the outcome and quality of life of patients with cancer has been the driving force for Novartis Oncology in developing new and novel compounds.

Working in collaboration with clinicians, support groups, patients and their families, efforts have been synchronized to reduce the burden of cancer.

Focus by Novartis Oncology on bringing real benefits for patients has resulted in significant breakthroughs and has enabled the launch of highly potent and specific treatments for use by the Oncology community.

Using rational drug design, molecular abnormalities can be targeted, preserving normal cells and offering minimal negative impact on patients. Exploiting these novel forms of research, Novartis Oncology has become the leading company in signal transduction inhibition worldwide.

Targeted therapies for advanced breast cancer, tumour-induced hypercalcaemia, skeletal-related events from malignancies involving bone, chronic myeloid leukaemia, gastrointestinal stromal tumours (GISTs) and other cancers are changing disease management.

With a Headquarters in Basle, Switzerland, over 60,000 Novartis employees in 140 countries worldwide are contributing to the effort to improve standards of patient care. The teamwork of these individuals has contributed to the significant scientific progress achieved in cancer and other areas of medicine.

And the research continues, bringing the innovation of the laboratory to the patient and supporting teams fighting the disease on the front line.

Using science to extend and improve quality of life.
The future of cancer therapy, made possible,
by Novartis Oncology, today.

For more information, please contact:
Novartis Oncology
Frimley Business Park, Frimley,
Camberley, Surrey GU16 7SR
Tel: 01276 692255, Fax: 01276 698605

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recurrence by about half*
in HER2-positive
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*Compared to observation

PRESCRIBING INFORMATION HERCEPTIN® (trastuzumab) 150mg powder concentrate for solution for infusion **Indications:** Treatment of HER2 positive early breast cancer (EBC) following surgery, chemotherapy (CT) (neo/adjuvant) and radiotherapy (RT) (if applicable). Treatment of HER2 positive metastatic breast cancer (MBC): (i) as monotherapy following at least 2 CT regimens for MBC. Prior CT to include at least an anthracycline and a taxane, unless unsuitable. Hormone receptor positive patients must have failed hormonal therapy, unless unsuitable. (ii) in combination with paclitaxel for patients who have not received CT for MBC and where anthracyclines are not suitable. (iii) in combination with docetaxel for patients who have not received CT for MBC. **Dosage and Administration:** HER2 testing mandatory prior to Herceptin. Tumours should have HER2 overexpression at 3+ level by immunohistochemistry (IHC) or HER2 gene amplification by fluorescence or chromogenic *in situ* hybridisation (FISH or CISH). Physicians experienced with cytotoxic chemotherapy should initiate treatment with Herceptin. Recommended dose (EBC): *loading dose* - 4mg/kg bodyweight, *subsequent doses* - 2mg/kg repeated at 1-weekly intervals administered as IV infusions over approximately 90minutes. Recommended dose (MBC): *loading dose* - 4mg/kg body weight as 90 minute IV infusion; *subsequent doses* - weekly 2mg/kg as 30 minute IV infusion, if loading dose well tolerated. Do not administer as an IV push or bolus. Observe for infusion-related symptoms for at least six hours following start of first infusion and for at least two hours for subsequent infusions. Interruption of infusion may help control symptoms; resume when symptoms abate. Resuscitation equipment must be available. Patients with EBC should be treated for 1 year or until disease recurrence. In MBC, administer until disease progression. **Contraindications:** Hypersensitivity to trastuzumab, murine proteins or any excipients. Severe dyspnoea at rest due to complications of advanced malignancy or requiring oxygen therapy. **Precautions:** HER2 testing must be performed in a specialised laboratory to ensure adequate validation of test. Herceptin is associated with cardiotoxicity. Congestive heart failure (CHF) observed in patients receiving monotherapy or in combination with paclitaxel or docetaxel, particularly following anthracycline-containing regimen; may be moderate to severe, has been fatal. Candidate patients to undergo baseline cardiac assessment including history and physical examination, ECG, echocardiogram, or MUGA scan or magnetic resonance imaging and risk-benefit assessment. Monitor cardiac function during treatment: e.g. every three months and as required in MBC. In addition, repeat cardiac assessment at 6, 12 and 24 months following cessation of treatment in EBC. Risk of cardiotoxicity increases when Herceptin is combined with anthracyclines; avoid use except in well controlled clinical trials with cardiac monitoring. Patients previously treated with anthracyclines are also at risk of cardiotoxicity. Avoid anthracycline based therapy for up to 34 weeks after stopping Herceptin. Consider discontinuing treatment in patients whose left ventricular function decreases but remain asymptomatic or in patients who develop clinically significant heart failure unless benefits outweigh risks. Caution in patients with symptomatic CHF, history of hypertension or coronary artery disease and in EBC, in those patients with an LVEF of 55 % or less. Please refer to the Herceptin Summary of Product Characteristics (SmPC) for further information. Symptomatic CHF should be treated with standard medications. Most who developed CHF in clinical trials improved with appropriate treatment and continued Herceptin therapy without additional clinical cardiac events. Safety of resumption in patients experiencing cardiotoxicity not studied. Serious infusion related reactions (IRR) reported infrequently (*see side effects and adverse reactions*), majority within 2.5 hours of start of first infusion. Should IRR occur, infusion should be discontinued and patient monitored until resolution. Serious IRRs have been successfully treated with oxygen, beta-agonists and corticosteroids, fatal outcome rare. Severe pulmonary events reported rarely, occasionally fatal, may occur as part of IRR or with delayed onset; patients with dyspnoea at rest may be at increased risk of fatal IRR and/or pulmonary events, these patients should not be treated with Herceptin. Caution should be exercised for pneumonitis, especially in patients being treated concomitantly with taxanes. **Drug Interactions:** Drug interaction studies not performed in humans. **Pregnancy and Lactation:** Avoid during pregnancy unless potential benefit outweighs risk. Oligohydramnios reported post-marketing in pregnant women. Do not breast-feed during Herceptin and for six months after last dose. **Side-effects and Adverse Reactions:** For full listings please refer to the Herceptin SmPC. Serious reactions: infusion/hypersensitivity reactions (can be fatal), anaphylaxis and anaphylactic shock, angioedema, ataxia, sepsis, chills and fever, asthenia, rigor, headache, paresis, pain (chest, bone), fatigue, infusion-related symptoms, coma, meningitis, abnormal thinking, progression of neoplasia, oedema (incl. cerebral, laryngeal, acute pulmonary, peripheral), angioedema, pupilloedema, cardiomyopathy, CHF, decreased ejection fraction, hypotension, pericardial effusion, bradycardia, cerebrovascular disorder, cardiac failure, cardiogenic shock, pericarditis, supraventricular tachyarrhythmia, hepatocellular damage, liver tenderness, diarrhoea, nausea and vomiting, pancreatitis, hepatic failure, jaundice, leukaemia, febrile neutropenia, neutropenia, thrombocytopenia, anaemia, hypoprothrombinaemia, cellulitis, erysipelas, hyperkalaemia, myalgia, paraneoplastic cerebellar degeneration, membranous glomerulonephritis, glomerulonephropathy, renal failure, bronchospasm, respiratory distress, respiratory insufficiency, dyspnoea, hypoxia, acute respiratory distress, acute respiratory distress syndrome, Cheynes-Stokes breathing, pulmonary infiltrates, pneumonia, pneumonitis, pulmonary fibrosis, pleural effusion, reduced oxygen saturation, wheezing, rash, dermatitis, urticaria, Stevens-Johnson syndrome, abnormal lacrimation, retinal haemorrhage, deafness. *Common reactions:* IRR (fever, chills, headache, rash, pain, asthenia, nausea, vomiting) usually during or following first infusion. Other signs and/or symptoms include hypertension, rigors, cough, dizziness; usually mild to moderate and rare with subsequent infusions. Can be treated with analgesic/ antipyretic or antihistamines), fatigue, malaise, myalgia, CHF, cardiomyopathy, hypotension, palpitation, decreased ejection fraction, vasodilation, diarrhoea, constipation, dyspepsia, dry mouth, haemorrhoids, leucopenia, ecchymosis, infection (incl. urinary tract, respiratory, herpes zoster), sepsis, weight loss, anorexia, pain (abdominal, neck, back, bone, chest wall, musculoskeletal), extremities), arthralgia, myalgia, muscle spasms, leg cramps, arthritis, paraesthesia, somnolence, hypertonia, peripheral neuropathy, tremor, insomnia, anxiety, depression, asthenia, epistaxis, pruritus, nail disorder, dry skin, alopecia, acne, taste perversion. *Other reactions:* orthopnoea, increased cough and Sugalbg observed. In HERA trial, NYHA class III-IV CHF seen in 0.6 % of patients in the one year arm. In MBC, haematological toxicity was infrequent following monotherapy. WHO Grade 3/4 haematological toxicity increased with Herceptin plus paclitaxel or docetaxel. In HERA trial, 3.6% of Herceptin-treated patients experienced a shift of 3 or 4 grades from baseline, compared with 0.4% in the observation arm. Grade 3/4 hepatic toxicity less frequent with Herceptin and paclitaxel than with paclitaxel alone. No Grade 3/4 renal toxicity observed. Any of the above may develop into serious side effects. **Legal Category:** POM. **Presentation and Basic NHS Cost:** Pack of one 150mg single dose vial (reconstituted solution contains 21mg/ml trastuzumab). £481.40 excluding VAT. **Marketing Authorisation Number:** EU/1/00/152/001. **Marketing Authorisation Holder:** Roche Registration Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, AL7 1TW, United Kingdom. Herceptin is a registered trade mark. **Date of Preparation:** May 2006. **References:** 1. Piccart-Gebhart MJ, et al. *N Engl J Med* 2005; 353(16): 1659–1672. JA45121 April 2007

Information about adverse event reporting can be found at www.yellowcard.gov.uk
Adverse events should also be reported to UK Drug Safety Centre on:
01707 367554. Full details of adverse events can be found in the SmPC.

TUESDAY 3 JULY

▸ 09.00 – 12.00 Boyd Orr · Lecture Theatre 1

SYMPOSIUM 1: ***The Importance of Stroma, Blood Vessels and Inflammation in the Development and Progression of Carcinomas***
Sponsored by Genentech Inc, USA.
Chair: Prof BA Gusterson, University of Glasgow
Prof CW Elston, Nottingham

09.00–09.30 **[S1]** ***Introduction to Mesenchymal Induction of Epithelium in Development, Tissue Remodelling and Cancer***
Prof BA Gusterson, Section of Pathology and Gene Regulation, University of Glasgow

09.30–10.00 **[S2]** ***Stromal recruitment in cancer***
Prof M Alison, Barts and The London School of Medicine and Dentistry

10.00–10.30 **[S3]** ***Evidence for functional immune responses against tumour antigens***
Dr JJ Going, University of Glasgow

10.30–11.00 **COFFEE** (Wolfson, The Atrium)

11.00–11.30 ***Epithelial/mesenchymal interactions in tumour initiation and progression***
Prof M Frame, Beatson Institute for Cancer Research, Glasgow

11.30–12.00 ***Tackling angiogenesis***
Dr K Hillan, Genentech Inc, USA

▸ 09.00 – 12.00 Boyd Orr · Lecture Theatre 2

SYMPOSIUM 2: ***Forensic Diagnoses and Decisions***
Chair: Dr M Black, Western Infirmary, Glasgow
Dr NRB Cary, Forensic Pathology Services, Abingdon

09.00–09.30 **[S4]** ***Forensic histopathology – is it different?***
Dr S Leadbeatter, Cardiff University, Wales Institute of Forensic Medicine

09.30–10.00 **[S5]** ***Medication is meant to help, not harm***
Dr JC Clark, University of Glasgow

10.00–10.30 **[S6]** ***Intra-cerebral haemorrhage – trauma, stress and other factors***
Dr C Smith, University of Edinburgh

10.30–11.00 **COFFEE** (Wolfson, The Atrium)

11.00–11.30 ***Chilly for June – studies in hypothermia***
Dr PN Cooper, Forensic Medicine Unit, Royal Victoria Infirmary, Newcastle-upon-Tyne

11.30–12.00 **[S7]** Cardiac disease and medico-legal issues
Dr NRB Cary, Forensic Pathology Services, Abingdon, Oxfordshire.

▸ 12.00 – 13.00 Boyd Orr · Lecture Theatre 1

12.00–12.15 **OPENING ADDRESS**
Prof J Coggins, Vice Principal of Life Science, Medicine and Veterinary Medicine, University of Glasgow

12.15–13.00 **KEYNOTE LECTURE**
Sponsored by Cancer Research UK
Chair: Prof BA Gusterson, Section of Pathology and Gene Regulation, University of Glasgow

[S8] ***Cancer and plasticity of the inflammatory response in tumour development and progression***
Prof F Balkwill, Centre for Translational Oncology, Institute of Cancer Research and CRUK Clinical Centre, Barts and The London School of Medicine and Dentistry

TUESDAY 3 JULY *continued*

13.00 – 15.00

LUNCH (Wolfson, The Atrium)

POSTER VIEWING (Wolfson, Seminar Rooms 2 & 3; Clinical Skills Area, Level 4)

TRADE EXHIBITION (Wolfson, The Atrium)

13.30 – 14.30 — **Wolfson · Seminar Room 1**

MEET THE EXPERTS
Chair: Prof NA Shepherd, Gloucestershire Royal Hospital, Gloucester
Dr J Bell, Glasgow
Dr C Dick, Glasgow

[S27] ***How to do it (Lung Pathology)***
{P} Prof B Corrin, Brompton Hospital, Imperial College, London

Lunch will be provided for participants at the session

14.30 – 15.30 — **Boyd Orr · Lecture Theatre A**

MOLECULAR PATHOLOGY GROUP: Group Promotion
Chair: Dr RJ Byers, University of Manchester

15.30 – 16.30 — **Boyd Orr · Lecture Theatre 1**

ORAL COMMUNICATIONS: ***Gastrointestinal***
Chair: Prof C Cuvelier, University of Ghent, Belgium
Prof AD Burt, University of Newcastle-upon-Tyne

15.30 **[O1]** ***Long-lived committed progenitor cells in the human colonic crypt – additional targets for colonic carcinogenesis?***
{P} S McDonald, P Tadrous, L Greaves, S Leedham, M Novelli, D Turnbull, J Jankowski, N Wright

15.45 **[O2]** ***Quality of Colonic Cancer Surgery Varies Widely. An Area for Educational Intervention?***
{P} N West, P Quirke

16.00 **[O3]** ***Expression of the miRNA Cluster mir-17-92 is Associated with DNA Copy Number Gain of 13q During Colorectal Adenoma to Carcinoma Progression***
{P} B Diosdado, L Bosch, S Mongera, C Postma, B Carvalho, G Meijer

16.15 **[O4]** ***Pattern of Expression of MMMR Proteins in Tumours from Patients with MLH1/MSH2 Germline Missense Mutations***
B O'Sullivan, M Walker, J Bell, G Caine, N Deshmukh, R Hejmadi, **{P}** P Taniere

16.30–17.00 **TEA** (Wolfson, The Atrium)

15.30 – 16.30 — **Boyd Orr · Lecture Theatre 2**

ORAL COMMUNICATIONS: ***Gynaecological, Lymphoreticular***

Chair: Prof M Wells, University of Sheffield
Prof AM Flanagan, University College, London

15.30 **[O7]** ***Clinicopathological Comparison of Tris-acryl Gelatin Microspheres (TGM) and Polyvinyl Alcohol Particles (PVA) Following Uterine Artery Embolization(UAE) for Leiomyomas***
{P} V Thonse, K Judson, HS Kim, TN Vinh, R Vang

15.45 **[O8]** ***Over-expression of the Oncostatin M Receptor in Cervical Squamous Cell Carcinoma is Associated with Ligand-Dependent Induction of Cell Motility and Invasiveness***
{P} G Ng, D Winder, B Muralidhar, J Huang, N Coleman

16.00 **[O9]** ***An Increase in DNA Double Strand Breaks, Induced by Ku70 Depletion, Inhibits Human Papillomavirus 16 Episome Maintenance in Cervical Keratinocytes and Permits New Viral Integration Events***
{P} D Winder, M Pett, M Shivji, M Stanley, A Venkitaraman, N Coleman

16.15 **[O10]** ***In Chemotherapy Refractory Diffuse Large B-Cell Lymphomas Apoptosis Resistance is Caused by Expression of XIAP and Can Be Restored Using Small-Molecule XIAP Inhibitors***
S Cillessen, J Reed, C Pinilla, GJ Schuurhuis, G Ossenkoppele, C Meijer, **{P}** J Oudejans

16.30–17.00 **TEA** (Wolfson, The Atrium)

▸ 17.00 – 17.30 **Boyd Orr · Lecture Theatre 1**

ORAL COMMUNICATIONS: ***Gastrointestinal, Hepatobiliary/Pancreas***
Chair: Prof C Cuvelier, University of Ghent, Belgium
Prof AD Burt, University of Newcastle-upon-Tyne

17.00 **[O5]** ***The Loss of Expression of Beta-Dystroglycan in Oesophageal Cancer is Due to Post-Translational Modifications***
C Parbery-Clark, S Winder, **{P}** S Cross

17.15 **[O6]** ***Nodular Regenerative Hyperplasia of the Liver: a UK Series***
{P} JM Morris, KA Oien, M McMahon, AJ Stanley, AJ Morris, EH Forrest, S Campbell

▸ 17.00 – 17.30 **Boyd Orr · Lecture Theatre 2**

ORAL COMMUNICATIONS: ***Osteoarticular/Soft Tissue, Skin***
Chair: Prof M Wells, University of Sheffield
Prof AM Flanagan, University College, London

17.00 **[O11]** ***Detection of FUS/CREB3L2 Fusion Transcripts in Paraffin Embedded Samples of Low Grade Fibromyxoid Sarcoma Using RT-PCR***
{P} T Diss, F Berisha, S Hing, A Flanagan, R Tirabosco

17.15 **[O12]** ***Evaluation of Survivin and $NF_{-k}B$ in Psoriasis, an Immunohistochemical study***
{P} A Abdou, H Hanout

▸ 17.30 – 18.30 **Boyd Orr · Lecture Theatre 1**

PUBLIC LECTURE: ***The Biology of Poverty***

Chair: Sir Kenneth Calman, Chancellor, University of Glasgow
Speaker: Dr H Burns, Chief Medical Officer for Scotland

▸ 19.00 – 20.30 **Glasgow City Chambers**

CIVIC RECEPTION
Hosted by the Lord Provost of Glasgow

WEDNESDAY 4 JULY

▸ 09.00 – 12.00 **Boyd Orr · Lecture Theatre 1**

SYMPOSIUM 1: ***Sarcoma / Soft Tissue***
Sponsored by Novartis Oncology
Chair: Dr RR Reid, Western Infirmary, Glasgow

09.00–09.30 **KEYNOTE LECTURE**
[S9] ***New entities and new twists on old entities***
Prof J Meis-Kindblom, Royal Orthopaedic Hospital NHS Foundation and Trust, University of Birmingham School of Medicine, Division of Cancer Studies

09.30-10.00 ***Applied molecular pathology of soft tissue tumours***
Prof C Cooper, Male Urological Cancer Research Centre, Surrey

10.00–10.30 **COFFEE** (Wolfson, The Atrium)

10.30–11.00 **[S10]** ***Reactive/pseudomalignant lesions of soft tissue***
Dr RR Reid, Western Infirmary, Glasgow

11.00–11.30 **[S11]** ***Paediatric soft tissue sarcomas – a paradigm of the role of the pathologist in oncology***
Dr AG Howatson, Royal Hospital for Sick Children, Glasgow

11.30–12.00 **[S12]** ***Gastrointestinal stromal tumours (GIST) – an up-date***
Prof L Gunnar Kindblom, Dept of Musculoskeletal Pathology, Royal Orthopaedic Hospital NHS Foundation Trust and Dept of Pathology, Division of Cancer Studies, University of Birmingham

▸ 09.00 – 12.00 **Boyd Orr · Lecture Theatre 2**

SYMPOSIUM 2: ***Molecular Controls of CNS Disease Phenotype, Behaviour and Repair***
Joint Symposium with the British Neuropathological Society
Sponsored by the British Neuropathological Society
Chair: Prof JW Ironside, Western General Hospital, Edinburgh
Prof JS Lowe, Queen's Medical Centre, University of Nottingham

09.00–10.00 **KEYNOTE LECTURE**
[S13] ***The clinicopathological significance of molecular abnormalities in medulloblastoma – a paradigm for the diagnosis and management of childhood brain tumours***
Prof D Ellison, St Jude's Children's Research Hospital, Memphis, Tennessee, USA

10.00–10.30 ***Why do gliomas invade the brain, and how can we stop it?***
Prof G Pilkington, Head of Cellular and Molecular Neuro-oncology School of Pharmacy and Biomedical Sciences, Portsmouth

10.30–11.00 **COFFEE** (Wolfson, The Atrium)

11.00–11.30 ***Neurodegeneration: molecular influences on the "silent epidemic"***
Prof JS Lowe, Queen's Medical Centre, University of Nottingham

11.30–12.00 **[S14]** Stem cells and the brain: a potential for repair?
Prof R Franklin, University of Cambridge

▸ 12.00 – 12.45 **Boyd Orr · Lecture Theatre 1**

Pathological Society of Great Britain & Ireland's
28th CL OAKLEY LECTURE
Chair: Prof M Pignatelli, University of Bristol and Bristol Royal Infirmary

[S15] ***Basal-like carcinomas: from pathology to mouse-models and beyond***
Dr JS Reis-Filho, The Breakthrough Breast Cancer Research Centre, London

▸ 12.45 – 15.00

LUNCH (Wolfson, The Atrium)

POSTER VIEWING (Wolfson, Seminar Rooms 2 & 3; Clinical Skills Area, Level 4)

TRADE EXHIBITION (Wolfson, The Atrium)

▸ 13.30 – 15.00 **Wolfson · Seminar Room 1**

SHO Trainers' Meeting

▸ 15.00 – 15.45 **Boyd Orr · Lecture Theatre 1**

PLENARY ORAL SESSION
Chair: Prof C Cuvelier, University of Ghent, Belgium
Prof M Pignatelli, University of Bristol and Bristol Royal Infirmary

15.00 **[PL1]** ***Near tiling microarray-based CGH identifies CCNE1 amplification in basal-like breast cancer***
{P} R Natrajan, SM Rodriguez-Pinilla, C Marchio, R Vatcheva, A Mackay, K Fenwick, N Tamber, M Lambros, J Palacios, A Ashworth, JS Reis-Filho

15.15 **[PL2]** ***Clonal heterogeneity, and the origin of columnar lined oesophagus in Barrett's***
{P} S Leedham, D Poller, R Harrison, M Novelli, J Jankowski, N Wright

15.30 **[PL3]** ***Changes in mechanotransduction during unloading of failing human hearts by a left ventricular assist device (LVAD)***
{P} M van Oosterhout, M Schipper, J van Kuik, E de Koning, W Sohns, N de Jonge, J Laphor, A van der Laarse, R de Weger

▸ 15.45 – 16.15 **Wolfson · The Atrium**

TEA (Wolfson, The Atrium)

▸ 16.15 – 17.00 **Boyd Orr · Lecture Theatre 1**

PLENARY ORAL SESSION
Chair: Prof C Cuvelier, University of Ghent, Belgium
Prof M Pignatelli, University of Bristol and Bristol Royal Infirmary

16.15 **[PL4]** ***Activation of the IGF1R pathway is a potential therapeutic target in relapsed Wilms tumours***
{P} A Bielen, R Natrajan, R Williams, R Vuononvirta, J Reis-Filho, G Vunanic, K Pritchard-Jones, C Jones

16.30 **[PL5]** ***Isolation, Characterisation and Prospects for Use of Endothelial Progenitor Cells to Repair Pancreatic Damage in Diabetes***
{P} CP Khoo, MG Valorani, MR Alison, C Guglielmi, G Warnes, U Johansson, M Hawa, P Pozzilli, M Brittan

16.45 **[PL6]** ***The Role of the PI3K/Akt Cascade in the Development of Hormone Refractory Prostate Cancer***
{P} P Traynor, L Gemmel, R Mukherjee, J Bartlett, J Edwards

▸ 17.00 – 17.45 **Boyd Orr · Lecture Theatre 1**

The British Division of the International Academy of Pathology's
2nd GEORGE CUNNINGHAM LECTURE
Chair: Prof C Cuvelier, University of Ghent, Belgium

[S16] ***The enigma of trophoblast – a 24 year perspective***
Prof M Wells, University of Sheffield

WEDNESDAY 4 JULY *continued*

17.45 – 18.15 Wolfson · Seminar Room 1

Biomarkers in Cancer
Sponsored by Roche
Dr M Kaufmann

18.15 – 20.30 Wolfson · Seminar Rooms 2 & 3 + Clinical Skills Area Level 4

FORMAL POSTER ROUNDS AND DRINKS RECEPTION
Sponsored by Roche

CATEGORY	POSTER NOS	CHAIR
Autopsy and Forensic	P01 – P08 *	Prof SB Lucas and Prof JE Martin
Breast 1	P09 – P31	Prof IO Ellis and Prof LB Jones
Breast 2	P32 – P53	Dr JJ Going and Prof RA Walker
Cardiovascular/Pulmonary	P54 – P57	Dr PJ Gallagher and Dr M Sheppard
Cellular/Molecular	P58 – P71 *	Prof GI Murray and Prof R Poulsom
Education and Audit	P72 – P86	Dr PJ Gallagher and Dr M Sheppard
Endocrine	P87 – P88	Dr A-M McNicol and Dr P Ramani
Experimental Tumour Pathology	P89 – P90	Prof CS Herrington and Prof AH Wyllie
Gastrointestinal 1	P91 – P110	Prof NA Shepherd and Prof Sir NA Wright
Gastrointestinal 2	P111 – P123	Prof D Harrison and Dr RFT McMahon
Genitourinary/Renal	P124 – P137	Dr SS Cross and Prof AJ Freemont
Gynaecological	P138 – P153	Prof CS Herrington and Prof AH Wyllie
Head and Neck	P154 – P157	Dr TR Helliwell and Dr MEF Smith
Hepatobiliary/Pancreas	P158 – P164	Prof D Harrison and Dr RFT McMahon
Lymphoreticular	P165 – P176	Dr TR Helliwell and Dr MEF Smith
Neonatal/Paediatric	P177 – P187	Dr A-M McNicol and Dr P Ramani
Neuropathology/Ophthalmic	P188 – P200	Prof SB Lucas and Prof JE Martin
Osteoarticular/Soft Tissue	P201 – P205	Dr SS Cross and Prof AJ Freemont
Skin	P206 – P210	Dr A-M McNicol and Dr P Ramani
Technical Advances	P211 – P220	Prof GI Murray and Prof R Poulsom

* Please note: Abstracts P05, P59 and P60 have been withdrawn

10.00 – 15.30 **Boyd Orr · Lecture Theatre A**

UK NEQAS for Cellular Pathology Technique

10.00–10.10 **Introduction and Annual Report**
D Evans, Scheme Organiser, UKNEQAS CPT

10.10–10.40 ***Lean Management and its application to Histopathology***
Sponsored by Leica (UK) Ltd
T Coaker, Newcastle

10.40–11.10 ***Microwave Tissue Processing***
Y Sinclair, The Wirral

11.10–11.30 **COFFEE** (Wolfson, The Atrium)

11.30–12.00 ***Workload Measurement***
D Muskett, East Lancs

12.00–12.30 ***SlidePath / Digibox – A Training Tool***
Sponsored by SlidePath Ltd
G Thompson, Nottingham

12.30–13.00 ***User Satisfaction Survey***
J Evans, Quality Manager, UKNEQAS CPT

13.00–14.00 **LUNCH** (Lunch will be provided for participants within the session)

14.00–14.30 ***Muscle Histochemical Techniques and the Case for an EQA Programme***
J Vickers, Newcastle

14.30–15.00 ***EQA Experiences***
Sponsored by Siemens Ltd
E Walsh, CPA (UK) Ltd

15.00–15.30 ***Pathology Re-profiling: The Process and its Implications***
J Elsam, HTEQA Services

15.30 **CLOSE**

THURSDAY 5 JULY

▸ 09.00 – 12.00 Boyd Orr · Lecture Theatre A

SLIDE SEMINAR DISCUSSION: ***Skin Pathology for Ordinary Folk***
Chair: Dr K Blessing, Western Infirmary, Glasgow

09.00–10.30 Speakers: Dr J Calonje, London
Dr T Brenn, Edinburgh
Dr A Husain, Newcastle

10.30–11.00 **COFFEE** (Wolfson, The Atrium)

11.00–12.00 Speakers: Dr N Leonard, Liverpool
Dr C Black, Glasgow
Dr S Digby, Glasgow

▸ 09.00 – 10.15 Boyd Orr · Lecture Theatre 1

ORAL COMMUNICATIONS: ***Genitourinary/Renal, Education and Audit***
Chair: Prof S Fleming, University of Dundee, Ninewells Hospital, Dundee (tbc)
Prof IO Ellis, Nottingham City Hospital, University of Nottingham

09.00 **[O13]** ***KiRas4A siRNA transfection reduces cell proliferation in renal cell carcinoma***
{P} S Fury, L Christie, S Fleming

09.15 **[O14]** ***Prognostic Value of AMACR Staining in High-Grade PIN***
{P} C Rajaguru, W Tsang, S Brewster, ISD Roberts

09.30 **[O15]** ***Mast Cells in Early Protocol Biopsies Following Renal Transplantation Predict Loss of Renal Function At 2 Years***
{P} ISD Roberts, T Thamboo, N Street, S Reddy, PJ Friend

09.45 **[O16]** ***What is the impact of training on histopathology turnaround time?***
A Maznyczka, **{P}** K West

10.00 **[O17]** ***Audit of Histopathology Reported Independently by Trainees According to Departmental Protocol***
{P} A Chaturvedi, O Rotimi, S Chilka, A Boon, W Merchant, J Wyatt

▸ 09.00 – 10.15 Boyd Orr · Lecture Theatre 2

ORAL COMMUNICATIONS: ***Cellular/Molecular***
Chair: Dr MJ Arends, University of Cambridge, Addenbrooke's Hospital, Cambridge
Dr H Grabsch, Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds

09.00 **[O23]** ***Multifaceted dysregulation of the EGFR pathway in clear cell sarcoma of the kidney***
S Little, **{P}** D Bax, SM Rodriguez-Pinilla, R Natrajan, B Messahel, K Pritchard-Jones, G Vujanic, J Reis-Filho, C Jones

09.15 **[O24]** ***Phenotypic Characterization of Plasmalemmal Vesicle Associated Protein (PLVAP) Knockout Mice***
{P} L Sanders, L Rangell, M van Hoy, H Koeppen

09.30 **[O25]** ***Expression of HGF and its receptor MET in Wilms tumours and nephrogenic rests***
{P} R Vuononvirta, N Sebire, B Messahel, J Reis-Filho, K Pritchard-Jones, G Vujanic, C Jones

09.45 **[O26]** ***Assessment of Histological Features Which May Aid Prediction of 1p Status in Gliomas***
T Kerr, A Easton, J Mackenzie, **{P}** W Stewart

10.00 **[O27]** ***A Matter of Life and Death: the Runx Gene Family Controls Senescence and Survival***
{P} J Neil, S Wotton, A Kilbey, K Blyth, K Wolyniec, A Terry, A Jenkins, E Cameron

▸ 10.15 – 10.45 **Wolfson · The Atrium**

COFFEE

▸ 10.45 – 12.00 **Boyd Orr · Lecture Theatre 1**

ORAL COMMUNICATIONS: ***Breast***
Chair: Prof S Fleming, University of Dundee, Ninewells Hospital, Dundee (tbc)
Prof IO Ellis, Nottingham City Hospital, University of Nottingham

10.45 **[O18]** ***Stromal Signals Influence Breast Cancer Behaviour: Findings from a Coculture Model***
{P} C Green, TA Hughes, AM Shaaban, AM Hanby, V Speirs

11.00 **[O19]** ***Expression of FANCD2 protein in sporadic and hereditary breast cancer***
P van der Groep, M Hoelzel, H Buerger, H Joenje, J de Winter, **{P}** P van Diest

11.15 **[O20]** ***High throughput analysis of promoter hypermethylation status of 22 tumour suppressor genes in invasive breast cancer***
D Purnomisari, N Ameziane, A Wahyono, G Meijer, G Pals, **{P}** P van Diest

11.30 **[O21]** ***Predictive value of tumour load in breast cancer sentinel lymph nodes for second echelon lymph node metastases***
C van Deurzen, R van Hillegersberg, M Hobelink, C Seldenrijk, **{P}** P van Diest

11.45 **[O22]** ***Morphological and Molecular Evolutionary Pathways of Low Grade Invasive Breast Cancers and their Putative Precursor Lesions: Further Evidence to Support the Concept of a Low Grade Breast Neoplasia Family***
{P} T Abdel-Fatah, D Powe, Z Hodi, J Reis-Filho, A Lee, I Ellis

▸ 10.45 – 12.00 **Boyd Orr · Lecture Theatre 2**

ORAL COMMUNICATIONS: ***Experimental Tumour Pathology, Technical Advances***
Chair: Dr MJ Arends, University of Cambridge, Addenbrooke's Hospital, Cambridge
Dr H Grabsch, Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds

10.45 **[O28]** ***Intestinal adenomagenesis in Msh2-deficient mice is accelerated by conditional expression of mutated K-ras***
F Luo, D Brooks, G Poulogiannis, H Ye, R Hamoudi, D Winton, C Patek, **{P}** M Arends

11.00 **[O29]** ***Can Cancer Stem Cells Be Seeded Through Solid Organ Transplants?***
{P} J Burkert, NA Wright

11.15 **[O30]** ***The Virtual Slide and Conventional Microscope – a Direct Comparison of Their Diagnostic Efficiency***
{P} D Treanor, P Quirke

11.30 **[O31]** ***A Novel Formalin-free Fixative That Allows Both Histological and Molecular Analysis of Tissues***
{P} G Reynolds, K Baumforth, B O'Sullivan, S Hubscher

11.45 **[O32]** ***Assessing proliferation in colorectal biopsies: a comparison of Ki-67 immunohistochemistry with counting mitoses in whole crypts***
L Croucher, H Norwood, S Riley, E Williams, B Corfe, **{P}** J Bury

THURSDAY 5 JULY *continued*

▸ 12.00 – 13.00 **Boyd Orr · Lecture Theatre 1**

Pathological Society of Great Britain & Ireland's
ANNUAL BUSINESS MEETING
(Members will have received an Agenda)

▸ 12.15 – 13.45 **Boyd Orr · Lecture Theatre 2**

RENAL EQA
Lunch will be provided for participants within the session

▸ 13.00 – 14.00

LUNCH (Wolfson, The Atrium)

POSTER VIEWING (Wolfson, Seminar Rooms 2 & 3; Clinical Skills Area, Level 4)

TRADE EXHIBITION (Wolfson, The Atrium)

▸ 14.00 – 17.00 **Boyd Orr · Lecture Theatre 1**

SYMPOSIUM 1
Personalised Pathology and Novel Diagnostics: The Way Ahead
Chair: Prof P Quirke, Leeds Institute of Molecular Medicine, St James's University Hospital, Leeds
Prof WG McCluggage, Royal Group of Hospitals, Belfast

14.00–14.30 ***Personalised pathology: where are we now?***
Prof IO Ellis, University of Nottingham

14.30–15.00 ***Microarray profiling of cancer for prognostication and treatment: part of future pathology practice?***
Professor JA Foekens, Department of Medical Oncology, Erasmus Medical Centre, Rotterdam
Sponsored by Breakthrough Breast Cancer

15.00–15.30 **[S18]** ***The drug pipeline and development of new predictive biomarkers***
Dr D McHale, Pfizer Ltd, Kent

15.30–16.00 **TEA** (Wolfson, The Atrium)

16.00–16.30 ***How do we get the new diagnostics into clinical practice?***
Prof I Tomlinson, Molecular and Population Genetics Laboratory, London Research Institute, Cancer Research UK

16.30–17.00 **Discussion**
Led by Chairmen and with speakers on the podium

▸ 14.00 – 17.00 **Boyd Orr · Lecture Theatre 2**

SYMPOSIUM 2
Kidney Pathology for the Generalist
Chair: Prof PN Furness, University Hospitals of Leicester
Prof S Fleming, University of Dundee, Ninewells Hospital

14.00–14.30 ***Renal tumour update***
Prof S Fleming, University of Dundee, Ninewells Hospital

14.30–15.00 ***Infections in transplant patients – and other non-renal pathology***
Dr C Bellamy, Royal Infirmary of Edinburgh

15.00–15.30 **[S19]** The kidney in systemic disease
Prof PN Furness, University Hospitals of Leicester

15.30–16.00 **TEA** (Wolfson, The Atrium)

16.00–16.30 **[S20]** Post Mortem Renal Pathology – What you can and can't tell from an Autopsy Kidney
Dr ISD Roberts, John Radcliffe Hospital, Oxford

16.30–17.00 **[S21]** How to diagnose glomerular disease
Dr BY Young, Greater Glasgow and Clyde Health Board and University of Glasgow

▸ 17.00 – 17.45 **Boyd Orr · Lecture Theatre 1**

Pathological Society of Great Britain & Ireland's
5TH DONIACH LECTURE
Chair: Prof DA Levison, President, Pathological Society of Great Britain & Ireland

[S22] ***Pathology: what does it mean to you?***
Prof Sir NA Wright, London Research Institute, Cancer Research UK and Institute of Cell and Molecular Science, Barts and the London

▸ 19.30 – 23.00 **Kelvingrove Art Gallery**

CONFERENCE DINNER

THURSDAY 5 JULY *continued*

09.40 – 17.00 **Boyd Orr · Lecture Theatre B**

Association of Clinical Electron Microscopists
10TH ANNUAL SCIENTIFIC MEETING

09.40–10.25 ***Overview of the role of EM in paediatric pathology***
Chair: Mr G Anderson, Great Ormond Street Hospital for Children, London
Speaker: Dr G Mierau, Children's Hospital, Denver USA

10.25–10.30 **GROUP PHOTOGRAPH**

10.30–11.00 **COFFEE** (Wolfson, The Atrium)

11.00–11.40 ***Ehlers-Danlos/extracellular matrix disorders***
Chair: Dr J Moss, Charing Cross Hospital, London
Speaker: Prof M Pope, West Middlesex University Hospital and Chelsea and Westminster Hospital, London

11.40–12.30 ***Ultrastructural characterisation of ichthyoses and related keratinisation disorders***
Chair: Dr J Schroeder, Regensburg, Germany
Speaker: Dr I Hausser, Heidelberg, Germany

12.30–13.00 **[S17]** ***Sperm centriole abnormalities are causative for Intracytoplasmic Sperm Injection (ICSI) fertilization failure***
Chair: Dr T Ryder, Charing Cross Hospital, London
Speaker: Dr J Schroder, Regensburg, Germany

13.00–14.00 **LUNCH** (Wolfson, The Atrium)

14.00–14.35 ***Technical EQA feed back talk***
Chair: Mr B Wagner, Northern General Hospital, Sheffield
Speaker: Mrs T de Haro, Leicester Royal Infirmary

14.35–15.15 ***Review of hereditary nephropathies***
Chair: Dr A Curry, Manchester Royal Infirmary
Speaker: Dr L McWilliam, Manchester Royal Infirmary

15.15–15.30 ***Society for Ultrastructural Pathology***
Chair: Mr G Anderson, Great Ormond Street Hospital for Children, London
Speaker: Dr G Mierau, Children's Hospital, Denver, USA

15.30–16.00 **TEA** (Wolfson, The Atrium)

16.00–17.00 **AGM** (Open to ACEM members and non-members)
Chair: Mr T Ryder, Charing Cross Hospital, London

FRIDAY 6 JULY

▶ 09.00 – 12.20 **Boyd Orr · Lecture Theatre 2**

SYMPOSIUM: ***Current Challenges in Gastrointestinal Pathology***
Sponsored by Novartis Oncology
Chair: Dr JJ Going, University of Glasgow
Prof NA Shepherd, Gloucestershire Royal Hospital, Gloucester

09.00–09.45 **KEYNOTE LECTURE**
[S26] ***Diagnostic pitfalls in inflammatory bowel disease***
Prof RH Riddell, University of Toronto, Mount Sinai Hospital Toronto, Ontario, Canada

09.45–10.25 **[S23]** ***Pathology and colorectal cancer screening***
Prof F Carey, Ninewells Hospital, Dundee

10.25–11.00 **COFFEE** (Wolfson, The Atrium)

11.00–11.40 **[S24]** ***Pathology-guided management of colorectal cancer***
Prof P Quirke, University of Leeds

11.40–12.20 **[S25]** ***Dysplasia-related pitfalls in the upper gastrointestinal tract***
Prof NA Shepherd, Gloucestershire Royal Hospital, Gloucester

▶ 12.30 – 14.00 **Boyd Orr · Lecture Theatre A**

LIVER EQA
Lunch will be provided for participants within the session

ABSTRACT REVIEWERS

Dr MJ Arends, Cambridge

Dr I Buley, Devon

Prof AD Burt, Newcastle-upon-Tyne

Dr SS Cross, Sheffield

Prof AJ Freemont, Manchester

Prof PN Furness, Leicester

Dr PJ Gallagher, Southampton

Prof KC Gatter, Oxford

Dr JJ Going, Glasgow

Dr J Gosney, Liverpool

Dr SJ Gould, Oxford

Prof DJ Harrison, Edinburgh

Dr TR Helliwell, Liverpool

Prof CS Herrington, St Andrews

Prof M Ilyas, Nottingham

Dr N Kirkham, Newcastle-upon-Tyne

Prof NR Lemoine, London

Prof S Love, Bristol

Prof J Lowe, Nottingham

Prof SB Lucas, London

Prof AJ Malcolm, Shrewsbury

Dr S Manek, Oxford

Dr RFT McMahon, Manchester

Dr A-M McNicol, Glasgow

Prof G Murray, Aberdeen

Prof JJ O'Leary, Dublin

Dr P Ramani, Bristol

Dr ISD Roberts, Oxford

Prof GN Rutty, Leicester

Dr E Sheffield, Bristol

Dr DN Slater, Sheffield

Prof RA Walker, Leicester

Dr BF Warren, Oxford

Prof M Wells, Sheffield

Dr B Wilkins, Newcastle-upon-Tyne

Abstracts

Oral

O1

Long-lived committed progenitor cells in the human colonic crypt – additional targets for colonic carcinogenesis?

{P} S McDonald[1], P Tadrous[6], L Greaves[3], S Leedham[2], M Novelli[4], D Turnbull[3], J Jankowski[1], N Wright[6]
[1]Oxford University, Oxford, United Kingdom, [2]Cancer Research UK, London, United Kingdom, [3]University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom, [4]University College London, London, United Kingdom, [5]Barts and the London School of Medicine and Dentistry, London, United Kingdom, [6]Queen's Hospital, Romford, United Kingdom

Introduction: Current dogma states that stem cells are located at or very near to the base of the human colonic crypt. There is currently no evidence for committed progenitor cells for any lineage. Here we use 2D mapping of crypts that are partially deficient in the mitochondrial enzyme cytochrome *c* oxidase (as a result of naturally occurring mutations that accumulate in stem cells; Taylor et al, 2003, J. Clin. Invest.), to identify, for the first time, committed progenitor cells within the human colon.
Methods: Enzyme histochemistry (for cytochrome *c* oxidase and succinate dehydrogenase) was performed on 6μM frozen human colon serial sections. Novel image software was used to 'cut' each crypt, allowing us to develop a linear image of a circular crypt. These were then combined from the base of the crypt to the surface providing a 2D map of cytochrome *c* oxidase deficiency.
Results: Many of the maps analysed showed cytochrome *c* oxidase deficiency appearing at the base of crypt, but interestingly revealed how their progeny do not always conform to a linear vertical migration pattern. Importantly, a map revealing enzyme deficiency half way up the crypt was discovered, outside the stem cell zone, indicating the presence of a committed progenitor cell.
Conclusions:. We have developed a novel technique that can trace stem cell progeny through the human colonic crypt and we have used this to reveal their complex migration patterns. Moreover, it is clear that there are committed progenitor cells in the human colonic crypt, which survive long enough to accumulate mtDNA mutations and thus are additional candidates for the origin of colonic tumours. Thus the current concepts of colonic stem cells being the only cells able to give rise to neoplasms will need re-examination

O2

Quality of Colonic Cancer Surgery Varies Widely. An Area for Educational Intervention?

{P} N West, P Quirke
Leeds Institute of Molecular Medicine, University of Leeds, Leeds, United Kingdom

The importance of the plane of surgery in rectal cancer surgery was proven in the MRC CR07 trial. This led us to investigate whether the quality of colonic surgery could potentially have a similar impact.
We identified 313 colonic cancer resections performed between 1997 and 2001, which had adequate photographic images to retrospectively grade the plane of surgical dissection. We defined quality of surgery as: dissection in the mesocolic plane with a high-tie, mesocolic plane, intramesocolic plane or muscularis plane surgery. All cases were assessed by two independent observers. Interobserver agreement occurred in 86.3% of cases.

Quality of Surgery	Number of cases (%)	Interobserver agreement (κ)
Mesocolic plane with a high-tie	0 (0)	100%
Mesocolic plane	108 (34.5)	90.7% (0.84)
Intramesocolic plane	134 (42.8)	88.1% (0.74)
Muscularis plane	71 (22.7)	78.9% (0.74)

There is wide variation in the quality of surgery for colonic cancer, although its relationship to outcome is currently unknown. No cases showing high tie surgery were seen and only one third of cases were mesocolic excisions.
This appears to be an exciting area for future research, which may have the potential to improve outcomes if appropriate education programs are developed.

O3

Expression of the miRNA Cluster mir-17-92 is Associated with DNA Copy Number Gain of 13q During Colorectal Adenoma to Carcinoma Progression

{P} B Diosdado, L Bosch, S Mongera, C Postma, B Carvalho, G Meijer
Tumour Profiling Unit, Department of Pathology, VUmc, Amsterdam, Netherlands

A novel class of non-coding RNAs called microRNAs have shown to regulate central mechanisms of tumorigenesis and contribute to tumour development as tumour suppressors or oncogenes due to altered expression. We have documented that in colorectal chromosomal instable tumours, the combination of gain of 8q and 13q is a major factor associated with colorectal adenoma to carcinoma progression. Functional studies on the mir-17-92 cluster localized on 13q31 have demonstrated that its transcription is activated by the transcription factor c-myc, located on 8q and has antiapoptotic, proliferative and angiogenic activities. These results show an oncogenic function of this miRNA cluster. Therefore, we propose to investigate the contribution of the hsa-mir-17-92 cluster in the tumour biology of colorectal cancer (CRC).
RNA expression levels of the mir-17-92 cluster was determined in 53 colorectal tumours by quantitative RT-PCR. Identification of target genes was accomplished by integrating array comparative genomic hybridization, mRNA and miRNA expression data from the same tumours and miRNA target prediction programs.
The mir-17-92 cluster shows increased expression in tumours showing 13q gain ($p<0.005$). Five putative target genes, one of which has known tumour suppressor activity have been identified.
The oncomir mir-17-92 cluster seems to play a role in CRC progression.

O4

Pattern of Expression of MMR Proteins in Tumours from Patients with MLH1/MSH2 Germline Missense Mutations

B O'Sullivan, M Walker, J Bell, G Caine, N Deshmukh, R Hejmadi, {P} P Taniere
University Hospital of Birmingham Foundation Trust, University of Birmingham, Birmingham, United Kingdom

Immunohistochemistry is a reliable pre-screening technique to detect patients with germline mutations in Mismatch Repair System (MMR) genes. It is routinely used in combination with Microsatellite instability testing.
Majority of germline mutations in MMR genes are complex alterations. Loss of the second allele in tumour cells leads to loss of nuclear expression in tumour cells.
However, a proportion of them are missense mutations with unknown consequences on expression in tumour cells. To clarify this, we have reviewed MMR immunohistochemistry in a series of cases with proven missense mutations.
Our series included 11 MLH1 and 6 MSH2 missense mutations. There were 15 colorectal cancers (CRC)/adenomas and 2 endometrial cancers (EC). For CRCs, 8/15 show total loss of expression, 3/15 patchy expression and 4/15 preserved expression. For EC, 1/2 showed loss of expression and 1/2 showed preserved expression. Patchy expression was defined as heterogeneous nuclear staining among tumour glands.
Our preliminary results reveal that patchy expression should be reported as such and not be considered as "no loss of"/normal.
Sensitivity and specificity of IHC to detect patients with germline mutations relies on a sound knowledge of variant patterns that may be seen, depending on the type of gene alteration present.

O5

The Loss of Expression of Beta-Dystroglycan in Oesophageal Cancer is Due to Post-Translational Modifications

C Parbery-Clark, S Winder, **{P}** S Cross
University of Sheffield, Sheffield, United Kingdom

We have previously shown that there is loss of expression of beta-dystroglycan (BDG) in oesophageal cancer by IHC. We now report on further, more detailed studies:

IHC was performed on 100 oesophageal cancers (24 squamous, 76 adeno) using 3 different antibodies directed against different parts of the BDG molecule. There was absent expression in 86-96% of cases with normal expression in only 2% of cases. Alpha dystroglycan was also absent and there was no relationship with subset parameters on cluster analysis.

RT-PCR was performed on 6 tumour samples and 10 normal background. DAG1 RNA was present in all the tumour samples at levels equivalent to the background. Western blots were performed on 6 tumour samples. The full molecular weight 43 kDa band was present in tumour samples but at levels much reduced from the background.

3 oesophageal adenocarcinoma cell lines (BIC, FLO, SEG-1) were grown in culture. DAG1 mRNA was present on RT-PCR analysis at a reasonably constant level for all 3 cell lines to confluency. Western blotting for BDG showed that the protein levels fell in the first two days after plating and fell to undetectable levels at confluency. These 3 cell lines were also grown in soft agar assays. There was some correlation between expression of BDG and number and size of colonies in that the cell line with the least amount of BDG protein expression, BIC, produced the highest number and largest colonies. BDG was transiently over-expressed in the cell lines and this produced a significant reduction in the number of colonies.

All this evidence shows that the loss of BDG expression in oesophageal cancer is due to post-translational modification. This likely to be cleavage by proteolytic enzymes such as matrix metalloproteinases. The soft agar assay suggests that BDG has a tumour suppressor effect so inhibitors of its cleavage could possibly have a therapeutic effect.

O6

Nodular Regenerative Hyperplasia of the Liver: a UK Series

{P} JM Morris[1], KA Oien[2], M McMahon[1], AJ Stanley[1], AJ Morris[1], EH Forrest[1], S Campbell[3]
[1]Dept Gastroenterology,Glasgow Royal Infirmary, Glasgow, Strathclyde, United Kingdom, [2]Dept Pathology, Glasgow Royal Infirmary, Glasgow, Strathclyde, United Kingdom, [3]Dept Gastroenterology, Southern General Hospital, Glasgow, Strathclyde, United Kingdom

Nodular Regenerative Hyperplasia (NRH) is a rare liver disorder diagnosed on biopsy and characterised by nodular hepatocyte regeneration without fibrosis. Its UK prevalence and prognosis are unknown.

Our aim was to identify our local NRH patients and determine their survival following diagnosis, associated clinico-pathological features and any underlying conditions.

44 patients (20 male) were identified over 13 years from liver biopsy reports in local pathology databases. Their LFTs were mainly cholestatic, with preserved synthetic function. 13 patients (30%) had portal hypertension. Varices were present in 11 of 25 patients who underwent endoscopy, with 5 (11%) variceal bleeds (one fatal). 2 additional patients developed ascites. Conditions associated with NRH included: rheumatological disorders in 10 (23%), haemato-oncological conditions in 9 (20%) and vascular causes in 5 (11%). 10 patients had no identifiable associations (23%). The overall mean survival was 8.1 years. The five-year survival in patients without malignancy was 66%, falling to 46% in patients with malignancy ($p<0.04$).

Survival following NRH diagnosis is related to patient age and the underlying disease process. Development of portal hypertension does not influence mortality, suggesting that associated complications can be managed effectively in this group of patients.

O7

Clinicopathological Comparison of Tris-acryl Gelatin Microspheres (TGM) and Polyvinyl Alcohol Particles (PVA) Following Uterine Artery Embolization(UAE) for Leiomyomas

{P} V Thonse[1], K Judson[2], HS Kim[3], TN Vinh[4], R Vang[5]
[1]Royal Victoria Hospital, Belfast, United Kingdom, [2]Johns Hopkins Hospital, Baltimore, United States, [3]Johns Hopkins Hospital, Baltimore, United States, [4]Armed Forces Institute of Pathology, Washington, United States, [5]Johns Hopkins Hospital, Baltimore, United States

Background: We aimed to compare the clinicopathological features of leiomyoma cases embolised with PVA and TGM.

Design: Four hundred patients underwent UAE with TGM (333) or PVA (67) from the years 2000 to 2005. Of patients who underwent myomectomies or hysterectomies, slides of surgical specimens were available from 19 patients who were treated with TGM (n=13) or PVA (n=6).

Results: The surgical rates after UAE were 4.2 % (TGM) and 9.0% (PVA). In PVA cases, a greater extent of microcystic change was seen in areas of infarcted tumour compared with TGM (67% vs. 15%, respectively). TGM showed a greater degree of infarction compared to PVA (100% of leiomyomas per case were infarcted with TGM vs. 75% with PVA, and 87% of the total tumour area per case was infarcted with TGM vs. 47% with PVA). TGM reached adnexae more frequently than PVA.

Conclusions: We conclude that TGM causes more tumours per patient to undergo infarction and to a greater degree than PVA. TGM and PVA show some differences in patterns of microcystic degeneration in infarcted tumours, as well as anatomical distribution of particles.

O8

Over-expression of the Oncostatin M Receptor in Cervical Squamous Cell Carcinoma is Associated with Ligand-Dependent Induction of Cell Motility and Invasiveness

{P} G Ng[1], D Winder[1], B Muralidhar[1], J Huang[2], N Coleman[1]
[1]Medical Research Council Cancer Cell Unit, Cambridge, United Kingdom, [2]Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, Massachusetts, United States

We show that copy number gain and over-expression of the oncostatin-M receptor (OSMR) occur frequently in advanced cervical squamous cell carcinoma (SCC) and are associated with adverse clinical outcome in patients treated by radiotherapy, independently of tumour stage. By genetic manipulation of cervical SCC cells we further demonstrate how OSMR over-expression can contribute to cell phenotype and affect disease outcome. In the OSMR-overexpressing cervical SCC lines CaSki and SW756, exogenous OSM activated the STAT3 and MAPK pathways and induced transcription of the angiogenic factor VEGF, effects that were inhibited by siRNA depletion of OSMR. Exogenous OSM and OSMR depletion had no effect on cell proliferation or radioresistance. However, OSM did significantly stimulate cell migration in a wound healing assay and invasion through matrigel in a Boyden chamber, with both effects inhibited by OSMR depletion using either pooled or individual siRNA duplexes ($p<0.001$ in all cases). OSMR over-expression by stable transfection of cervical keratinocytes without copy number gain also enabled effects on migration and invasion to be investigated. We conclude that copy number driven over-expression of OSMR can contribute to adverse clinical outcome in cervical SCC indirectly by inducing angiogenesis and directly by increasing tumour cell motility/invasiveness. OSMR is a candidate prognostic marker and cell surface therapeutic target in cervical SCC.

O9

An Increase in DNA Double Strand Breaks, Induced by Ku70 Depletion, Inhibits Human Papillomavirus 16 Episome Maintenance in Cervical Keratinocytes and Permits New Viral Integration Events

{P} D Winder[1], M Pett[1], M Shivji[1], M Stanley[2], A Venkitaraman[1], N Coleman[1]
[1]Medical Research Council Cancer Cell Unit, Cambridge, United Kingdom, [2]Department of Pathology, Cambridge University, Cambridge, United Kingdom

Integration of human papillomavirus type 16 (HPV16) is a common event in cervical carcinogenesis, although mechanisms of integration are poorly understood. We tested the hypothesis that induction of DNA double strand breaks (DSBs) affects HPV16 episome maintenance and integration in cervical keratinocytes. We induced DSBs over a prolonged period of up to 50 population doublings in the unique polyclonal cervical keratinocyte cell line W12, which stably maintains HPV16 episomes. This was achieved using repeated treatments with siRNA to obtain sustained depletion of Ku70, a key mediator of DNA non-homologous end joining. An increase in DSBs was seen shortly after commencement of Ku70 depletion. Continuous depletion was reproducibly associated with loss of HPV16 episomes and also with a new viral integration event, which was rapidly selected in outgrowing cells. Despite the prolonged presence of DSBs, high-level chromosomal instability (detected by marked changes in genomic copy number) was not observed until cells containing the new integrant were almost fully selected, with no evidence of such chromosomal instability prior to integration. Our data shows that induction of DNA DSBs accelerates HPV16 episomal loss and integration in cervical keratinocytes, and suggests a role for host DNA repair proteins in episome maintenance and prevention of integration. We found no evidence to support the notion that major chromosomal instability precedes HPV16 integration.

O10

In Chemotherapy Refractory Diffuse Large B-Cell Lymphomas Apoptosis Resistance is Caused by Expression of XIAP and Can Be Restored Using Small-Molecule XIAP Inhibitors

S Cillessen[1], J Reed[2], C Pinilla[2], GJ Schuurhuis[1], G Ossenkoppele[1], C Meijer[1], **{P}** J Oudejans[1]
[1]VU University Medical Centre, Amsterdam, Netherlands, [2]Burnham Institute for Medical Research, La Jolla, CA, United States

We investigated the functional integrity of the intrinsic apoptosis pathway and expression levels of apoptosis regulating genes in isolated and selected lymphoma cells of diffuse large B-cell lymphoma (DLBCL) biopsies and in cell lines.
Using multiplex quantitative RT-PCR analysis 2 distinct DLBCL groups were identified; one with low and one with high expression levels of both pro- and anti-apoptotic genes including XIAP. High expression of pro- and anti-apoptotic correlated with high levels of spontaneous caspase 9 activity, however without induction of apoptosis. These cases were frequently chemotherapy refractory. Disruption of the apoptosis pathway could be restored using small molecule XIAP antagonist 1396-12. This XIAP inhibitor restored caspase 9 dependent caspase 3 activation in DLBCL cells and strongly induced apoptosis. Response to the XIAP inhibitor correlated with expression levels of XIAP. Adding Etoposide to the XIAP inhibitor did not further increase levels of apoptosis.
We conclude that the intrinsic, caspase 9-mediated, apoptosis pathway is constitutively activated in part of chemotherapy-refractory DLBCL with concomitant inhibition of the downstream apoptosis pathway by XIAP and that XIAP small molecule antagonists induce apoptosis in these samples. Thus, inhibition of XIAP using small antagonistic molecules may be a valuable alternative therapy for XIAP positive DLBCL.

O11

Detection of FUS/CREB3L2 Fusion Transcripts in Paraffin Embedded Samples of Low Grade Fibromyxoid Sarcoma Using RT-PCR

{P} T Diss[1], F Berisha[2], S Hing[2], A Flanagan[3], R Tirabosco[2]
[1]University College London Hospital, London, United Kingdom, [2]Royal National Orthopaedic Hospital, London, United Kingdom, [3]Institute of Orthopaedics and Musculoskeletal Sciences, London, United Kingdom

Low-grade fibromyxoid sarcoma (LGFMS) is a soft tissue neoplasm characterised by t(7;16)(q33-34;p11) with gene fusion of FUS and CREB3L2. It can be difficult to distinguish from other entities within the low-grade myxoid neoplasms group. We evaluated RT-PCR detection of FUS/CREB3L2 transcripts as a means of distinguishing LGFMS from other tumours. RNA was extracted from paraffin-embedded samples from 69 cases submitted for molecular diagnosis (38 for FUS/CREB3L2, 31 for other transcripts). cDNA was generated using gene specific primers. Due to the existence of multiple breakpoints in both genes, RT-PCR was performed using six FUS/CREB3L2 primer pairs along with G6PD amplification. A LGFMS with t(7;16)(q33-34;p11) was the positive control. All 69 samples yielded adequate RNA as determined by G6PD amplification. FUS/CREB3L2 transcripts were detected in 12 of 21 cases diagnosed by morphology as LGFMS (57% detection), in 1 case diagnosed as low-grade myxoid sarcoma, NOS and in none of 47 others. Specificity was confirmed by amplification of predicted sized products in alternative primer sets in 10 of 12 positive cases. Although RT-PCR is a useful adjunct to conventional histopathology in diagnosing LGFMS, the characteristic fusion genes are not detected in all cases due to breakpoint complexity. Hence a more sensitive interphase FISH approach is under development.

O12

Abstract withdrawn

O13

KiRas4A siRNA transfection reduces cell proliferation in renal cell carcinoma

{P} S Fury, L Christie, S Fleming
University of Dundee, Dundee, United Kingdom

We investigated the expression of downstream effector proteins following siRNA transfection to knockdown KiRas4A in renal cell carcinoma (RCC) cell lines. KiRas4A is a protein involved in the mineralocorticoid response in renal tissue. Following aldosterone stimulation, KiRas4A is recruited to the plasma membrane where it is activated. A kinase cascade reaction proceeds activating proteins required for cell signalling leading to increased expression of proteins involved in salt reabsorption. However experimental data suggests that under its oncogenic form, KiRas4A can encourage tumorigenesis due to unregulated cell activation. We have examined the effects of the expression of KiRas on cell growth and downstream effector proteins in the Ras-Raf and Ras-PI3K pathways following Kiras4A knockdown. We designed KiRas4A specific siRNAs. Optimal KiRas4A knockdown was established as 2 hours post siRNA transfection. At this time protein was extracted and using western blotting techniques and antibodies to phosphor-specific epitopes the activation of downstream effector proteins were studied. These studies have confirmed that following KiRas4A siRNA transfection, protein expression is reduced in Kras, Raf, PDK1, Akt and S6 kinase ultimately leading to reduced cell proliferation. We hypothesis that KiRas4A has a growth promoting role during the mineralocorticoid response in renal cell carcinoma and may support renal tumourigenesis.

O14

Prognostic Value of AMACR Staining in High-Grade PIN

{P} C Rajaguru[1], W Tsang[2], S Brewster[2], ISD Roberts[1]
[1]John Radcliffe Hospital, Oxford, United Kingdom, [2]Churchill Hospital, Oxford, United Kingdom

Alpha-methylacyl-CoA racemase (AMACR) is a marker of invasive prostatic adenocarcinoma. Positive staining has also been reported in 64-90% of cases of high-grade prostatic intraepithelial neoplasia (HGPIN). In this study we investigate the predictive value of AMACR staining in HGPIN, for the presence of carcinoma in follow-up biopsies.
Review of 3362 prostate biopsies on our unit (1998-2005) revealed 111 (3.3%) showing HGPIN. These patients were offered re-biopsy, that was subsequently performed in 61% of cases. HGPIN diagnosis was based entirely on H&E morphology. AMACR staining was performed retrospectively on unstained spare sections from 55 biopsies (2003-2005) showing HGPIN and staining correlated with histology of follow-up biopsies.
Positivity for AMACR was seen within HGPIN lesions in 33/55 (60%) biopsies. Adenocarcinoma was diagnosed on re-biopsy in 16/55 (29%) patients, with the frequency being significantly higher in those whose first biopsies showed AMACR-positive HGPIN.

Diagnosis on re-biopsy	AMACR-staining of HGPIN in first biopsy	
	Positive	Negative
Benign	20	19
Adenocarcinoma	13	3
% adenocarcinoma	*39%	*14%

*Chi-square p=<0.05
We conclude that AMACR staining is a useful marker for identifying those patients most likely to have a diagnosis of adenocarcinoma on re-biopsy. We recommend its use in all biopsies showing changes of HGPIN.

O15

Mast Cells in Early Protocol Biopsies Following Renal Transplantation Predict Loss of Renal Function At 2 Years

{P} ISD Roberts[1], T Thamboo[1], N Street[1], S Reddy[2], PJ Friend[2]
[1]John Radcliffe Hospital, Oxford, United Kingdom, [2]Churchill Hospital, Oxford, United Kingdom

Protocol biopsies following renal transplantation detect early chronic damage, before irreversible loss of renal function, allowing therapeutic intervention. Traditional methods for quantifying fibrosis assess extent of matrix deposition rather than fibrogenic activity. Mast cells (MC) are sparse in normal kidney (<3/mm^2), are not increased in acute rejection, but are a potential indicator of early fibrosis. In this study we assess the prognostic value of quantifying MC in 1-month protocol biopsies (n=56), correlating MC and Banff criteria with renal function at 2-years follow-up.
Two-year serum creatinine (sCr) did not differ between patients whose one-month biopsy showed subclinical rejection (n=4), borderline changes (n=9) or no rejection (141umol/l, 140umol/l and 145umol/l respectively). Twenty-two biopsies showed no fibrosis; 21 showed mild and 3 moderate chronic damage. There was no difference in 2-year sCr between these groups (no fibrosis 135umol/l; Banff 5-1/2 150 umol/l, T-test p=ns).
Increased MC (>3/mm^2) were seen in 33/56 biopsies. These patients showed significantly higher 2-year sCr than patients whose biopsies showed normal mast cell numbers.

sCr (mean)	MC<3/mm^2	MC>3/mm^2	P-value
1-month	133	148	ns
2-year	123	174	<0.0002

We conclude that quantification of mast cells is of potential clinical value, identifying those patients at risk of progressive chronic allograft damage.

O16

What is the impact of training on histopathology turnaround time?

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There is widespread acceptance of the apprenticeship model of training in histopathology. This involves the reporting of 'live' cases rather than relying on previously reported material. The purpose of this study was to assess the effect of training on histopathology turnaround time. The reporting time for endoscopic biopsies, endometrial samples and skin biopsies was recorded over an eight year period (August- July) and the time taken for supervised and unsupervised cases was compared. The reporting time was calculated as the day of authorisation minus the day that sections were released by the laboratory. No corrections were made for weekends. The mean differences between supervised and unsupervised reports were as follows:
1998-1999 1.58 days
1999-2000 2.56 days
2000-2001 0.32 days
2001-2002 0.45 days
2002-2003 0.39 days
2003-2004 0.50 days
2004-2005 0.12 days
2005-2006 0.79 days
In general, there has been a reduction in the additional time taken for the issuing of supervised reports over the period of the study. This may reflect a greater emphasis on the timeliness of reporting. With the looming prospect of increased private sector involvement, the impact of training may become more important to NHS histopathology departments as they try to compete with commercial organisations.

O17

Audit of Histopathology Reported Independently by Trainees According to Departmental Protocol

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BACKGROUND. Assessment of competency for independent reporting by pre-part 2 MRCPath trainees is challenging in large sub-specialised departments. We developed a validation scheme for trainee-identified specimens appropriate to stage of training, according to the 2005 RCPath trainee logbook. We present our first 10% annual audit of independent reports in GI and skin pathology.
METHOD. From a computer-generated list of all authorised reports with no consultant pathologist (630 cases), slides and reports of a random 10% sample were reviewed by a trainee and specialist consultant. Diagnostic discrepancies, report style and turnaround times were recorded. We compared results for validated trainees with those of post- part 2 MRCPath (who did not require this validation process).
RESULTS. Of 63 audited independent cases, 42 were by pre-part 2, validated trainees. Three diagnostic discrepancies with minor but potential clinical impact were identified, all in the post-part 2 group. The comparative turnaround times for the validated group were shorter than for the post- part 2 group.
CONCLUSIONS. The validation process worked effectively and safely, enabling pre-part 2 trainees to work independently and efficiently in a risk-managed framework. This audit data will encourage the validation process to be rolled out into other specialties.

O18

Stromal Signals Influence Breast Cancer Behaviour: Findings from a Coculture Model

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Fibroblasts comprise the major part of breast stroma and can influence cancer cell behaviour. The aim of this study was to assess how primary mammary fibroblasts affect proliferation of normal and tumour mammary epithelial cells. Benign (HB2) or malignant (MCF7) mammary epithelial cells were both stably transfected to express GFP and incorporated into a coculture model with fibroblasts. Epithelial proliferation was determined alone or in coculture, using GFP to distinguish epithelial cells from fibroblasts by flow cytometry. A differential effect was seen in the two cell types: proliferation of MCF7 cells was enhanced in the coculture whereas proliferation of HB2 cells was repressed.
Previously we have shown strong immunoreactivity of ERbeta1 and ERbeta2 in mammary fibroblasts. We therefore, additionally set out to determine whether fibroblastic ERbeta expression modulates fibroblast/epithelial interaction. When DPN, a selective ERbeta agonist, was added to either mammary epithelial cells or fibroblasts, changes in cell proliferation and fibroblast migration during wound healing were observed. Increased proliferation of fibroblasts and malignant but not benign epithelial cells was observed in response to DPN. These findings advocate a role for fibroblasts in modulating epithelial cell behaviour, which is possibly dictated by ERbeta.

O19

Expression of FANCD2 protein in sporadic and hereditary breast cancer

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Background: Fanconi anemia (FA) is an autosomal recessive disorder associated with progressive pancytopenia, multiple developmental defects and marked predisposition to malignancies, especially acute myeloid leukemia and squamous cell carcinoma of the head and neck. FA is genetically heterogeneous and comprises at least twelve complementation groups (A-M).
Activation of FANCD2 by mono-ubiquitination is an essential step in the DNA damage response. As FANCD2 interacts with BRCA1, is expressed in proliferating cells of the normal breast, and FANCD2 knockout mice develop breast tumors, we investigated the expression of FANCD2 in sporadic and hereditary invasive breast cancer patients to evaluate its possible role in human hereditary and sporadic breast carcinogenesis.
Material and Methods: Tissue microarrays of 129 sporadic and 25 BRCA1 germline mutation related invasive breast cancers were stained for FANCD2 by immunohistochemistry, and expression results were compared with several clinicopathological variables and tested for prognostic value.
Results: 18/96(19%) of sporadic breast cancers and 2/21 (10%) of BRCA1 related breast cancers were completely FANCD2 negative. In the other cases, the percentage of FANCD2 expressing cells correlated strongly positively with the percentage of positive cells of the proliferation markers MAI (R=0.552, p=0.0001), Ki67 (R=0.502, p= 0.0001) and cylin A (R=0.482, p=0.0001). In immunofluorescence double staining, co-expression of FANCD2 and Ki67 was apparent. In survival analysis, high FANCD2 expression appeared to be prognostically unfavorable for overall survival, independent from other major prognosticators (p=0.026).
Discussion: FANCD2 expression is absent in 10-20%of sporadic and BRCA1 related breast cancers, indicating that somatic inactivating (epi)genetic events in FANCD2 may be an important genetic event in both sporadic and hereditary breast carcinogenesis. Levels of FANCD2 expression strongly correlate with rate of proliferation and seem to be of independent prognostic value in invasive sporadic breast cancer.

O20

High throughput analysis of promoter hypermethylation status of 22 tumour suppressor genes in invasive breast cancer

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A number of different tumour suppressor genes are known to be inactivated by aberrant hypermethylation in breast cancer, but it is still unknown to what extent these epigenetic alterations differ according to specific breast cancer phenotypes. This is largely caused by the fact that most studies concern only a few genes due to the low throughput of traditional techniques. We therefore investigated hypermethylation of 22 tumour suppressor genes in 168 breast cancers by methylation-specific multiplex ligation-probe dependent amplification (MS-MLPA), a new high throughput technique, to assess whether hypermethylation identifies breast cancers with distinctive clinicopathological features.
MS-MLPA showed methylation frequencies ranging from 0% for *CDKN2A* ($p14^{ARK}$), *CDKN1B* ($p27^{KIP1}$), *ATM*, *PTEN*, *BRCA2* and *VHL* to 26% for CDH13, 33% for GSTP1, 40% for APC and 61% for *RASSF1*. Tumors with frequent methylation (4-8 genes) were more often poorly differentiated (P=0.007) and HER-2/*neu* amplified (P=0.041) compared to those with infrequent methylation (0-2 genes).
In conclusion, this comprehensive analysis of tumour suppressor gene promoter methylation status in invasive breast cancer by high throughput MS-MLPA reveals remarkable differences in methylation frequency for various genes. Promoter methylation of multiple genes seems to be correlated to poor differentiation and HER-2/*neu* amplification. A more comprehensive hypermethylation profile as assessed by MS-MLPA could therefore potentially be useful for breast cancer detection and classification, and understanding the biology of this disease.
Supported by grant IN-2001-008 of the Dutch Cancer Society

O21

Predictive value of tumour load in breast cancer sentinel lymph nodes for second echelon lymph node metastases

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Background: The need for routine axillary lymph node dissection (ALND) in patients with invasive breast cancer and low-volume sentinel node (SN) involvement is questionable. Accurate prediction of non-SN involvement could identify those patients most likely to benefit from ALND.
Methods: A consecutive series of 317 patients with invasive breast cancer and a tumour positive axillary SN followed by ALND was reviewed. Clinicopathologic features of the primary tumour and the SN were assessed as possible predictors of metastatic involvement of the non-SN.
Results: Non-SN metastases were found in 116/317 cases (36.6%). Frequency of non-SN metastases in patients with isolated tumour cells (ITC, N= 23), micro- (N=101) and macrometastases (N=193) according to the UICC classification was 13%, 20% and 48%, respectively ($p<0.001$). By univariate analysis the total number of positive SNs, extracapsular extension (ECE), diameter and area of the SN metastases, and the % area of SN involved by tumour were also significantly correlated with non-SN involvement. In multivariate analysis the area % of SN occupied by tumour was the only independent factor that was significant ($p<0.001$) in predicting non-SN involvement. Based on this feature, however, no subgroup of patients could be selected with less than 20% non-SN involvement, so % area of SN occupied by tumour does not improve the accuracy of selecting SN positive patients with a low probability to have non-SN metastases compared to the UICC classification. However, none of the patients with SN ITC or micrometastases and a primary tumour size ≤ 1 cm (n=12, 3.8%) had non-SN involvement.
Conclusions: Accurately measured SN tumour load predicts non-SN involvement. However, even patients with ITC still had a 13% risk of non-SN involvement and should therefore according to current standards be considered for ALND. The only small subgroup of SN positive patients in this study without non-SN involvement that could therefore be spared ALND were patients with SN ITC or micrometastases and a primary tumour size ≤ 1 cm (n=12, 3.8% of patients).

O22

Morphological and Molecular Evolutionary Pathways of Low Grade Invasive Breast Cancers and Their Putative Precursor Lesions: Further Evidence to Support the Concept of a Low Grade Breast Neoplasia Family

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In this study, further support for our proposed route of pathogenesis concerning low grade breast cancer (LGBC) and their precursor lesions was provided using immunophenotyping of tissue microarrays containing 775 lesions for putative tumour suppressor genes, cell cycle regulators, proliferation and differentiation markers. The putative precursor lesions were compared with their co-existing low and high grade carcinomas.
Results: The epithelial cells in the flat epithelial atypia, Lobular neoplasia, ADH/ low grade DCIS and the intrinsic LGBC shared a common phenotype of CK19/18/8, ER-α, Bcl-2, and Cyclin D1 positivity. The ER-α/ER-β ratio and Cyclin D1 expression increased from precursor lesions to the invasive LGBC.
Conclusion: Our results support the concept of a low grade breast neoplasia (LGBN) family of precursor, in situ and invasive neoplastic lesions belonging to the luminal 'A' subclass of breast cancer. The committed progenitor cells (PCs) for LGBN are CK19/18/8 + and exhibit ER-α mediated CCND1 and BCL2 gene expression. Alternatively, PCs acquire genetic and epigenetic hits that lead to the activation of the 'luminal A' pathway and these events determine the phenotype of the pre-invasive and invasive lesions. Once PCs committed to this specific 'molecular pathway', progression to a 'high grade' phenotype would be an unlikely.

O23

Multifaceted dysregulation of the EGFR pathway in clear cell sarcoma of the kidney

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EGFR is a receptor tyrosine kinase overexpressed in a variety of human malignancies, against which targetted therapies have shown efficacy in lung and brain tumours. In non small cell lung cancer, clinical responses to EGFR inhibitors have been found to be highly dependent on the presence of activating mutations, whilst gene amplification, downstream activation of Akt, and abnormalities in *PTEN* are also reported predictive factors. We screened a series of paediatric renal tumours for EGFR expression by immunohistochemistry, and identified a striking predilection for certain histologies. Although only 23/177 (13.0%) favourable histology Wilms tumours were EGFR positive, 4/11 (36.4%) anaplastic tumours, 5/9 (55.6%) congenital mesoblastic nephromas and 12/12 (100%) clear cell sarcomas of the kidney (CCSKs) were strongly immunoreactive. Studying the CCSKs in more detail, we identified gene amplification by chromogenic in situ hybridisation in 1/12 (8.3%) cases, and a somatic T790M *EGFR* mutation in a further case. These two samples additionally harboured mutations in *PTEN*. Downstream pathway activation by expression of phospho-Akt was observed in 8/12 (66.7%) cases. Together, these data demonstrate dysregulation of the EGFR pathway at multiple levels in CCSKs, may provide a rationale for upfront trials with irreversible inhibitors of EGFR in children with these tumours.

O24

Phenotypic Characterization of Plasmalemmal Vesicle Associated Protein (PLVAP) Knockout Mice

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PLVAP is an endothelial-specific gene that is believed to be a structural component of the diaphragms that can associate with stomtal, fenestral and caveolar openings on endothelial cells. We have shown previously that PLVAP is expressed on both normal and tumour-associated endothelial cells in most organs and that expression of this gene is regulated by VEGF but the precise function of this gene is unknown. To determine the physiologic role of PLVAP we used a knockout mouse that was produced in a collaboration between Genentech and Lexicon Genetics to analyze the function of 500 secreted and transmembrane proteins. The initial characterization of this mouse is reported here.
KO animals show reduced viability; only 5% of mice born are homozygous for the PLVAP deletion compared to 65% that are heterozygous and 30% that are homozygous for the wildtype allele. This is in contrast to the expected ratios of 25%, 50% and 25%, respectively. KO animals that do survive to birth either die or become moribund between 4 and 11 weeks of age.
Diagnostic necropsy of animals between 4 and 10 weeks of age has been undertaken. KO animals are smaller in size and weight. The most consistent morphological abnormality observed is seen in the kidney and consists of collapsed and focally sclerotic glomeruli. Ultrastructural analysis of the kidney illustrates thickening of the peritubular and glomerular capillaries and their associated basement membranes, an absence of endothelial fenestrations, lipid pools and fused podocytes. Preliminary clinical pathology demonstrates anaemia, hypoproteinaemia and elevated serum levels of triglycerides and cholesterol. These observations may point to a role of PLVAP in homeostasis of macromolecules. Studies to further evaluate the *in vivo* importance of PLVAP are in progress.

O25

Expression of HGF and its receptor MET in Wilms tumours and nephrogenic rests

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Nephrogenic rests (NRs) are abnormally persistent foci of embryonal cells that are thought to be precursors of Wilms tumour (WT), although little is known about molecular alterations in these lesions. We identified by arrayCGH an amplification at 7q12-q21 in two cases of paired NR/WT samples, mapping to the hepatocyte growth factor (HGF) locus. As expression of both HGF and its tyrosine kinase receptor MET has been implicated in development and tumour progression, we analysed HGF and MET protein expression by immunohistochemistry in a series of 36 matched NR/WT cases. We observed HGF expression in 21/36 (58%) NRs, with only a single positive case in the corresponding WT (1/36, 3%). MET expression was restricted to the well-differentiated epithelial cells in 5/36 NR/WT pairs. In a paediatric renal tumour tissue microarray, HGF and MET were expressed in 16/203 (8%) and 26/188 (14%) of WTs respectively; co-expression was observed in 6/171 (4%) of cases. There was no association with histological subtype or prior exposure to chemotherapy. HGF/MET expression appeared to confer a better prognosis for WT patients, however this failed to reach statistical significance ($p>0.05$, log-rank test for RFS/OS). HGF/MET expression may represent an indolent stage in the multistep model of Wilms tumorigenesis.

O26

Assessment of Histological Features Which May Aid Prediction of 1p Status in Gliomas

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Loss of heterozygosity (LOH) analysis in oligodendrogliomas is of value in informing patient management. However, molecular facilities are not available in all centres and strategies to target cases for investigation may be of benefit in planning referral practice. We have assessed gliomas in which 1p status is known to identify features which may aid prediction of the molecular profile.

Gliomas in which molecular status had been assessed over a twelve-month period were selected. From these an anonymised, H&E-stained section was reviewed, a prediction of LOH status at 1p made and histological features of oligodendroglioma scored.

Fifty-four cases for which LOH analysis had been performed were available for review. At best LOH 1p status was correctly predicted in 44 cases (sensitivity 79%). With formal assessment of 'oligodendroglial' features, those scoring highest (>4 features) all had LOH at 1p (n=9). No cases with scores <2 showed LOH 1p (n=15). Cases scoring 2, 3 or 4 comprised 19 with LOH and 11 without LOH 1p.

Formal assessment of oligodendroglial features may identify a population of gliomas in which LOH at 1p can be predicted thereby allowing limited resources to be targeted to the remaining lesions where 1p status cannot be predicted with confidence.

O27

A Matter of Life and Death : the Runx Gene Family Controls Senescence and Survival

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The three mammalian Runx genes play paradoxical role in cancer, where they function either as oncogenes or tumour suppressors according to context. One family member, RUNX1, has a major role in human leukaemias through involvement in various chromosomal translocations (RUNX1-ETO, TEL-RUNX1) or point mutations. Reflecting this dualistic function, the effects of ectopic Runx expression are generally anti-proliferative in primary cells, and become growth-promoting only in the presence of complementing lesions such as p53 loss or Myc activation. Intriguingly, the Runx genes and their fusion oncoprotein derivatives induce senescence-like growth arrest in primary fibroblasts, while in cells lacking Ink4a/p53 function this effect is attenuated and Runx can instead promote tumorigenicity and cell survival under growth-limiting or stress conditions. We have been exploring the underlying mechanisms by global gene expression analysis. We find that the Runx genes regulate a common target set which is strongly over-represented in genes with annotated functions in cancer, development and differentiation. Of particular interest is our finding of direct Runx regulation of key enzymes controlling the ceramide-Sphingosine-1-phosphate "rheostat", providing a novel link between the fields of transcription factor oncogenes and lipid signalling, and identifying novel targets for therapeutic inhibition of Runx function in cancer.

O28

Intestinal adenomagenesis in Msh2-deficient mice is accelerated by conditional expression of mutated K-ras

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Human colorectal adenomas and carcinomas show K-ras mutations in 40-50% cases, but its contribution to adenoma formation in vivo is unclear. We developed a K-ras^{V12} transgenic mouse model that when crossed with Ah-Cre mice to generate K-ras^{V12}/Cre mice, allowed β-naphthoflavone-induction of Cre-mediated recombination that activated intestinal expression of K-ras^{V12} 4A & 4B transcripts and proteins. Only very occasional intestinal adenomas were observed in β-naphthoflavone-treated K-ras^{V12}/Cre mice aged up to 2 years, suggesting that mutated K-ras expression alone does not significantly initiate intestinal adenomagenesis. To investigate the effects of mutated K-ras on DNA mismatch repair deficient intestinal adenoma formation, these mice were crossed with Msh2$^{-/-}$ mice to generate K-ras^{V12}/Cre/Msh2$^{-/-}$ offspring. After β-naphthoflavone treatment, the average lifespan of the K-ras^{V12}/Cre/Msh2$^{-/-}$ mice was reduced to17.3±5.0 weeks from 26.9±6.8 (control Msh2$^{-/-}$ mice) ($p<0.01$). There was an increase in adenomas in the small intestine from 1.41 (Msh2$^{-/-}$ controls) to 7.75 per mouse (increased 5 fold, $p<0.01$); and in the large intestine from 0.13 to 2.70 per mouse (increased 20 fold, $p<0.01$). Over 80% adenomas from K-ras^{V12}/Cre/Msh2$^{-/-}$ mice showed transgene recombination with expression of K-ras^{V12} 4A & 4B transcripts and proteins. Expression of K-ras^{V12} in adenomas caused activation of the MAPK and Akt/PKB signaling pathways. Thus, mutated K-ras cooperates synergistically with mismatch repair deficiency to accelerate intestinal adenomagenesis, particularly in the large intestine.

O29

Can Cancer Stem Cells Be Seeded Through Solid Organ Transplants?

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Seeding of leukemic progenitors has previously been reported in haematopoietic malignancies of solid organ recipients. Additionally, in a preliminary study, donor cells have also been detected in skin lesions of kidney transplant recipients. However, little is known about the extent to which donor cells contribute to the tumours and about their role in tumour development. We have tested the hypothesis, that skin cancer stem cells or cancer progenitors may be seeded through solid organ transplants on 242 skin lesions from 42 female recipients of male kidney allografts. Y-FISH and quantitative Real Time PCR revealed location and extent of donor cell engraftment in post-transplant skin lesions. By combining Y-FISH with fluorescent immunohistochemistry and morphological analysis, we investigated whether donor cell incorporation is cell type specific and restricted to neoplastic and HPV-infected cells.
This extensive study allowed us to determine whether skin cancer progenitors can be seeded through solid organ transplants and may thus present an additional risk factor to transplant medicine. Future research needs to investigate the histological and spatial origins of the engrafted donor-derived cells.

O30

The Virtual Slide and Conventional Microscope – a Direct Comparison of Their Diagnostic Efficiency

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BACKGROUND
Virtual slides are digital images produced by scanning histopathology slides at high resolution. They have the potential to transform the practice of microscopy, but their efficiency remains unproven and few studies have directly compared the virtual slide with the conventional microscope.
METHODS
An observed controlled assessment of seven diagnostic tasks was undertaken with two pathologist subjects using either a conventional microscope or a virtual slide. The same diagnostic tasks were then repeated with the other modality ("within subject" design).
The tasks were chosen to reflect the range of tasks performed in routine diagnostic work (for example, make a simple "spot diagnosis" or score an immunohistochemical stain). The time taken to perform the diagnostic task was measured. Pathologists were asked to indicate their preferred modality for each task.
RESULTS
The virtual slide was slower than the conventional microscope for all tasks. The average time taken per task was 41% longer with the virtual slide than the conventional microscope (120 vs. 75 seconds, $P < 0.05$). The conventional microscope was three times as efficient as the virtual slides in a task to detect rare events on a slides (finding asbestos bodies in a section of lung – 25 versus 8 bodies found in 4 minutes). The conventional microscope was the preferred modality for all diagnostic tasks.
CONCLUSIONS
Virtual slides are significantly slower than the conventional microscope for many diagnostic tasks, particularly those involving scanning a slide for rare events. Pathologists preferred using the conventional microscope to the virtual slide.

O31

A Novel Formalin-free Fixative That Allows Both Histological and Molecular Analysis of Tissues

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Whilst the "ideal" fixative for the preservation of tissues and tissue substances does not exist, formaldehyde-based fixation has been accepted for many years as the best for morphological and protein preservation. However, as routine laboratory practice develops to accommodate essential molecular diagnostic and prognostic techniques, the features required from a modern fixative have shifted. FineFIX is a novel fixative, which offers a combination of good morphological preservation along with preservation of tissues in a way that permits broad-spectrum molecular profiling techniques.
Evaluation of the fixative was performed on explanted livers and tumour resection specimens. Samples were snap frozen in liquid nitrogen, placed into FineFIX or in a routinely used formalin fixative. After routine processing through to paraffin wax, haematoxylin and eosin, traditional tinctorial staining, immunohistochemistry, and molecular biological techniques were investigated. Microscopy confirmed no difference in quality of morphological preservation and staining compared with conventional formaldehyde-based fixatives. DNA preservation and sequencing was far superior to that of formalin fixed tissues and comparable to that of frozen tissue samples. RNA extracted was of high quality and produced good results for techniques such as RT-PCR.
In conclusion, FineFIX offers the potential to enable established and novel diagnostic techniques to complement each other, in one single procedure.

O32

Assessing proliferation in colorectal biopsies: a comparison of Ki-67 immunohistochemistry with counting mitoses in whole crypts.

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Introduction: A variety of methods exist for assessing the cell proliferation index (PI) in colonic mucosa. The aim of this study was to compare the PI assessed using Ki-67 immunohistchemistry with that derived by counting mitoses in whole-mount preparations of microdissected crypts. **Methods**: Fifteen paired biopsies of colonic mucosa from patients with normal bowel health were obtained. One biopsy from each subject was fixed in formalin and processed in the usual way. Six 4-micron sections were taken from 40-micron intervals through the tissue and Ki-67 immunohistochemistry performed. The PI was calculated as the number of Ki-67 positive nuclei divided by the total number of nuclei per hemicrypt. Whole biopsies from adjacent mucosa were fixed in Carnoy's fixative and Feulgen stained as whole-mounted tissue. Mitotic figures were counted in microdissected isolated crypts and the PI calculated as the number of mitoses per crypt. **Results**: The correlation between scores using the two methods was positive with a Pearson correlation coefficient of 0.655 ($p=0.008$). The Cronbach's Alpha statistic of the reliability of measurements was of 0.9476 for Ki-67 scoring and 0.9164 for mitotic counting, indicating excellent reliability for both techniques. **Conclusions**: The correlation between PIs calculated by these two techniques is high and these results do not support the dogmatic advocacy of either technique. Visualising sufficient well-orientated crypts can be problematic in sections from small biopsies, but the sectioning strategy employed here prior to Ki-67 staining maximised the number of assessable hemicrypts. Moreover, sections in between those used for Ki-67 staining are available for other immunohistochemical analyses – something not possible using the whole-mount approach.

Abstracts

Plenary

PL1

Near tiling microarray-based CGH identifies CCNE1 amplification in basal-like breast cancer

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Basal-like breast cancers (BLBC) constitute a heterogeneous group of aggressive neoplasms, accounting for around 15% of invasive breast carcinomas. BLBCs are characterised at the molecular level by lack of oestrogen receptor (ER) and HER2 expression, and expression of genes consistently expressed in normal basal/ myoepithelial cells. Current tailored therapies are not amenable for the management of these tumours, given that they lack hormone receptors and HER2 expression. The aims of this study were to characterise the molecular genetic profiles of BLBCs using a high resolution microarray-based CGH (aCGH) platform and to novel amplifications in BLBCs. A series of 20 fresh frozen grade 3 BLBCs were subjected to aCGH analysis using whole genome 16K near tiling bacterial artificial chromosome (BAC) arrays. Specific amplifications were confirmed by means of chromogenic *in situ* hybridisation (CISH) analysis using in-house generated probes. 20%, 50% and 30% of cases exhibited the recently described "simplex", 'sawtooth' and "firestorm" patterns of genomic alterations, respectively. The most common regions of gain (>25% of cases), included 1q, 6p, 8q, 10p and 17q, and the most common regions of loss (>25% of cases), encompassed 3p, 6q, 8p, 13q and 17p. Common amplifications observed in greater than 10% of cases included 1p12-q25.3, 7q11.21, 8q24.21, 11q13.3, 12p13.33-p13.31, and a novel amplification on 19q12. Further delineation of this novel amplicon identified *CCNE1* (cyclin E1) as a possible amplicon driver. *CCNE1* amplification was confirmed by means of CISH in all samples identified as *CCNE1* amplified by aCGH. Furthermore, we investigated the prevalence of *CCNE1* amplifications with CISH on a tissue microarray containing 97 grade III tumours. *CCNE1* gene amplification was found in 7% (6/91) cases and was significantly associated with a basal-like phenotype (p=0.0082, Fishers exact test). Amplification was also strongly associated with CCNE1 protein positivity as determined by Immunohistochemistry (p=0.008, Fishers exact test) and lack of *CCND1* (cyclin D1) amplification (p<0.001, Fishers exact test) as defined by CISH. Although CCNE1 protein expression has been previously reported to correlate with poor prognosis in breast cancer, these results demonstrate a novel mechanism of high protein expression through gene amplification, and show a distinct correlation with the basal like phenotype. These results also suggest that *CCNE1* and *CCND1* amplification act in a mutually exclusive manner and that selective amplification of cyclin E may be an alternative mechanism for basal like tumours.

PL2

Clonal heterogeneity, and the origin of columnar lined oesophagus in Barrett's

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INTRODUCTION: Barrett's oesophagus is am important pre-malignant condition, yet the origin of the metaplastic tissue is unproven. Work on clonal expansion in Barrett's biopsies suggests that in some patients a single clone can expand to populate an entire Barrett's segment. METHODS: We aimed to re-examine the clonality of Barretts dysplasia by identifying p16 and p53 point mutations and LOH patterns from single Barretts glands. Individual glands from across dysplastic patches from paraffin embedded Barretts tissue were isolated by laser capture microdissection. Gland lysate underwent microsatellite marker analysis for LOH of APC, p53, p16 and nested PCR amplification to allow p16 and p53 gene sequencing. Individual gland mutations were compared with the results obtained from whole biopsy lysates. Squamous duct glands were seen opening out to neo-squamous islands and columnar lined oesophagus (CLO), and these were micro-dissected to determine their clonal origins. RESULTS: Dissected tissue was classified histologically. p16, p53 point mutations and LOH patterns showed a great deal of clonal heterogeneity. Both CLO glands and neo-squamous islands were seen arising from squamous gland ducts and we demonstrate that the origin of the CLO is from a mutated squamous duct. CONCLUSION: Individual gland dissection and analysis reveals clonal diversity within Barretts segments not detectable by whole biopsy analysis. Gland to gland clonal heterogeneity suggests that previous models of mutational selective sweeps across entire Barretts segments may be over simplifications. We demonstrate a mutated CLO gland arising from a clonally mutated squamous duct and propose that a squamous duct stem cell niche is the source of multiple clones of CLO and neo-squamous islands in the oesophagus.

PL3

Changes in mechanotransduction during unloading of failing human hearts by a left ventricular assist device (LVAD)

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Mechanical support of hearts with end stage heart failure with an LVAD induces regression of features characteristic of failing human hearts (reverse remodelling). To identify transcriptional adaptations during LVAD support Q-PCR analysis was performed using a low density array to analyze 96 genes (Applied Biosystems) on paired myocardial samples before and after LVAD support (average support 270 days, dilated cardiomyopathy(DCM), n=8; ischaemic heart disease(IHD), n=8). Non failing hearts (n=5) served as control.
Results: In DCM and IHD 20% and 11% of the genes showed a statistical significant change after LVAD. Analysis of the ECM showed increased expression of the collagens but not of other matricellular proteins. mRNAs of membrane bound proteins cadherin, laminin and most of the integrins were increased after LVAD. The expression of perlecan and filamin beta had increased during LVAD in DCM but not in IHD and was significantly higher compared to control after LVAD. Integrin alpha 6 and cadherin expression were lower than control values and increased after LVAD in both groups whereas integrin alpha 1and alpha 10 expression increased in DCM only.
Conclusion: LVAD therapy leads to a partial normalization of the gene profile, with a different response of DCM and IHD.
Supported by the Netherlands Heart Foundation (2004T31)

PL4

Activation of the IGF1R pathway is a potential therapeutic target in relapsed Wilms tumours

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Despite the favourable outcome of the majority of Wilms tumours, there remains a group of patients whose tumours recur, and for whom intensive salvage regimens result in survival of only 50%. In an array CGH study of 127 Wilms tumours, we identified a significant correlation between increased copy number of *IGF1R* (15q26.3), present in 13% of cases, and tumour relapse. Expression profiling by cDNA microarrays revealed an co-ordinated dysregulation of the IGF1R network in relapsing cases. In a tissue microarray consisting of >300 paediatric renal tumours, 12% Wilms were found to express IGF1R protein at the membrane in the blastemal cells, correlating with an increased copy number by CISH, and a shorter relapse-free survival time ($p = 0.027$). Screening of the kinase domain revealed a previously unreported missense mutation (pG1328S) in a single tumour without copy number gain. Stable transfection of *IGF1R* into Wilms tumour (WiT49) and normal embryonic kidney (HEK293) cells conferred an increased rate of cell growth and proliferation. Treatment with the cyclolignan PPP, a specific IGF1R inhibitor, resulted in significant cell death with an IC50 of approximately 0.3 μM. These data provide evidence that the IGF1R pathway represents a novel target for therapy in relapsed Wilms tumours.

PL5

Isolation, Characterisation and Prospects for Use of Endothelial Progenitor Cells to Repair Pancreatic Damage in Diabetes

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Endothelial progenitor cells (EPCs) in the bone marrow (BM) and peripheral blood (PB) contribute to tissue repair in various pathological conditions *via* the formation of new blood vessels. Previous studies indicate that diabetic patients have reduced EPC number and dysregulated EPC function, although the regenerative properties of EPCs in diabetes are unknown. We wish to characterise and compare EPCs from pre-diabetic and diabetic non-obese diabetic (NOD) mice, a model of type 1 diabetes, in order to delineate the role of these cells in diabetes. We isolated BM and PB from pre-diabetic and diabetic NOD mice, in which the diabetic status was confirmed by measuring blood glucose levels (≥11.5 mmol/l). Morphological and immunohistochemical studies revealed that in pancreata from diabetic mice compared to pre-diabetic mice, blood vessel density was significantly increased with vessels containing elevated numbers of both endothelial (Factor VIII$^+$) and vascular smooth muscle cells (SMA$^+$). FACS analyses revealed a significant decrease in EPC number (CD31+, c-Kit+, Sca-1+, Lin-) in BM from diabetic compared to pre-diabetic mice (P-value: 0.021), which is consistent with human studies. Conversely, EPC number was significantly increased in PB from diabetic compared to pre-diabetic mice (P-value: 0.015). These preliminary data suggest that at the onset of diabetes, BM-derived EPCs are stimulated to enter the systemic circulation in response to signals from the pancreas. Our observations of increased EPC-derived lineages and vessel density in the NOD mouse imply that circulating EPCs engraft within the pancreas. Thus these observations demonstrate an involvement of EPCs in diabetes, which could lead to future therapies using these cells to facilitate pancreatic repair and regeneration.

PL6

The Role of the PI3K/Akt Cascade in the Development of Hormone Refractory Prostate Cancer

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The current study aims to establish if up-regulation of the PI3K/Akt cascade observed in cell line studies applies to clinical hormone refractory prostate cancer. Sixty eight patients with matched hormone sensitive and hormone refractory tumour pairs were retrospectively selected for analysis. Immunohistochemistry was employed to determine staining intensity of key members of the PI3K/Akt cascade. Expression levels of androgen receptor phosphorylated at the Akt consensus site (serine 213) significantly increased in the transition from hormone sensitive to hormone refractory disease ($p<0.0001$). When changes in protein expression levels of matched tumours for individual patients were compared, an increase in expression of PI3K was independently linked to time to biochemical relapse ($p=0.014$), and an increase in expression of Akt phosphorylated at serine 473 or androgen receptor phosphorylated at serine 213 was linked to shorter disease specific survival ($p= 0.0019$ and $p=0.0015$, respectively). In addition, there was a strong significant association between phosphorylated Akt and phosphorylated AR protein expression ($p<0.001$, R^2 0.711) in the hormone refractory tumours only. This study demonstrates a role for the PI3K/Akt/androgen receptor axis in the development of hormone refractory prostate cancer.

Abstracts

Posters

P1

Do brains need to be examined at autopsy?

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RCPath Guidelines on autopsy practice state that the brain should be examined in all Coronial autopsies. The recent NCEPOD study of Coronial autopsies identified 14% of cases where the brain was not examined.
The aim of this study was to identify the proportion of cases in our mortuary where the brain was not examined and to assess the impact of the brain examination in those cases where it was examined. We made a retrospective review of 328 Coronial autopsy reports from a single jurisdiction in 2005. In 5 cases (1.5%) the brain was not examined with the most common explanation being that the cause of death had been identified in another organ system (80%).
Where the brain was examined a cause of death was identified involving the brain in 30 cases (9.1%). These included traumatic head injury (53%), haemorrhagic/non-haemorrhagic stroke (13.3%), subarachnoid haemorrhage (10%) and meningitis (6.7%). In 7 of these 30 cases significant pathology was present in other organ systems that could have been formulated as a cause of death had the brain not been examined, the most common being ischaemic heart disease. Overall this represents 2.1% of cases in which the cause of death could potentially be inaccurate. In many cases the history gave an indication that the brain should be examined e.g. hypertension and headaches.
All of these cases were non-suspicious deaths and the significant other pathology was natural, raising the important question as to whether the aim of a Coronial autopsy is to identify a cause or the cause of death?

P2

Hypercalcaemia in Non-Hodgkin's Lymphoma Presenting as a Myocardial Infarct

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We report a case of sudden death of a 50 year old male who died of multi-organ failure secondary to extensive metastatic calcification present in the heart and lungs.
The patient had been previously well and presented with a three day history of generalized weakness. On investigation he had hypercalcaemia and his cardiac enzymes were raised. The provisional working diagnosis was possible myocardial infarction.
However, he did not respond to treatment and collapsed and died suddenly. A full coronial autopsy was undertaken. The only findings were those of extensive metastatic calcification within the heart with myocyte necrosis, calcification of the kidneys and lungs and a lymphomatous infiltrate in the pancreas and liver which after immunophenotyping was characterised as a high grade B-cell lymphoma, most likely pancreatic in origin.
Calcification is known to occur in association with non-neoplastic and neoplastic systemic diseases and there is a reported association between metastatic calcification and lymphomas. However, extensive myocyte calcification secondary to a high grade pancreatic B-cell lymphoma presenting as a myocardial infarct, has to our knowledge, not been reported in literature. This case serves to highlight this entity which is important in autopsy practice.

P3

Homicidal Smothering in An Adult: Vital Histological Evidence Despite a Prolonged Post-Mortem Interval

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Homicidal smothering is the deliberate occlusion of the external airways, usually using the hands, pillows or bedding. Victims are often those who are unable to resist, such as the young or the old. The limited resistance offered by these individuals results in a comparative lack of injury, an obvious advantage to the perpetrator.
We present a case of a 72 year old female, found deceased on her bed. The case was initially not considered suspicious and a coronial autopsy was performed. Concerns were subsequently raised and the body was frozen. Six months after the initial examination, an opinion was requested whether further examination would be worthwhile to consider allegations of deliberate smothering. Review of the scene photographs showed eversion of the upper lip with suspected intra-oral bruising. A bloodstained pillow was adjacent to the face. At autopsy, the body was putrefying and the facial tissues were very desiccated. The upper lip was excised and processed, confirming extensive recent bruising.
This case illustrates the subtle pathological findings apparent in these cases and reinforces the need for thorough external examination and correlation with forensic scene investigation. Histological sampling of suspected injuries can be rewarding, even in the presence of severe post-mortem deterioration.

P4

Audit of Cocaine Associated Deaths in East London 2004-2006

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Aim: To assess the range of pathology encountered during coroner's autopsies in the context of cocaine abuse.
Methods: Retrospective review of coroner's autopsy records with toxicology (including hair analysis) of deaths associated with cocaine abuse.
Results: 35 cases were identified (males 23 females 3), age range 22 to 49. Causes of death: neurological (subarachnoid haemorrhage1, excited delirium1) cardiac (ischaemic heart disease 4, myocarditis 2 aortic dissection 1, traumatic aortic rupture 2) pulmonary (infarction 1, aspiration 1, empyema 1, asphyxiation 1) gastrointestinal (haemorrhagic gastritis 3, haemorrhagic pancreatitis 3), multiple injuries 1, drug toxicity (cocaine 8, mixed drug toxicity 8). Additional findings: moderate to severe coronary artery disease 9 cases (6 triple vessel, 2 dual vessel) left ventricular hypertrophy 14 (mean heart weight: 418g males), hepatic (steatosis 5, bridging-fibrosis 2, cirrhosis 1). Polydrug-users 25 (opiates 19, amphetamines 7, benzodiazepines 5).
Discussion: The majority of cases were polydrug-abusers in keeping with the trends among users to co-administer stimulants and depressants. Hair analysis proved to be a useful component of toxicological assessment by providing combined screening (for cocaine, amphetamines, opiates and benzodiazepines) and establishing the time scale (chronicity) of drug usage. The latter is important when drugs are either absent or present at low levels in the presence of pathology attributable to substance abuse.

P5

Abstract withdrawn

P6

Sudden Cardiac Death due to Thrombotic Thrombocytopenic Purpura

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Thrombotic thrombocytopenic purpura (TTP) is associated with focal intravascular microthrombus formation with local ischaemic damage. Often only appreciated at autopsy, we describe 2 cases in which differential diagnoses of myocardial infarction and myocarditis were considered.
Case 1. A 51 year old female with chest pain, haemolytic anaemia, episodic expressive dysphasia and a punctuate rash over the limbs, died suddenly with rapidly progressive cardiac failure. Autopsy showed coronary atheroma, widespread gastritis, renal scarring and reactive changes in the marrow. Classic microthrombi were present within the myocardium, as well as in the stomach. Moderate scarring fibrosis was also present in the myocardium, indicating chronicity.
Case 2. This 38 year old male presented with unheralded cardiorespiratory arrest, with some brief atypical chest pain antemortem. Autopsy showed focally a haemorrhagic myocardium, with moderate atheroma. The remainder of the examination was unremarkable. Histology confirmed classic microthrombi within the myocardium.
Conclusions. These cases reinforce the need for histology at autopsy with appropriate sampling to identify this relatively rare cardiac pathology. The use of CD61 immunohistochemistry is highlighted alongside standard PAS histochemistry for microthrombus identification.

P7

Isolated Splenic Peliosis with Spontaneous Splenic Rupture Causing Sudden Death

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We report a case of sudden death resulting from spontaneous splenic rupture due to isolated splenic peliosis. Peliosis is a rare disorder characterised by multiple blood-filled cyst-like cavities within the parenchyma of solid organs. Isolated splenic peliosis is a very rare pathological entity and spontaneous splenic rupture from isolated splenic peliosis is particularly rare. Nevertheless despite being extremely rare, it is an important entity to recognise because it may become a relevant differential diagnosis in cases of sudden death and as a cause of fatal intra-abdominal haemorrhage mimicking a violent death.

P8

Phaeochromocytoma Presenting with Hypoglycaemia and Subsequent Hypertension

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We present the case of a 47 year old Macedonian Personal Trainer who presented with 4 days of vomiting, abdominal pain and profuse sweating. He admitted abusing anabolic steroids 20 years previously but never insulin. The presenting capillary blood glucose (CBG) was 1.7mmol/L, blood pressure (BP) 182/106mmHg, pulse 62bpm. He was sweaty, pale and cold. He was treated with dextrose and i.m.hydrocortisone resulting in CBG elevation to 7.1mmol/L and BP drop to 115/90mmHg.The initial differential diagnosis was hypoglycaemia secondary to insulin abuse, hypoadrenalism or insulinoma, the transient hypertension being considered a consequence of sympathetic stimulation.
His condition was stable overnight. Next morning he complained of nausea and abdominal pain. His BP had risen to 203/127. Shortly, he developed acute pulmonary oedema and had become hypoglycaemic again. He was given α-adrenoceptor blockade with i.v. phenoxybenzamine to control his BP. However, the patient deteriorated and died on the ITU within 2 hours. Blood was taken to assess troponin and insulin level shortly before he died and both were high (25.2 mU/L and 3.4µg/L respectively).
Post mortem findings included a left adrenal mass measuring 6.5x6x5cm with central haemorrhage together with haemorrhage within the head of pancreas. There was no evidence of pancreatic tumour or myocardial infarction. Sections from the adrenal mass were positive for synaptophysin and chromogranin with S100 positivity in sustentacular cells confirming a phaeochromocytoma. The tumour did not stain for insulin.
This is an unusual case of a phaeochromocytoma crisis presenting with hypoglycaemia and only later with hypertension. The mechanism of the hypoglycaemia remains unclear. Hypotheses include a β-adrenoceptor-mediated release of insulin from the pancreas, release of insulin from damaged pancreatic tissue, or co-secretion of incretins by the tumour.

P9

Lymphovascular invasion in breast cancer; improved methods of detection and prognostic significance.

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The presence of vascular invasion (VI); encompassing both lymphovascular invasion (LVI) and blood vascular invasion (BVI), in breast cancer has been found to be a poor prognostic factor. It is not clear; however, which type plays the major role in metastasis. The aims of this study were to use an immunohistochemical approach to distinguish between LVI and BVI by comparing the differential expression of blood vascular (CD34 and CD31) and lymphatic markers (podoplanin/D2-40) in a well characterized group of breast cancer patients with known long term follow up. Sections from177 consecutive paraffin-embedded specimens were stained with the four markers. BVI and LVI were identified and results correlated with clinicopathological criteria and patient survival. VI was detected in 56/177 specimens (31.6%); 54 (96.4%) were LVI and 2 (3.5%) were BVI. The presence of LVI was significantly associated with the presence of LN metastasis, development of distant metastasis, regional recurrence and worse disease free interval (DFI) and overall survival (OS). In multivariate analysis, LVI retained significance association with decreased DFI and OS. In conclusion, VI in breast cancer is predominantly of lymph vessels and is a powerful independent prognostic factor. The use of immunohistochemical staining with podoplanin/ D2-40 increases accuracy of identification.

P10

Outcome of "Non-Diagnostic Categories" (B3/B4) of Breast Needle Core Biopsies (NCB): a 10-Year Audit in a Large District General Hospital

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Aim: To audit the frequency and follow-up of B3 (uncertain malignant potential) and B4 (suspicious of malignancy) diagnosis in breast needle core biopsies.

Methods and Results: Over a 10-year period (1996-2006), 5100 NCB were performed. A diagnosis of B3 was made in 135 cases (2.6%) and B4 in 101 cases (1.98%) giving a total "nondiagnostic category" diagnosis in 236 cases (4.5%).

The common diagnoses in the B3 category were papillary lesions(33%), radial scar(20%), atypical epithelial proliferation(17%), fibroepithelial lesions(15.4%) and lobular neoplasia(6.6%). In the B4 category, the common diagnoses were suspicious for DCIS(51%), suspicious for malignancy(41%) and atypical ductal hyperplasia(8%). Final diagnosis was available in 107 B3 (79%) and 97 B4 cases (96%).

Positive predictive value(PPV) of a B3 diagnosis was 11.8% (16 cases - 8 invasive/ 8 DCIS). PPV of a B4 diagnosis was 82.5% (80 cases - 36 invasive/ 44 DCIS).

Conclusion: Patients with B4 diagnosis should undergo a diagnostic biopsy or excision of the lesion, since the rate of malignancy was high (82.5%). Further management of B3 cases should be discussed at the Multi Disciplinary Team meeting. "Non-diagnostic" diagnosis rates showed a decline particularly over the latter half reflecting increasing core biopsy numbers and pathologist experience.

P11

Distribution and significance of Caveolin 2 expression in normal breast and breast cancer: an immunofluorescence and immunohistochemical analysis

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The distribution and significance of caveolin 2 (CAV2) in normal breast and breast cancers remain poorly understood. The aims of this study were to define the distribution of caveolin 2 in frozen and formalin fixed, paraffin embedded (FFPE) normal breast samples and the significance of CAV2 expression in breast cancer. Caveolin 2 distribution in frozen and paraffin-embedded whole tissue sections of normal breast was evaluated using immunohistochemistry and immunofluorescence, in conjunction with antibodies to define luminal epithelial cells (oestrogen receptor and cytokeratin 8/18) and myoepithelial/ basal cells (cytokeratins 14 and 5/6, p63 and smooth muscle actin). CAV2 expression was also immunohistochemically analyzed in a cohort of 245 invasive breast carcinomas from patients treated with surgery followed by anthracycline-based chemotherapy. In normal breast, CAV2 was expressed in myoepithelial cells, endothelial cells, fibroblasts and adipocytes. Luminal epithelial cells showed no or only negligible staining. CAV2 expression was observed in 6.2% of all breast cancers and was strongly correlated with lack of oestrogen and progesterone receptor expression and cyclin D1, and positivity for epidermal growth factor receptor, cytokeratins 5/6, 14 and 17 and p53, and high proliferation index. Furthermore, CAV2 expression was significantly associated with basal-like immunophenotype and proved to be a prognostic factor for overall survival independent of tumour size and grade. Our results demonstrate that CAV2 is preferentially expressed in basal-like cancers and is associated with poor prognosis. Further *in vitro* studies are required to determine whether CAV2 has oncogenic properties or is only a surrogate marker of basal-like carcinomas.

P12

BAC to INFINIUM: a comparison of near-tiling path BAC arrays and illumina HAP300 SNP arrays for molecular genetic profiling of breast cancer

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Array-based comparative genomic hybridisation (aCGH) has proven to be a powerful tool to characterise the molecular genetic profiles of cell lines and human tumours, to fine map specific amplicons and to identify the likeliest 'amplicon drivers'. Whilst providing accurate copy number alterations within tumours, bacterial artificial chromosome (BAC) arrays do not provide information regarding copy neutral events (e.g., endoreduplication and mitotic recombination). On the other hand, profiles obtained with SNP platforms are reported to show a greater variation for regions with no copy number alterations. Our aims were to define whether Infinium SNP analysis accurately identifies single copy number gains and whether copy neutral events could be reliably identified. We compared the molecular genetic profiles of a series of grade III breast carcinomas of distinct subtypes. Tumour samples were microdissected to ensure >90% of neoplastic cells and profiled with both platforms. Normalised and smoothed Log2 ratios were converted into categorical variables (i.e., homozygous deletions, losses, no change, gains and amplifications) according to previously defined and FISH-validated thresholds. Results of BAC array analysis were directly compared to the copy number scores as generated by Illumina's proprietary software 'Bead studio v3' using the log R ratios and B allele frequencies. Amplifications were confirmed by means of in situ hybridisation.

In general there was good agreement between whole arm gains and losses and high-level amplifications, however the Bead studio software failed to identify a number of low level gains and deletions detected by BAC arrays. On the other hand, Illumina arrays identified regions with copy number silent LOH not detected by aCGH in 83% of samples. Identification of such events will enhance the understanding of the genetic evolution of the tumour and provide a greater insight into the mechanisms involved with inactivation of tumour suppressor genes. By comparing the log R ratios from the SNP chip analysis with B allele frequency, one can more readily discern copy number variation from the norm. However, in this study, it was observed that this approach is hindered by the inclusion of as little as 10% of normal cells within the tumour sample, making its application to micro-dissected tumour samples challenging. Based on our analysis so far, it is apparent that the thresholds for determining copy number alterations are sub-optimal with the Beadstudio software v3. Our results also demonstrate that BAC arrays and SNP chips can be used in a complementary fashion.

P13

Microarray CGH analysis of invasive micropapillary carcinomas of the breast

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Micropapillary carcinomas (MPC) comprise a special type of breast carcinomas with distinct histological growth pattern defined by morula-like epithelial cell clusters with inside-out growth pattern and inversion of polarisation. MPCs are reported to display a rather aggressive clinical behaviour. At the molecular genetic levels, these tumours are characterised by recurrent gains of 8q and occasional *HER2* amplification. The aim of this study was to determine the molecular genetic profiles of MPCs.

We studied a series of 11 primary micropapillary carcinomas and 2 lymph node metastases. All tumours showed the typical inverted micropapillary growth pattern and the characteristic 'inside-out' growth pattern as defined by EMA staining. For two cases both the primary carcinoma and the synchronous metastasis could be investigated. All cases were microdissected to ensure >75% of tumour cells. Array-based comparative genomic hybridisation (aCGH) was carried out using the Breakthrough Breast Cancer Research Centre aCGH platform containing 16K bacterial artificial chromosomes clones arranged at ~100Kb intervals throughout the genome. Normalised data were smoothed using a local polynomial adaptive weights smoothing procedure. Confirmation of the genetic alterations was by chromogenic *in situ* hybridisation (CISH) with probes for *HER2*, *CCND1*, *MYC* and *FGFR1*.

aCGH analysis revealed recurrent (> 30% of cases) copy number gains at 1q12-q44, 6p21.1, 7p22.3-p22.1, 8p12-q24.3, 16p13.3-q11.2, 17p13.3-p13.2, 17p11.2-q11.2, 17q11.2-q25.3, 20q11.21-q11.23, 20q13.12-q13.33; losses at 3q24, 6q14.1-q21, 6q21-q22.31, 8p23.3-p12, 9p13-1q12, 13q31.1-q31.2, 13q33.1-q33.3, 16q12.1-q22.1, 16q23.1-q24.1, 17p13.1-p12, 18p11.32-q11.1, 18q12.1-q12.3, 18q21.2, 22q11.22-q12.3. Recurrent amplifications at 1q23.3, 1q31.3-q32.1, 8p12-p11.21 (*FGFR1*), 8q21.12-q24.3 (*MYC*), 11q13.3-q13.4 (*CCND1*), 16p13.3, and 17q21 were also found. Amplifications of *CCND1*, *FGFR1*, *MYC* and *HER2* were confirmed by CISH. HER2 amplification was found only in one case which has been verified by CISH.

The genomic profiles of 2 lymph node metastases were similar to those of matched primary tumours. Interestingly, two lymph node metastases and matched invasive cancers displayed *MYC* gene amplifications.

In conclusion, our results demonstrate that, at the molecular genetic level, invasive micropapillary carcinomas comprise a heterogeneous group of tumours with varying degrees of genomic aberrations and patterns of genomic aberrations.

P14

PathScore™ – An Automated Breast Cancer Grading Demonstrator

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The project reported has developed automated computer analysis for grading breast cancer using the Elston and Ellis grading scheme. The dataset consisted of 47 samples of invasive carcinoma from the NHSBSP EQA scheme assessed by 733 pathologists. Gland formation, nuclear atypia/pleomorphism, mitotic frequency and overall grade were scored automatically by the system. Evaluation used the majority view of all pathologists. The grade allocated by pathologists was usually not unanimously agreed, the level of agreement varied widely. Evaluation showed that PathScore's performance was similar to that of the human pathologists. Overall grade agreement between the Pathologists and PathScore grade was good, although there was some tendency for PathScore to overestimate the severity of Nuclear Pleomorphism. The observed agreement (68.09) is twice as high as could have been observed by chance. The weighted kappa of 0.591 is statistically very highly significant and there is no evidence of any significant disagreement over any category or its asymmetry. By coincidence the level of agreement on the final grade amongst the pathologists yielded an identical kappa value (kappa = 0.59).
PathScore provides the potential for enhanced objectivity and reproducibility offering a standardized reliable method for histological grading of breast cancer on routine clinical samples.

P15

Abstract withdrawn

P16

Breast Cancer in women ≥75 years old has more favourable Pathobiological Characteristics

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One third of breast cancers will develop in women over 70 years. There is evidence from North American and Italian studies that breast cancers in the older age group differ in relation to pathological and biological features, but these studies had a lack of uniformity in data collection and pathology review. 244 patients 75 and over who had surgery for breast cancer between 1997 and 2006 were identified, plus 70 patients who had only non-operative core biopsy (1999-2001). Data on type and grade were available. Immunohistochemistry was used to assess ERα, PgR, p53, HER-2 and Ki67.
64% were 75-79 years, 22% 80-84 years and 14% ≥85 years. 10% had DCIS and 10.5% special type invasive cancer. 23.8% were grade I and 28.7% grade III, all age groups being similar. 81% of invasive cancers were ERα positive and 68% PgR positive. P53 protein was detected in 11.5% and Her2 in 8.5%, with half of the cancers having a low proliferation rate, measured by Ki67.
In this study from one centre, of breast cancers in women aged 75years or greater, there is strong evidence that invasive breast cancers in this age group are better differentiated, with high ER positive rate, low frequency of HER-2 and p53 and low proliferation rate, thereby differing from breast cancers arising in pre- and younger post-menopausal women.

P17

Prognostic Significance of ERbeta2/cx in Invasive Breast Carcinoma; Tissue Microarray Study

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Previous studies on prognostic significance of oestrogen receptor beta (ERβ) in breast carcinoma have yielded contradictory results The role of ERβ2/cx in breast carcinoma remains to be elucidated.
A total of 777 cases of invasive breast carcinomas were selected and tissue microarrays (TMAs) were constructed. Sections were stained with a specific ERβ2/cx monoclonal antibody and both nuclear and cytoplasmic expression were scored. Results were correlated with patient and tumour characteristics, cumulative and disease free survival (CS and DFS, respectively) as well as Nottingham Prognostic Index (NPI), ERα, progesterone receptor (PR), androgen receptor (AR) and Her2.

Nuclear expression of ERβ2 significantly correlated with tumour grade and size, NPI, CS, distant metastasis, death from breast cancer, ERα, PR and AR. High nuclear expression correlated with better CS and longer DFS. Low levels of the protein could predict relapse on tamoxifen independent of ERα. Interestingly, cytoplasmic expression, whether alone or in combination with nuclear staining, resulted in a decrease in CS.
This is the largest study of ERβ2 in invasive mammary carcinomas. Our data show that nuclear expression of ERβ2 is associated with better CS and DFS. It also highlights the importance of cytoplasmic as well as nuclear expression in dictating outcome.

P18

The biological and clinical characteristics of breast cancer with single hormone receptor (ER and/or PgR) positive phenotype

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In clinical management, it is usually easier to decide treatment strategies and predict response to hormonal therapy in double hormone receptor positive/negative phenotypes than in single receptor positive tumours (ER and/or PgR only positive). By using tissue microarray on a large and well-characterized series (1743 cases) of primary invasive breast carcinoma with a long-term clinical follow-up, we examined the main features of single hormone receptor positive group. ER^+/PgR^- tumours (15.6%) were found more frequently in elderly, postmenopausal women. The majority were grade 2, ductal/no specific type carcinomas. Associations were found with positive expression of androgen and c-erbB3 and negative expression of p53 and basal cytokeratins. When compared to the double negative phenotype, ER^+/PgR^- tumours (3.4%) showed an association with better outcome but no such survival advantage was detected in case of ER^-/PgR^+ tumours. In the group of patients with ER positive tumours who received adjuvant hormonal therapy, absence of PgR (ER^+/PgR^-) was an independent predictor of development of recurrence and shorter survival and hence poorer response to hormonal therapy. We conclude that ER^+/PgR^- and ER^-/PgR^+ tumours are biologically and clinically distinct groups of breast cancer that may require different treatment strategies with ER^-/PgR^+ exhibiting more aggressive behavioural characteristics.

P19

The biological and clinical characteristics of breast carcinoma with mixed ductal and lobular morphology

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Although invasive ductal (IDC) and lobular (ILC) breast carcinomas are well characterised in the literature, the biological and clinical significance of mixed tumours (both ductal and lobular components) has not been investigated. In the current study, we have compared 140 mixed tumours with 2170 IDC and 380 ILC cases. Mixed tumours constituted 3.1% of the breast cancers. The majority of these were grade 2 (58.5%, compared to 26% in IDC and 80.5% in ILC). Positive lymph nodes (LN) were found in 41% and definite vascular invasion (VI) in 26% of the cases. In-situ component (DCIS only 53%, LCIS only 3%, both 27.5%) was seen in 93.5% of the cases. When compared to pure IDC, mixed tumours showed an association with lower grade, ER positivity and less development of distant metastases. When compared to pure ILC, mixed tumours showed an association with higher grade, positive LN metastasis, VI and development of regional metastasis. After adjustment for grade most of these differences were no longer apparent. We are currently analysing the type and pattern of distant metastases mixed tumours especially in relation to the proportion and histologic grade of each component.

P20

Extending the Role of Biomedical Scientists (BMS) in Specimen Description, Dissection and Sampling in Breast Cancer-- is it Worthwhile?

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AIM: To evaluate/audit the performance of a Senior BMS performing description, dissection and sampling for all breast specimens.
METHODS:Breast specimens dissected by the BMS over a 9-month period were audited using a questionnaire filled in by the reporting Pathologist. The parameters noted were tumour size, nearest circumferential margin for wide local excisions(WLE), re-examination and further sampling, if any. Discrepancy was defined as macroscopic-microscopic difference greater than 3mm.
RESULTS:172 cases were dissected(85 mastectomies, 73 WLEs, 2 markers, 3 re-excisions, 9 others). 35 cases were excluded due to non-visible tumours(DCIS), re-excisions, prophylactic mastectomies, Gynaecomastia. The rest included 70 mastectomies and 67 WLEs(137 cases). Tumour size measurement was within range in 108 cases(79%). Causes for discrepancy included diffuse tumour(5 cases), DCIS(5 cases), lobular carcinoma(4 cases), tumour not identified(2 cases) and No-cause(11 cases). Margin measurement was acceptable in 81%(54 cases). Causes for discrepancy were DCIS(5 cases), diffuse tumour(1 case) and No-cause(7 cases). The specimen was re-examined in 8 cases(6%) with further sampling in 4 cases(3%).
CONCLUSIONS:Specialist roles like breast cancer specimen description/dissection and sampling can be delegated provided adequate training and support is available. In our audit, there were no serious errors or incidents and only 4 cases had further sampling.

P21

Intranodal Papillary Epithelial Inclusion Against a Background of Ductal Carcinoma in Situ. Is it Benign or Malignant?

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Aim: To describe a case of a papillary epithelial inclusion, of uncertain biological potential, within an axillary lymph node following mastectomy.
Case Report: A 58 year old lady who had an isotope localised excision biopsy for a screen-detected lesion, went on to have a mastectomy following MDT evaluation. Histology showed multifocal intermediate grade solid DCIS with micropapillary and usual type epithelial hyperplasia.
Four sentinel lymph nodes were received with the specimen, one of which showed an epithelial inclusion composed of well-differentiated glandular structures lined by bland columnar epithelial cells. The inclusion showed hyperplastic changes similar to those seen in the micropapillary epithelial hyperplasia within the mastectomy specimen. Immunohistochemistry for smooth muscle actin (Dako, dilution 1:400) was positive, confirming the benign nature of the inclusion
Conclusion: The finding of nodal epithelial inclusions is a rare occurrence, the aetiology of which is uncertain. They are important histologically, as they may be confused with metastatic disease. The inclusion in this case appears to have responded in a similar way to the stimulus that induced the hyperplastic changes in the benign epithelium of the breast.
Or, could it represent a benign “metastatic” deposit independent to or related to her previous excision biopsy?
Immunohistochemistry is key to determining the true nature of such lesions.

P22

ER expression level influences response to tamoxifen.

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Introduction
In breast cancer, tumour oestrogen receptor (ER) status is used to guide endocrine therapy. This study aims to determine the effect of ER protein expression level on response to tamoxifen therapy and define a level of ER expression that will guide hormonal therapy.
Methods
Follow up data is available for 1671 woman diagnosed with breast cancer between October 1995 and September 1998. Tumour samples had previously been scored for ER expression levels (0-100%) by the clinical pathologist at time of definitive surgery. Kaplan Meier curves were constructed and log rank test were performed.
Results.
1316 patients received 5 years adjuvant tamoxifen therapy. Risk of disease recurrence and overall survival was significantly associated with level of ER expression ($p<0.0005$). ER expression between 80-100% (high expression, n=815) had the lowest levels of recurrence and improved survival. Patients with <10% (poor or no expression, n=213) had the poorest survival and higher recurrence rates. Patients with ER expression between 10-75% (intermediate expressers, n=231) received some benefit from hormonal therapy but had lower survival rates and higher recurrence rates than the high expressers.
Conclusions
We propose that ER expression of 80% and above should define ER positivity in clinical practise and guide tamoxifen therapy.

P23

Increasing incidence of breast cancer: distinguishing between the effects of birth cohort and a national breast screening programme.

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Rising incidence of breast cancer in middle-aged women in the UK has been attributed to nationwide mammographic screening. However the incidence rise may be true rather than artefactual, perhaps as a result of changes in reproductive patterns; these factors affect birth cohort incidence of breast cancer. This study aimed to describe the incidence of breast cancer by birth cohort in relation to the screening programme in Scotland, to distinguish between true changes in incidence and the effects of screening. Data on breast cancer registrations for women aged 45-69 between 1977-2003 were obtained from the Scottish Cancer Registry. Birth year-specific incidence rates were then calculated for each 5-year age range. Trends in incidence before and after each age group entered the initial round of screening were analysed. In the years before screening, there was no change in incidence of breast cancer by birth cohort. As expected during the initial screening round, incidence increased with rising birth cohort, but even after it ended incidence continued to rise with rising birth cohort. The rising birth cohort incidence of breast cancer in Scotland since the prevalent round of screening ended suggests that changing reproductive patterns could be causing true rises in breast cancer incidence.

P24

Invasive micropapillary carcinomas of the breast: an immunohistochemical and chromogenic in situ hybridisation analysis

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Invasive micropapillary carcinomas (MPCs) of the breast are clinically aggressive tumours characterised by papillary cell clusters with inside-out growth patterns and inverted polarization. We studied 28 primary MPCs, 14 pure (PMPCs) and 14 mixed (MMPCs), with the aim of defining the prevalence of basal-like, luminal and HER2 molecular subtypes (as defined by the immunohistochemical panel described by Nielsen & colleagues), and the frequency of amplification of key oncogenes. Using a tissue microarray, immunohistochemistry for ER, PR, HER2, p53, basal markers (CK5/6, CK14, CK17, CAV-1, EGFR) and adhesion proteins (E-cadherin, Beta-catenin) was performed together with chromogenic-*in-situ* hybridization using probes for *CCND1*, *EGFR*, *HER2*, *TOP2A*, *MYC* and *FGFR1*. The vast majority of the carcinomas showed luminal (93% of PMPCs, 71% of MMPCs) or HER2+ (7% of PMPCs, 29% of MMPCs) immunophenotype. None of the cases showed positivity for basal markers. E-cadherin was expressed in both PMPCs and MMPCs, and beta-catenin showed only membranous and cytoplasmic staining in all cases, with one displaying nuclear positivity as well. p53 was positive in 21% of PMPCs and in 42% of MMPCs. Although *CCND1* amplification was only found in 7% and 14% of PMPCs and MMPCs respectively, 79% of both tumours strongly overexpressed cyclin D1. *HER2* amplification and overexpression was found in 7% of PMPCs and 29% of MMPCs, whilst *TOP2A* gene amplification was found in 2 MMPCs. *MYC* amplification was found in 21% of PMPCs and 28% of MMPCs, with only the micropapillary component showing *MYC* gene amplification in 2 MMPCs. *FGFR1* amplification was found in 14% of PMPCs and MMPCs. No *EGFR* gene amplification was found. Co-amplification of *MYC* with *CCND1* was found in 1/14 PMPC. Of the MMPCs, coamplification of *HER2* and *TOPO2A* was found in 2 cases, *HER2*, *TOPO2A* and *CCND1* in 1 case, and *HER2*, *MYC*, *FGFR1* in 1 case. MPCs do not display a basal-like immunophenotype and frequent coamplification of key oncogenes may account for their aggressive clinical behavior.

P25

Integrin alphavbeta6 promotes invasion and defines a novel poor prognosis molecular subtype of breast cancer

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Molecular characterisation is defining a more functional classification of breast cancer. The epithelial-specific integrin αvβ6 is rarely detected on normal tissues but may be up-regulated by many types of carcinoma. This study examined the functional and clinical importance of αvβ6 in breast cancer. αvβ6 promoted breast cancer cell invasion in vitro and in an analysis of two patient cohorts totalling >1800 breast cancers, expression of αvβ6 was an independent predictor of reduced survival, even when adjusted for tumour grade, size and lymph node status [HR 1.70; CI 1.19-2.44], and was significantly associated with the presence of distant metastases ($p<0.001$). Expression of αvβ6 correlated with the basal subtype ($p=<0.007$) and Her2-positive status ($p<0.001$) but was of greater prognostic importance than either group. Thus, 10 year survival for Her2+ve/αvβ6+ve cases dropped to 34% compared with Her2+ve/αvβ6-ve (52%) or Her2-ve/αvβ6-ve (79%) subgroups. In conclusion αvβ6 promotes breast cancer cell invasion and identifies a novel sub-group of poor prognosis breast cancers. Data suggest that determining αvβ6 expression should precede classification into Her2-positive and basal subtypes and as a membrane molecule rarely expressed in normal tissues, αvβ6 represents a viable new target for therapy of aggressive breast disease.

P26

Ethnic Differences in Breast Cancer in the UK

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African American (AA) women present much younger with invasive breast cancer than their white counterparts. Until now there are no data on the British Black population. This study aimed to compare the features of breast carcinoma arising in an East London African population compared with Caucasians. Incident cases of breast carcinoma were obtained for 1994 to 2005 from a single hospital in East London. Cases were verified with histopathology reports and age, self-reported ethnicity, grade, stage and tumour type were recorded. The Caucasian population presented at a median age of 69 years (29-98 years; n=202), compared to the Black African population who presented at of 46 (26-89; n=102). Thus there is a 23 year difference in age at presentation ($p<0.00001$). The Black women had significantly more grade 3 tumours (58% vs 39%; p=0.004), a greater incidence of positive lymph nodes (59% vs 49.5%; p=0.02) and ER negative tumours (34% vs 23%, p=0.1), although the latter was not significant. There was no difference in frequency of Her2 positivity between the two groups.
In conclusion, Black women in the UK present 23 years earlier than their white counterparts and with more adverse prognostic factors. Biological differences are likely to play a role and this is currently being investigated.

P27

Expression of the Tenascin Receptor α9β1 Integrin in Relation to Molecular Subtypes of Breast Cancer

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Cellular interactions with the extracellular matrix (ECM) are vital for the transduction and integration of signals from the microenvironment and influence many aspects of cell behaviour. These interactions are mediated primarily by the integrin receptor family. α9β1 is an integrin receptor for the ECM protein Tenascin. Tenascin is up-regulated in the majority of breast cancers therefore expression of this receptor by tumour cells has the potential to generate novel interactions with the tumour microenvironment.
This study examined expression of α9β1 integrin by standard immunohistochemistry in 96 frozen breast carcinoma samples and related expression to prognostic indices and molecular subtype.
α9β1 was restricted to myoepithelial cells in normal breast. Expression was detected in 19% of breast carcinomas but there was no significant association with grade or lymph node status. When compared to molecular phenotype, α9β1 was associated with basal phenotype, as defined by expression of either CK5 or CK14, though not to the triple receptor negative tumour subgroup. The association with normal myoepithelial cells and with basal cytokeratins in breast cancers suggests that α9β1 may identify a subset of basal tumours. Functional studies are now being undertaken to establish the role of α9β1 on breast cancer cell behaviour.

P28

BRCA1 and BRCA2 germline mutation analysis in the Indonesian population

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Germline alterations in BRCA1 and BRCA2 genes account for 30–50% of all forms of familial breast and ovarian cancer syndromes in which specific mutations have been identified in specific populations and ethnic groups. However, little is known about the contribution of BRCA1 and BRCA2 mutations to breast cancers in the Indonesian population. One hundred-twenty moderate to high risk breast cancer patients were tested using PCR-DGGE, and any aberrant band was sequenced. Multiplex ligation-dependent probe amplification (MLPA) was performed on all samples to detect large deletions in the two genes. Twenty-three different mutations were detected in 30 individuals, ten were deleterious mutations and 20 were "unclassified variants" with uncertain clinical consequences. Three of seven (c.2784_2875insT, p.Leu1415X and del exon 13-15) and two of four (p.Glu2183X and p.Gln2894X) deleterious mutations that were found in BRCA1 and BRCA2 respectively, are novel, as well as seven of 16 unclassified variants (p.Leu1209Val, c.5313-31A>G, p.Arg1835Gln, p.Thr1852Ile, p.Gln609Glu, p.Gln699Leu and p.Val901Ile). Some of these unclassified variant mutations are potentially pathogenic. In conclusion, several novel, pathogenic BRCA1 and BRCA2 germline mutations are found in early onset Indonesian breast cancer patients, as well as a variety of novel, "unclassified variant" mutations of which some are potentially pathogenic. These may therefore be specific for the Indonesian population.
Supported by grant IN-2001-008 of the Dutch Cancer Society

P29

High throughput analysis of gene amplification of 27 genes in invasive breast cancer by MLPA

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Genomic instability is a hallmark of cancer, and specific copy number changes are thought to play a driving role in the transformation of normal cells to malignant clones. Gene copy number alteration has mostly been studied using conventional or array CGH or single gene analyses. Here we performed Multiplex Ligation dependent Probe Amplification (MLPA) to detect copy number changes of 27 genes that often have an increased copy number in one or more types of human cancer on 191 Indonesian breast cancer samples. These genes span the human genome, from *MYCL1* that is located on 1p34.2 to *BCL2L13* on 22q11.
No cases were amplified for *BIRC4, PDGFRA, PDGFRB* or *HMGA*. Amplification frequencies by MLPA ranged from 1% for *MYBL2, BIRC2, hTERT, BCL2A1, BCL2L1, BCL2L13* and *MYCN* to 26% for HER-2/*neu*, consistent with previous studies on single genes and CGH. Tumors with frequent amplification (>2 genes) were more often poorly differentiated (p=0.021) and presented at advanced stage (p=0.025) compared to those with infrequent amplification (0-2 genes).
In conclusion, we present a novel high throughput MLPA method that allows a reliable, quick and cheap comprehensive analysis of copy number of a large set of genes that play a role in carcinogenesis in breast and other cancers. This method thereby allows efficient analysis of gene copy number status for better understanding the biology and possibly clinical behavior of breast and other cancers.
Supported by grant IN-2001-008 of the Dutch Cancer Society

P30

Re-assessment and Clinicopathological Analysis of Intracystic Papillary Carcinoma of the Breast

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There are some uncertainty and discrepancy in reporting papillary carcinoma (PC) of the breast, especially when they are completely devoid of myoepithelium. It is not clear if these lesions are truly in situ carcinomas, or circumscribed encapsulated invasive papillary carcinoma.
This study is to characterise previously diagnosed PC by immunostaining for myoepithelium using antibodies to smooth muscle myosin heavy chain and cytokeratin 5/6, and correlate with clinical outcome.
Ten PC, 8 invasive papillary carcinoma (IPC) and 8 intracystic papilloma (P) were analysed {mean follow up, PC 83.6 (10-108) month, IPC 31 month (12-88), P 45 month (12-96)}. The PC was further divided into three groups: PC only, PC with DCIS, and PC with invasive components 1 - 5mm. Of 10 cases originally classified as PC, 6 showed complete absence of myoepithelial cells. Recurrence was seen in 3 patients after 1, 4 and 5 years follow up. All of these 3 cases were from PC group with complete loss of myoepithelial cells (1 from each group). The recurrent lesions were invasive papillary carcinoma (2 cases) and PC with invasion, respectively. None died of their tumours.
The results indicate that 60% of previously diagnosed papillary carcinoma show complete loss of myoepithelium and may actually represent invasive papillary carcinoma. In our data, they have a higher tendency to recur with more advance disease.

P31

Assessing the Diagnostic Outcome of B3 and B4 Breast Core Lesions

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Needle core biopsies are widely used to investigate mammographically suspicious lesions in an attempt to reach a definitive diagnosis. In the majority of biopsies a definitive diagnosis of normal (B1), benign (B2) or malignant (B5) is made. However there are some borderline lesions (B3) and suspicious lesions (B4) that are not diagnostic of malignancy on the tissue examined.
The QA Guidelines of the NHSBSP set two major targets in relation to the diagnosis of core biopsies, the first being that the majority (>90%) of breast cores should have a definitive diagnosis. The second aims to minimise surgery in women with benign disease and requires that there should be less than 1.8 open biopsies/1000 patients. The rate in our region is 1.9/1000 we need to identity the B3 lesions that are benign on excision that account for this high rate.
We conducted an audit of breast core biopsies performed in our department from August 2002 to December 2006 with their follow-up excisions to determine the positive predictive value of B3 and B4 lesions. Each of the five subcategories of B3 lesions were analysed to identify those lesions that are most commonly benign.
Borderline and suspicious lesions represented 7% of the sample, hence reaching the target. B3 was commoner than B4 (120:30). Of the five sub-categories of B3, papillary lesions stood out as the predominant benign category. The positive predictive value of reports classified as B3 was 35.3% and for B4 as 90%, values being well above the regional mean for both the categories.

P32

Core Biopsy Characteristics Identify Patients At Risk of Compromised margins in Breast Conservation Therapy

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Selection of patients for breast conserving therapy (BCT) is currently based on tumour size assessed non-operatively using clinical & radiological examination. This study investigates the value of needle core biopsy (NCB) findings, in particular the relative quantity of DCIS, in assisting patient selection for BCT.

The study population (N = 281) comprised patients undergoing BCT from 1999 – 2004 who had invasive carcinoma (IC), ductal carcinoma in situ (DCIS), or IC and DCIS, on NCB, and a final diagnosis of IC at excision. All NCBs were reviewed to document the relative quantity and characteristics of IC and DCIS. Compromised margin (CM) status at excision was defined as DCIS or invasive carcinoma within 5mmof a radial resection margin.

129/281 (46%) had IC with minimal DCIS (< 5%) (group 1) and 152 (54%) had DCIS accounting for at least 5% of the overall tumour (group 2) on NCB. Group I had a CM rate of 26% compared with 41% for group 2 (p=0.005). CM rate increased with percentage DCIS component, reaching 79% (n=19/24) in patients with 100% DCIS on NCB. High grade DCIS (p=0.027) and solid architecture (p=0.016) were also associated with CM.

The presence, grade and relative quantity of DCIS on NCB provides important information in predicting patients at increased risk of compromised margins at BCT.

P33

Core Biopsy Diagnosis of Radial Scar / Complex Sclerosing Lesions: Excision is Necessary.

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Recent reports in the literature have suggested that a confident diagnosis of benign radial scar/complex sclerosing lesion (RS/CSL) may be made on core biopsy, avoiding the need for excision. We reviewed our experience of such lesions in a large breast cancer centre.
All breast core biopsies coded as RS/CSL over a 6 year period (2000 – 2006) were identified from our computer system (n = 128). 110 of these had excision biopsies at our hospital, 102 of which were available from our files for review. Core biopsies were reviewed jointly by two pathologists. Excision specimens were similarly reviewed subsequently. Core biopsy diagnoses were thereafter correlated with their paired excision specimens.
5 of 102 core biopsies lacked a definite elastotic central scar. On excision only one of these cases contained a definite RS/CSL and one contained unsuspected DCIS.
97 cores contained well defined central scars with elastosis. Of these 2 contained DCIS and 1 ALH on the core biopsy.
The remaining 94 cases were benign RS/CSLs on core biopsy but 7 of these (7.4%) contained unsuspected carcinoma on excision (3 DCIS, 3 LCIS, 1 tubular carcinoma).
There is a low but significant association of carcinoma (both in situ and invasive) with RS/CSL which may not be adequately sampled on core biopsy. We conclude that excision of these lesions is necessary, in keeping with current NHSBSP guidelines.

P34

Her-2 Audit: Does Testing On Core Biopsy Increase the 2+ Rate?

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Her-2 testing on core biopsy provides timely results for clinical management decisions. However, it is suggested that this may increase the 2+ rate, with a resulting in increase in FISH testing.
We audited our Her-2 reporting from a 6 month period (January – June 2006) when we moved from testing on excision specimen to testing on core biopsy. As our gold standard we used data from over 16000 tests carried out in 28 centres across the UK. All core biopsies and their associated excisions with a diagnosis of invasive breast carcinoma were identified (n=372) and their reports reviewed. HercepTest results had been reported on 315 cases (84.7%) - 131 on core, 172 on excision, 12 on both.
Our results compared favourably with the gold standard:

	Audit	Gold Standard
0/1+	66.3%	68%
2+	19.4%	18%
3+	13.9%	13%
FISH positive	13.1%	25%
Her-2 positive	16.5%	17%

Tumour grade was significantly associated with the Her-2 positive rate (Chi^2 test, $p<0.001$). Lymph node status approached significance ($p=0.052$) but oestrogen receptor status ($p=0.112$) did not. Testing on core versus excision was not associated with either the Her-2 positive rate ($p=0.221$) or the 2+ rate ($p=0.176$).
In our experience Her-2 testing on core biopsy does not significantly increase the 2+ / FISH rate.

P35

The Prognostic Significance of Steroid Receptor Co-Regulators in Breast Cancer

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Recent evidence suggests a role for steroid receptor co-regulators in breast cancer development and progression, in particular those that regulate the promotion of gene transcription by oestrogen receptor. Expression levels of three co-activators; SRC1, CBP, RAC3 and the co-repressor SMRT, were quantified in breast tumour samples using tissue microarray technology and immunohistochemistry. Associations with patho-clinical parameters and expression of steroid receptors, cytokines, biomarkers and modified histones were analysed. Kaplan-Meier analyses were used to find relationships among the co-regulators and patient outcomes. Significant co-expression was found between all four co-regulators. Expression of the co-activators SRC1, CBP and RAC3 was associated with good prognostic factors, e.g. low grade, small tumour size, longer survival, and longer disease free interval, in comparison to SMRT which was associated with poorer prognosis and shorter survival. Significant associations were found between all co-activators and steroid receptors (ER-α, PgR and AR), IL-8, BRCA1 and specific modified histones. These results suggest that steroid receptor co-regulator expression can be used in the prediction of patient outcome from breast cancer, and that there is cross talk between the steroid receptor pathways and other non-steroid pathways controlling gene transcription.

P36

The Prognostic Significance of Interleukins 1α/β and 8 in Breast Cancer

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Recent evidence suggests that cytokines and NFκB are central contributors to underlying biology of breast cancer disease progression and may act as prognostic indicators. Therefore, protein expression for interleukins IL-1α, IL-1β, IL-8 together with NFκB were determined in breast tumours (n=880) using tissue microarray technology and immunohistochemistry. Associations with patho-clinical parameters and expression of other biomarkers were analysed. Kaplan-Meier analyses were used to find relationships among the cytokines and patient outcomes. Expression of NFκB was significantly correlated with IL-1α, IL-1β, and IL-8 expression. IL-1α and NFκB were associated with ductal carcinoma of no-specific type (NST), tubular mixed and lobular tumours. A significant relationship was found between the level of IL-1α and NFκB expression with higher grade tumours and a poor Nottingham Prognostic Index (NPI). IL-8 was associated with vascular invasion and negative lymph node status. Patients with a high expression of IL-1β had significantly better overall survival ($p=0.034$) and longer disease-free survival ($p=0.026$) that those with no/low levels of IL-1β. Our data suggests that IL-1β could be used as a potential prognostic indicator, where its expression is associated with a better prognosis, and could act as potential target for novel adjuvant therapy.

P37

The Effect of Growth Factors EGF, TGFβ and HGF on Tenascin Isoform Expression in Breast Epithelial and Stromal Cells

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Tenascin (TN) is an ECM glycoprotein that is upregulated during inflammation, wound healing and tumourgenesis. TN exists as multiple isoforms which are thought to be functionally distinct with the larger isoforms stimulating invasion and proliferation, however, little is known about the factors regulating the pattern of isoform expression.
This study examined the effect of growth factors EGF, TGFβ and HGF on TN isoform expression by breast cancer cell lines and fibroblasts at the mRNA and protein level. Both EGF and TGFβ induced expression of the large TN isoform (LTN) in MCF7 cells, whereas TGFβ but not EGF stimulated expression of LTN in MDA-MB 231 breast cancer cells. In contrast, EGF but not TGFβ increased LTN expression in fibroblasts. HGF stimulated LTN in 231 cells and fibroblasts only in serum-supplemented conditions.
These findings indicate cell-type specific regulation of TN isoform expression by EGF, TGFβ and HGF. The upregulation of LTN is of particular relevance since this isoform has been shown to enhance tumour invasion and growth and demonstrates the importance of epithelial-stromal interactions in modulating tumour behaviour.

P38

An Audit of Breast Biopsies of Uncertain Malignant Potential (B 3 Category)

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The UK NHS breast screening programme has proposed five categories for reporting of breast core biopsies. The majority of breast biopsies are classified as normal (B1), benign (B2) or malignant (B5), however in some cases a definitive diagnosis is not possible (lesions with uncertain malignant potential/ B3, or suspicious/ B4). We studied all breast biopsies reported as B 3 in a five year period (Jan 2000 - September 2005). 155 of 4097 breast biopsies reported as B3 (rate 3.78%) were sub-categorized as atypical ductal hyperplasia, lobular neoplasia, radial scar/complex sclerosing lesion, papillary lesions, fibro-epithelial lesions and others. Histology in excision specimens was correlated with biopsy findings and the overall positive predictive value for a B3 diagnosis and the positive predictive value for each category were determined. The results showed an acceptable positive predictive value of 14.1% for a B3 diagnosis. There was concurrence with the observation that there is an increased rate of malignancy associated with ADH and lobular neoplasia. In conclusion, the diagnostic category B3 includes a heterogeneous group of lesions associated with a low but variable risk of malignancy. Subsequent management should be individually tailored after discussion at a multidisciplinary meeting.

P39

CCND1 amplification and cyclin D1 expression in breast cancer and their relation with histological phenotype and patient outcome

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Introduction:Despite strong evidence regarding the role of *CCND*1 amplification and protein overexpression in breast carcinoma, there is still a controversy data on the associations between *CCND*1 amplification/cyclin D1 overexpression and clinicopathological variables and clinical outcome.
Aim of the study: The aims of this study are fourfold: (i) to correlate cyclin D1 expression with gene amplification (ii) to analyse the correlations between *CCND1* amplification and overexpression with clinicopathological features and patients' outcome in invasive breast cancer (iii) to define the prevalence of cyclin D1 overexpression and *CCND1* amplification in ER positive breast carcinomas and its relation to outcome in those who receive tamoxafen as adjuvant chemotherapy (iv) to define the prevalence of cyclin D1 overexpression and *CCND1* amplification in the basal–like group of invasive breast cancer.
Material and method:*CCND1* amplification and protein expression were assessed on a tissue microarray of 880 unselected invasive breast cancer cases, using Chromogenic *in situ* hybridisation (CISH) and Immunohistochemistry.
Result:There is a strong correlation between *CCND1* amplification and cyclin D1 expression. Reduced cyclin D1 expression is associated with basal –like breast carcinoma. While gene amplification is associated with shorter overall survival (OAS) in ER positive cases and a higher rate of recurrence in patients received tamoxafen.
Conclusion: Despite the strong association between CCND1 amplification and its protein expression, there is a controversy in the their relation with patient prognosis and outcome .This support the hypothesis of maintenance of cyclin D1 expression by other transcription factors in the absence of gene expression .

P40

Global histone modifications in breast cancer tissue correlate with tumour phenotype, prognostic factors and patient outcome.

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Background: Epigenetic changes in the form of global histone modification patterns have recently been shown to predict patient outcome in human prostatic carcinoma. However, the clinical significance of these modifications in breast cancer is unknown.
Methods: Seven specific antibodies were used to detect selected histone modifications in tissue microarrays of a large (n=880) well-characterized series of human breast carcinomas using blinded semiquantitative scoring, in addition a set of well known markers in breast cancer
Results: There is a highly significant correlation of histone modification status with tumour biological/morphological characteristics and clinical outcome. High levels of histone modifications were detected in luminal steroid receptor positive tumours, including lobular, mucinous and tubular carcinomas. However, significantly reduced levels of histone lysine acetylation (H3K9, H3K18, H4K12, H4K20), lysine methylation (H3K4,H4K16) and arginine methylation (H4R3) were observed in the poorer prognostic biological and morphological subtypes of breast cancer including basal and HER2-positive carcinomas, invasive duct carcinoma and medullary-type carcinoma. Low levels of these epigenetic marks were also associated with shorter disease free interval (DFI) and overall survival (OAS), particularly AcH3K18 that has an independent prognostic influence.
Conclusions: Our results show, for the first time, that global changes in specific histone modifications patterns may play an important role in breast cancer development and progression and their reduced expression is associated with poor prognosis and shorter survival.

P41

Stromal-epithelial interactions: does nuclear β-catenin in fibroblasts influence breast cancer behaviour ?

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β-catenin is a molecule involved in both cell adhesion and transcription. In its transcriptional role it localises to the nucleus and modulates transcription of a number of effector genes, notably c-myc and cyclin-D1 resulting in changes to cell growth, cell division and apoptosis. Upregulated nuclear β-catenin has been noted in fibroblasts associated with wound healing and phyllodes tumours. Nuclear expression of β-catenin documented in phyllodes tumours is proposed to form part of a feedback loop in which these fibroblasts, in turn, stimulate the growth of the epithelial component.
We have observed nuclear β-catenin expression in fibroblasts adjacent to breast cancer. We hypothesise that these fibroblasts might feedback and stimulate the growth of the malignant epithelium as we have proposed for phyllodes tumours. We have tested this hypothesis in a series of experiments in which the effects of conditioned media from fibroblasts transfected to express nuclear β-catenin, upon MCF-7 were studied. Compared to controls, the MCF-7 cells so exposed, exhibited increased proliferative activity. Further experiments have also shown an increased invasiveness of MCF-7 cells in matrigel invasion assays.
Our study underscores the importance of stromal-epithelial interactions in breast cancer and its vital consideration in all future breast cancer research.

P42

Triple Hormone Negativity Predicts CK14 status in Grade3 Tumours - a Comparision with the Fulford Morphological Score.

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Introduction
Microarray work has identified a group of tumours whose prognosis is worse with an increased propensity to early cerebral and lung metastases and are designated "basal type" carcinomas as they express basal markers. Additionally, these tumours are usually triple hormone negative .Fulford et al (2006) proposed a morphology based predictive scoring system and reported that 72% of basal type tumours could be identified by morphology alone. This study then aimed to test the reproducibility and the predictive power of the proposed scoring system in a district general hospital setting.
Methods
All grade 3 tumours received by the pathology department in 2005 were reviewed and scored by two pathologists independently according to the modified Fulford scheme. The hormone status was recorded and basal markers performed on all of the tumours.
Results
Only preliminary data is available.
79% of ck14 positive tumours (11/14) were identified as likely basal tumours by the Fulford scoring protocol with a sensitivity of 41% but specificity of 92%. Triple negative hormone status predicted ck14 status with a sensitivity of 79% and 96%.
Conclusions
The Fulford system predicted 79% of ck14 positive tumours but triple hormone negativity was a more powerful predictor of ck14 status

P43

A case of basal type adenocarcinoma of the breast with features of metaplastic carcinoma with unusual cytomorphologic findings

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We describe the histology of an unusual basal-type breast cancer with metaplastic features.

The patient, a 49 year old woman presented with a clinically and radiologically suspicious palpable breast mass. Following core biopsy, wide local excision was performed.

Grossly the lesion measured 4 cm, was very well circumscribed with a heterogenous cut surface including white schirrhous and glistening myxoid areas. On histology, the tumour showed a very striking biphasic pattern. It included an epithelial component which comprised well differentiated glandular and cribriform structures, tumour cells with low grade nuclear features and rare mitoses. Focal infiltration of adjacent breast parenchyma was evident. The epithelial component was intimately admixed with abundant chondromyxoid stroma with foci of metaplastic bone formation and bland bipolar stromal cells reminiscent of a pleomorphic adenoma.

Immunohistochemical studies showed the tumour to have a 'triple negative' phenotype (ER, PR, HER2/NEU) and to exhibit positivity for CK14, CK5, S100 and CD117. CK18 was negative.

Diagnostic considerations included an epithelial-dominant malignant myoepithelioma and a salivary gland-type adenocarcinoma with pleomorphic adenoma-type appearance. Overall, however the lesion was classified as a basal type adenocarcinoma of the breast with focal features of matrix-producing metaplastic carcinoma with an unusually well-differentiated glandular pattern.

P44

TSC22 in Mammary Gland Development and Breast Cancer

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Mammary gland involution is characterised by a high degree of apoptosis. By identifying genes that are up-regulated at this developmental stage, we aimed to discover key factors that are involved in the induction of mammary epithelial cell death and therefore present potential tumour suppressors for breast cancer. Among 96 genes recently identified as specifically up regulated early during involution was the TGFbeta stimulated clone 22 homologue (TSC-22/transforming growth factor beta 1 induced transcript 4). TGFbeta 3 has recently been shown to be necessary for involution. Here we show that TSC-22 mRNA expression can be induced by TGFbeta3 and that TSC-22 can enhance a TGFbeta3-induced Smad-response. In addition, over-expression of TSC-22 alone can induce a Smad-response and apoptosis in mammary epithelial cell cultures. A pilot study on a small cohort of archival breast cancer cases, representing all stages of malignant progression, shows that TSC-22 protein was reduced or undetectable in 60% of breast carcinomas when compared to adjacent normal breast tissue, suggesting that TSC-22 could indeed be a potential novel tumour suppressor gene.

P45

Primary Leiomyosarcoma in the Breast.

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Sarcomas of the breast are rare tumours accounting for about only 1% of all breast malignancies. Leiomyosarcoma (LMS) constitutes only 7% of breast sarcomas. This report describes two unusual cases of leiomyosarcoma of the breast. The patients are a 58 year old male and a 65 year old female with a previously treated primary breast cancer. In both cases pre-operative diagnosis was difficult. A definitive diagnosis of (LMS) was only arrived at following immunohistochemical analysis of excision specimens. Both tumours showed strong positivity for smooth muscle actin on immunohistochemistry. In our patient previously treated for breast cancer there were also features consistent with her radiotherapy. There are few well documented cases of leiomyosarcoma of the breast in the literature. The incidence of sarcoma following breast surgery and irradiation to the chest wall is reported to be 0.2% at 10 years. Leiomyosarcoma of the breast in the male is even more unusual.
As breast conserving surgery with radiotherapy becomes more prevalent it will be important to monitor this complication.

P46

Ras/Raf-1/MAPK pathway mediates response to tamoxifen in breast cancer patients

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The Ras/Raf-1/MAPK pathway controls multiple cellular processes, including the ligand-independent phosphorylation and activation of the oestrogen receptor (ER). We therefore hypothesised that activation of this pathway in breast tumours might lead to the development of tamoxifen resistance.

402 ER+ve tumours from tamoxifen treated patients were analysed for H-/K-/N-Ras, Raf-1, pRaf(ser259), pRaf(ser338), MAPK and pMAPK expression, using immunohistochemistry. Two observers independently scored tissues using a weighted histoscore. Survival analysis was performed with SPSSv9.

Patients were more likely to relapse during tamoxifen treatment if tumours presented with elevated expression of cytoplasmic N-Ras (p=0.0318), nuclear pRaf(ser338) (p=0.005) and cytoplasmic MAPK (p=0.0012). Of the 402 patients, 99 also received chemotherapy. Analysis of the 303 tamoxifen only treated patients confirmed pRaf(ser338) and MAPK as predictive for poor outcome (p=0.0006 & p=0.0021). Multivariate analysis showed pRaf(ser338) expression to be independent of known prognostic markers in predicting recurrence (p=0.0439).

This study presents evidence that expression and activation of the Ras/Raf-1/MAPK pathway in clinical breast tumours is associated with a poor outcome. These results suggest that activated Raf-1 is a potential predictive factor for identifying patients who are least likely to respond to tamoxifen and would require either additional or alternative therapies, such as chemotherapy or AIs.

P47

Analysis of Cell-Free Plasma DNA from Breast Cancer Patients

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Increasing evidence suggests that tumour DNA isolated from plasma represents a promising biomarker for cancer diagnosis and follow up. The aim of this study was to compare the concentration and integrity of cell-free plasma DNA isolated from 33 primary breast cancers, 30 metastatic breast cancers and 25 healthy female controls. DNA was extracted with the QiAmp blood kit (Qiagen) and analysed by a real time quantitative PCR assay using a common minor groove binding probe to detect amplicons 96bp and 291bp in size. The ratio of the concentration of the two amplicons served as a measure of DNA integrity. Plasma DNA concentration ranged widely (2ng/ml to 900ng/ml) with some overlap seen between the groups. However, mean plasma DNA concentration was significantly higher in breast cancers than controls ($P < 0.001$). Similarly, the mean DNA integrity index was significantly higher in primary (0.56 ± 0.24) and metastaic breast cancers (0.59 ± 0.14) than controls (0.14 ± 0.08) ($P = 0.003$). These data confirm that combined quantitative and qualitative analysis of plasma DNA can be used to discriminate breast cancers from healthy female controls and the approach may be useful for screening and monitoring of patients.

P48

Basal Phenotype of Breast Carcinoma An Example of Confused Terminology

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Breast carcinomas arise in the TDLU. Cytokeratins 5 and 14 are expressed in basal cells in many epithelia and became 'basal keratins'. The exception is breast where CK5/14 are heterogeneous in luminal and myoepithelail cells. Expression microarrays cluster some cancers as basal-like on the basis of these cytokeratins. Many researchers and pathologists have assumed that these basal-like tumours arise from the normal myoepithelium. We studied 15 reduction mammoplasties, 15 ADH/Grade1 DCIS, 44 Grade 2 DCIS and 39 Grade 3 DCIS for p63, SMA, CD10 (myoepithelial markers), and CK5, CK14, Annexin V111 and MMP14 (part of the basal micro-array cluster). In the TDLUs of normal breast and DCIS of all grades, myoepithelial cells are identified by p63, SMA and CD10. MMP14 is a myoepithelial marker in normal epithelium. Annexin V111, CK5 and CK14 are variable being negative in some TDLU, heterogeneously luminal and myoepithelial or purely luminal. Five cases of DCIS were positive for CK5/14, but only one co-expressed SMA. In DCIS CK5/14 are consistent normal myoepithelial markers. These results suggest that either negative myoepithelial cells express CK5 /14, when 'injured' or that DCIS arises in the terminal ducts and not the ductules. CK5/14 positive tumours may arise from luminal cells.

P49

Histological Patterns of Epithelial Breast Cancers in Ile-Ife Nigeria.

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Introduction: Breast cancer is the leading female malignancy in the world and also the most common cancer in our country. The aim of this study is to describe the various histological types of primary epithelial breast cancer seen in our practice.
Material and Method: The histological database of our department 1997 and 2001 were used for the study.
Results**:** A total of 145 cases of histologically diagnosed breast cancer were seen with. age range of 20-85 years.(mean 50.5 +/- 12.5years)**.** The peak age group is 50-59 years.18.8% of cases occurred between 30-39years.The male to female ratio is 1:143 and the right breast was more affected .Majority of the patients have tumour size of 3cm .Infiltrating ductal carcinoma (NOS) was the most predominant histological type (82.8%). Of the 73 cases with nuclear grading, 80.8% were high grade tumours with lymphovascular invasion at diagnosis. Most of the cases elicit inflammatory response with a predominant diffuse pattern. 35 cases had accompanied lymph nodes with 30 showing metastasis.
Conclusion; Breast cancer in our women is of high grade and tends to have an aggressive outlook from the onset. The high percentage in young adults is worrisome and the late presentation needs urgent attention.

P50

Analysis of the mononuclear inflammatory cell infiltrate in the normal breast, benign proliferative breast disease, in situ and infiltrating ductal Breast carcinomas: Preliminary observations

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Background: Mammary carcinogenesis is a multistep process entailing transitions from normal breast→ benign proliferative breast disease (ductal hyperplasia) → duct carcinoma in situ →infiltrating duct carcinoma. We hypothesized that these transitions are associated with alterations in the mononuclear inflammatory cell infiltrate. Materials and methods: A total of 53 mastectomy specimens, each entailing normal breast, benign proliferative breast disease, duct carcinoma in situ and infiltrating duct carcinoma were evaluated for mononuclear inflammatory cell infiltrate using immunohistological methods and monoclonal antibodies including: CD20, CD68, CD3, and Granzyme B, for B cells, histiocytes, T cells, and cytotoxic T cells. Results: Transitions from normal breast to the subsequent lesional steps (normal skin vs. benign proliferative breast disease vs. duct carcinoma in situ vs. infiltrating duct carcinoma was associated with statistically significantly ($p<0.01$) increased density of mononuclear inflammatory cell infiltrate at the parenchyma (3.2 ±1.0 vs. 26.4±7.8 vs. 33.6±7.9 vs. 39.1±4.7 for CD20 + B cells; 2.8 ±1.0 vs. 81.5 ±14.0 vs. 84.0 ± 14.9 vs.103.7± 3.9 for CD3; 1.3±2.0 vs. 3.8±4.0 vs. 12.7±23 vs. 22.1± 25 for CD68 + macrophages; 2.0±1.0 vs. 58.3± 5.0 vs. 60.0±10 vs. 74.1± 28 for Granzyme B + cytototoxic T cells) and stroma: (0.7±1.0 vs. 3.0±5.0 vs. 13.3± 20 vs. 16.7±30 for CD20 + B cells; 1.0± 2.0.6 vs. 4.0±2.5 vs. 16.7±5.0 vs. 21.7±15 for CD68 + macrophages; 1.4± 0.6 vs. 4.2± 1.2 vs. 46.6± 16.7 vs. 77.0± 5.0 for CD3 + cells and 0.0±0.0 vs. 0.5± 1.0 vs. 0.7±1.0 vs. 0.7±1.0for Granzyme B + cytototoxic T cells) . Conclusions: Our preliminary findings of an increased mononuclear inflammatory cell infiltrate during mammary carcinogenesis may reflect either non-specific or specific immunological processes

P51

Prognostic significance of tumour-infiltrating lymphocyte density in breast cancer H&E sections

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Background: The ability of immune-cell responses to prevent metastatic cancer progression remains controversial. We investigated the predictive value of total tumour infiltrating lymphocyte (TIL) density in a case-control study of 88 breast cancers which metastasized and 176 control cancers which did not over 5-10 years of follow-up.
Methods: Eighty-eight breast cancers diagnosed during 1996-2000 which later metastasized to remote sites were matched by size, grade, ER, lymph node and patient menopausal status with two control cancers which did not metastasise. In all primary cancers the number of TIL was counted on H&E sections in 10 hpf at the infiltrating margin.
Results: TIL density was highly variable in primary breast cancers irrespective of whether or not they later established metastatic growth at distant sites. A scatter plot of TIL density in 'cases' versus the mean TIL density for the two control cancers gave no indication of correlation (95% CI of Pearson correlation coefficient -0.15-0.26) and non-parametric statistical comparison of both groups showed no significant difference ($P>0.05$).
Conclusions: Total H&E TIL density has no prognostic value in breast cancer. This is not, perhaps, surprising given the many participating cell types and the complexity of their possible roles in tumour immune responses. TIL may include cells (e.g. T-reg cells) with immuno-suppressive and tumour-promoting functions as well as cells with anti-tumour activity.

P52

Validation of a novel brightfield in situ hybridisation technique for routine HER2 testing in breast cancer.

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For the past 12 months we have been using a frontline brightfield ISH gene test for all newly diagnosed breast cancer cases in order to assess the HER2 status for Herceptin eligibility. Chromogenic in situ hybridisation (CISH) was compared to immunohistochemistry and FISH in order to validate the technique (Di Palma 2007). Whilst CISH is a simple and robust technique and it can be partly automated it is still a reasonably labour intensive technique. Here we report a new-to-the-market ISH technique which is fully automated. Silver in situ hybridisation (SISH) uses the process of reducing the hybridised silver ions to metallic silver atoms in order to visualise the bound HER2 probe. We tested 50 breast cancer cases using SISH and compared the results to previously obtained CISH data. It was noted that the nuclear detail was very well-preserved, the hybridised signals were distinct and clearly visualised within the nucleus and the background was very clean making interpretation of the data straightforward. A detailed interpretation guide of the SISH staining added to the ease of interpretation. There was 100% concordance of the data using the two techniques. It was noted in this preliminary study that only 6% samples required a repeat hybridisation with SISH compared with 20% in preliminary studies using manual CISH. Whilst the consumables for SISH are approximately twice the cost of those for CISH, the limited staff time involved in performing SISH makes the cost per test very comparable

P53

High rate of HercepTest 3+ tumours with normal gene copy number as assessed by CISH and FISH

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By convention breast cancers graded 3+ by IHC tests are considered to have HER2 gene amplification and consequently patients are offered trastuzumab therapy on this basis. However, false positive results with the approved IHC tests have been reported on several previous occasions. The inconsistency of the IHC assay may be due to any or a combination of a number of variables inherent in the process. Variables include adequacy of tissue fixation and sectioning, antigen retrieval, reagents and controls and, post-analysis, inter-observer variation and interpretation.
During a validation procedure for the introduction of a CISH assay for HER2 gene amplification in our laboratory, 60 cases of invasive ductal carcinoma with a HercepTest score of 3+, as reported by regional reference laboratories, were identified. Nineteen (32%) of these cases were found by CISH to have no amplification of the HER2 gene. This finding was confirmed in each case by use of FISH performed externally.
Therefore we suggest that a gene-based assay should be used routinely in order to more accurately identify those patients most likely to require and benefit from trastuzumab. This has the dual benefit of being more effective for both patient health and targeting the use of limited resources.

P54

Abnormal Fibrin in Human Atherosclerotic Plaque Macrophages: Absence of Plasmin Action

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The majority of human plaque foamy macrophages contain fibrin as well as lipid. In a series of 40 plaques from carotid artery, coronary artery and aorta, foamy macrophages contained fibrin detected by specific immunostaining directed against the sequence located in fibrin fragment E in all lesions except for one fatty streak. Macrophages in inflammatory lesions such as an abscess contain phagocytosed fibrin with early and late plasmin cleavage sites detectable with two antibodies targeting adjacent sequences anti- 15-27 and anti-γ 54-62. Fibrin itself is unstained. 36 of 40 plaques contain foamy macrophage fibrin that is only weakly positive or negative with these antibodies. Strong positive immunostaining is obtained however, after brief exposure to plasmin digestion (plasmin 128 mg/ml for 15 min).

Therefore there is a failure of exposure of fibrin within foamy macrophages to plasmin activity, despite the adhesion of plasminogen to fibrin. It is proposed that this reveals a mechanism that slows clearance of surface-derived fibrin after thrombotic events. Further, it is proposed that this is why the human plaque does not "heal", and that atherogenesis is driven by a failure of fibrinolysis.

P55

Modelling the abnormal fibrin of the human plaque: the fibrin filtration hypothesis of human atherogenesis

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What mechanism underlies the apparent failure of plasmin fibrinolysis in the human plaque foamy macrophage, despite the presence of fibrin-bound plasminogen, and where does it occur? These questions were addressed by a series of immunostaining experiments following exposure of cultured monocytes to LDL and fibrin particles. Phagocytosis of fibrin particles and LDL results in normal positivity of fibrin using the specific whole antifibrin antibody and antibodies to plasmin cleavage sites. This occurs at the cell surface before phagocytosis. Surface location protects plasminogen activator and plasmin from plasma antiproteases. The plasmin-dependent immunostaining is absent, however, if the fibrin particles and LDL are gently admixed before phagocytosis, reproducing the plaque foamy macrophage fibrin. Such admixture seems unlikely to occur within the human arterial wall. Exposure of the sieve of fibrin mesh in thrombus to high pressure filtration of plasma proteins and lipid is known experimentally to result in lipid accumulation.

This provokes the thought that coating of fibrin by lipid slows later removal and leads to atherosclerosis. Atherosclerosis is therefore seen in arteries and vein grafts not veins, exacerbated by hypertension, hyperlipidaemia, reduced plasma fibrinolytic capacity, and high fibrinogen levels.

This is the fibrin filtration hypothesis of atherogenesis.

P56

Comparison of cytology and histology in the diagnosis of bronchial carcinoma

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The diagnosis of bronchial carcinoma can be made by cytological and more accurately by histological investigations. A number of physicians use cytological investigations such as bronchial washing as a screening tool for the disease. Thus the aim of our study was to evaluate the efficiency of cytological findings compared to histological ones.

We audited cytological and histological results over a period of one year. The cytological investigations included were both bronchial washing and brushing. Histology was assessed from bronchoscopic biopsy.

A comparison between cytological and histological findings was carried out on 96 pairs of results. There was a negative cytological finding with a positive biopsy of carcinoma in 33.3% of patients. A positive cytological result with no evidence of carcinoma on biopsy was found in 2.1% of patients.

Our audit showed that there is a discrepancy in the results of cytological and histological investigations in the diagnosis of bronchial carcinoma. Therefore we recommend clinicians to perform both sets of investigation on all patients.

P57

I/D polymorphism of ACE and susceptibility to ARDS after pneumonectomy- a pilot study

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Acute Respiratory Distress Syndrome (ARDS) causes significant morbidity and mortality after pneumonectomy. Only a minority of patients develop ARDS despite commonly occurring risk factors so genetic predisposition may play a role. Possession of the D (deletion) allele at the insertion/ deletion (I/D) polymorphism of the angiotensin-converting enzyme (ACE) gene has been associated with increased risk of, and worse outcome in ARDS after cardiac surgery. We hypothesised that a similar pattern may occur after pneumonectomy.

DNA extracted from paraffin wax-embedded lymph node material from 50 patients who underwent pneumonectomy was genotyped for the I/D ACE polymorphism. These cases comprised six patients who developed ARDS after pneumonectomy and 41 age and sex matched controls. 191 healthy blood donors who had been genotyped in an earlier study provided a further control group.

Genotype frequencies in our control group were not significantly different from the larger healthy control group. There was no difference in the frequency of the D allele ($\chi 2 = 1.003$ $p = 0.316$) or DD genotype ($\chi 2 = 1.733$ $p = 0.420$) in patients with ARDS and our control group.

We demonstrated no association between the I/D polymorphism and the development of ARDS post-pneumonectomy but this study may have been underpowered to do so.

P58

Tissue Microarray Quality Control Prior to their Use – Results from an International Interobserver Study

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Hundreds of publications have been published using tissue microarrays (TMAs) for investigating protein expression. We think that quality control, e.g. confirmation of the absence or presence of tumour cells in a particular core, is necessary before interpreting immunohistochemical stainings. The aim of this study was to investigate interobserver agreement in determining the presence or absence of tumour cells in presumed gastric cancer cores.

A total of 581 tissue cores were reviewed by 10 pathologists which included pathologists with different experience levels from four countries. Each pathologist independently evaluated scanned images of H+E stained slides from TMAs and classified individual cores as 'tumour cells present', 'no tumour cells' or 'inadequate'.

Overall, good interobserver agreement was observed using Bland-Altman plots and Kappa statistics (kappa median 0.73, range 0.33 – 0.88). However, a strong association between interobserver agreement and level of pathology experience was seen. Importantly, even the four most experienced observers still disagreed amongst each other in 12.6% of cores originating from 33 cases.

Our data demonstrates, that in order to minimise misleading results, particularly when assessing cores presumed to contain cancer, TMAs require quality control which should ideally be undertaken by two independent senior pathologists to minimise problems due to interobserver variation. We would recommend eliminating disputed cores from analyses.

P59

Abstract withdrawn

P60

Abstract withdrawn

P61

A Novel Approach in the Analysis of ZAP 70 Status and Chromosomal Abnormalities in Chronic Lymphocytic Leukaemia

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Chronic lymphocytic leukaemia (CLL) is a B-cell lymphoproliferative disease. It is the most common leukaemia in the western world. The use of ZAP 70 and chromosomal abnormalities as prognostic markers assists with improved management of patients. ZAP 70 expression correlates with VH gene mutational status, subdividing patients into good or standard/poor risk groups.

We developed methods for quantifying ZAP 70 expression by Immunohistochemistry and for identifying chromosomal abnormalities using fluorescent in situ hybridization (FISH).

Mononuclear cells were isolated from peripheral blood samples , half were resuspended in plasma and clotted using thrombin. The resultant clot was formalin fixed and paraffin embedded.

Immunohistochemistry on sections from the clot were analysed for the expression of CD3, CD20, CD23 and ZAP70. The remaining cells were fixed in methanol acetic acid (MAA) and assessed for the deletion of 13q14.3, 13q43,11q22.3 and/or 17p13.1 and trisomy 12 by FISH.

Analysing samples in this way allowed us to establish the degree of ZAP 70 expression in B CLL and to identify cytogenetic prognostic markers.

P62

What Are the Baseline Signal Levels for the Diagnosis of Translocations by Fluorescence in-situ Hybridisation in Paraffin Embedded Diagnostic Biopsies?

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Interphase fluorescence in-situ hybridisation (FISH) is increasingly used to identify chromosomal translocations in the diagnosis of lymphomas. False positive results may occur due to the identification of fusion and break-apart signals in paraffin embedded reactive tissues as a consequence of random co-localisation of chromosomes or truncation of signals due to the thinness of sections. It is therefore essential to establish baseline patterns of FISH signals in paraffin embedded reactive material to avoid a false positive diagnosis.

We have carried out interphase FISH on 1um sections of 10 paraffin embedded reactive lymph nodes using the dual fusion probes t(14:18), t(8:14), t(11:14) and t(11:18) in addition to the breakapart probes for translocations involving the bcl6, C-Myc and MALT1 loci. The number of fusion signals identified using the dual fusion probes was 6-22 per 100 nuclei, the highest number being recorded for the t(11;14) probe set. Between 1 and 8 breakapart signals were identified per 100 cells using the various breakapart probes, the highest count occurring with the bcl6 probe set.

Taking account of these results could prevent samples being wrongly assigned as positive and in many cases could have significant implications for diagnosis and management of the patient.

P63

WT1 behaves as an oncogene in glioblastoma.

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The WT1 gene encodes for a zinc finger transcription factor, the mutated form of which has been associated with Wilms' tumour development. In these instances mutation and loss of wild type allele (two hit model) is required for tumour formation. This has led to the classification of WT1 as a tumour suppressor gene. However recent studies have shown that wild type WT1 is expressed at high levels in certain adult malignancies such as breast and colorectal carcinoma and in glioblastoma. The tumour suppressor PTEN has a WT1/Egr1 recognition sequence in its promotor. We investigated whether WT1 binding to this sequence may down regulate PTEN expression and hence increase activity of the Akt pathway. In A172 glioblastoma cells WT1 expression is high, PTEN suppressed and the Akt pathway active. WT1 suppression by siRNA led to a specific gain of PTEN expression detected by western blotting. Furthermore increased expression of WT1 by LIF treatment lead to a reduction in PTEN expression. This was accompanied by increased activity of the kinase members of the Akt pathway demonstrated by the levels of the phosphorylated form of Akt and S6kinase. Our results suggest that WT1 normally down regulates the expression of PTEN and therefore promotes activity of the Akt pathway. This new evidence suggests that by down regulating PTEN, WT1 may behave as an oncogene in adult tumours.

P64

Serial Analysis of Gene Expression of Primary Material from Hodgkin Lymphoma

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Classical Hodgkin lymphoma (cHL) is one of the commonest lymphomas in the Western world. The aetiology of cHL is not completely understood largely because the malignant cells, the Hodgkin and Reed-Sternberg (HRS) cells constitute only ~1% of the tumour mass, and this has hindered their characterisation. Epstein-Barr virus (EBV) is causally associated with a proportion of cHL cases and epidemiological data suggest that an infectious agent may be involved in the remaining cases, although this agent remains elusive. The generation of gene expression libraries from primary HRS cells may enable identification of genes involved in disease pathogenesis. The primary aim of this study was to identify genes that are differentially expressed in HRS cells and their 'normal' counterpart. Serial Analysis of Gene Expression (SAGE) libraries were generated from CD30-positive cells enriched from an EBV-positive and EBV-negative case of cHL, as well as CD77-positive cells from a reactive lymph node. Among the genes that had increased expression in the cHL cases compared with the "normal" counterpart were Protein Kinase C eta and Galectin 2. Although these data are preliminary, further investigation of cHL cases is warranted to determine whether these genes are involved in the pathogenesis of cHL.

P65

Mutations of NFKBIA Are Frequent in Hodgkin and Reed-Sternberg Cells in Classical Hodgkin Lymphoma

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Constitutive activation of NF-κB is characteristic of the malignant Hodgkin and Reed-Sternberg (HRS) cells in classical Hodgkin lymphoma (cHL). We and others have described inactivating mutations of the NFKBIA gene with subsequent loss of the functional inhibitor protein IκBα providing a possible mechanism for deregulation of NF-κB activity. The aim of this study was to determine the frequency and functional relevance of these mutations as this has implications for both the biology and treatment of cHL. Single HRS cells were isolated from cytospins of 20 cHL cases using laser microdissection and the entire coding sequence of NFKBIA was PCR-amplified and sequenced. Abnormalities of NFKBIA including point mutations, small deletions and insertions were found in all cases analysed; however, clonal bi-allelic inactivating mutations were detected in only one case. Mono-allelic deleterious mutations were present in a significant minority of cases but were not always clonal. The significance of these mutations is unclear but these results suggest they are secondary events. The results therefore suggest that targeting the NF-κB pathway may have therapeutic potential in cHL.

P66

Mouse Mammary Gland Involution Defines Pathways to Predict Breast Cancer Metastasis

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Background: Mouse mammary gland involution resembles a wound healing response with suppressed inflammation. Wound healing and inflammation are also associated with tumour development, and a 'wound-healing' gene expression signature can predict metastasis formation and survival. Recent studies have shown that an involuting mammary gland stroma can promote metastasis. We hypothesised that gene expression signatures from an involuting mouse mammary gland may provide new insights into stromal-epithelial interactions during breast cancer progression.
Methods / Principal Findings: Gene sets with differential expression and those with different temporal expression patterns during the first four days of mouse mammary gland involution were identified using oligonucleotide-microarrays. The human orthologue gene sets were used to cluster the NKI 295 breast cancer dataset using the HOPACH method. Metastasis formation and survival was measured for each cancer cluster. MAPPFinder analysis specified over-representation of biological pathways associated with each gene set. Genes differentially regulated at day 3 of involution and those with prolonged expression throughout the first four days of involution identified pairs of breast cancer clusters with low and high metastatic activity. Similar results were obtained with probe sets present in both signatures. This prognostic ability was independent of other clinical parameters or previously identified prognostic gene signatures. Genes associated with copper ion homeostasis and with HIF-1 promoter binding sites were the most over-represented, linking our signatures to hypoxia and angiogenesis.
Conclusions: Gene signatures from an involuting mouse mammary gland can identify breast cancers with high metastatic potential and poor survival. Our results elucidate the biological processes that occur during mammary gland involution, and which may be critical in promoting breast cancer metastasis.

P67

Erythropoietin Receptor Expression in Non-Small Cell Lung Carcinoma – a Question of Antibody Specificity

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Immunohistochemical studies on formalin-fixed, paraffin-embedded (FFPE) tissue utilising polyclonal antibodies form the cornerstone of many reports claiming to demonstrate erythropoietin receptor (EPOR) expression in malignant tissue. Recently, Elliott et al. (Blood 2006;107:1892–1895) reported that the antibodies commonly used to detect EPOR expression also detect non-EPOR proteins, and that their binding to EPOR was severely abrogated by two synthetic peptides based on the sequence of heat shock protein (HSP) 70, HSP70-2, and HSP70-5. We have investigated the specificity of the C20 antibody for detecting EPOR expression in non-small cell lung carcinoma (NSCLC) utilising tissue microarrays. A total of 34 cases were available for study. Antibody absorbed with peptide resulted in marked suppression of cytoplasmic staining compared with nonabsorbed antibody. Four tumours that initially showed a membranous pattern of staining retained this pattern with absorbed antibody. Positive membranous immunoreactivity was also observed in 6 of 30 tumours that originally showed a predominantly cytoplasmic pattern of staining. Using the C20 antibody for Western blots, we detected three main bands, at 100, 66, and 59 kDa. Preincubation with either peptide caused abolition of the 66 kDa band, which contains non-EPOR sequences including heat shock peptides. These results call into question the significance of previous immunohistochemical studies of EPOR expression in malignancy and emphasise the need for more specific anti-EPOR antibodies to define the true extent of EPOR expression in neoplastic tissue.

P68

Characterization of the Regulatory Landscape at the SCL (TAL1) Locus using Genomic Microarrays

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Understanding the events which occur as stem cells differentiate into committed cell lineages is a fundamental issue in cell biology for both normal and disease states. It has been shown that the SCL transcription factor, also known as TAL1, is central to the mechanisms whereby pluripotent stem cells differentiate into haematopoietic stem cells (HSCs) that ultimately give rise to the various blood lineages. To further understand the biology of SCL and the key regulatory interactions it is involved in during blood development, the powerful techniques of genomic microarray resources in combination with chromatin immunoprecipitation (ChIP-chip) were used. High resolution (400-500 bp) genomic tiling path microarrays spanning the human and mouse SCL loci were constructed. ChIP-chip experiments using a large battery of antibodies raised against various histone modifications, transcription factors, and other regulatory proteins were performed in a number of SCL expressing and non-expressing cell lines. Based on the ChIP-chip data that was generated, relationships between transcriptional regulatory events and the underlying DNA sequence were studied across the SCL locus. The results obtained will greatly accelerate our understanding of important biological events which are essential for the expression of SCL, as well as provide insights into mechanisms of mammalian gene regulation likely to be widely applicable.

P69

Identification of Target Genes of an Erythroid Transcription Factor Complex Containing SCL (TAL1)

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The SCL (TAL1) gene, originally identified by chromosomal translocations associated with T-cell acute lymphocytic leukaemia (T-ALL), encodes a key transcription factor (TF) which is essential for haematopoietic differentiation. The SCL protein forms a multi-protein complex during erythroid development with other TFs (GATA1, E2A, LDB1, and LMO2) which binds to a sequence-specific motif to regulate the expression of the genes. We have used two complementary approaches to identify novel target genes regulated by this TF complex during erythroid development. In the first approach, we have transfected short interfering RNAs (siRNAs) into the K562 cell line to knockdown the TFs of the erythroid complex. The consequences of the knockdown at the level of gene expression were observed using Affymetrix GeneChips. In the second approach, chromatin immunoprecipitation (ChIP) was performed for each member of the complex in the K562 cell line and the ChIP material hybridised to a human transcription factor promoter microarray in a ChIP-on-chip approach. A number of novel target genes for the SCL erythroid complex have been identified and verified independently using both approaches. We have evidence that members of the erythroid complex are involved in auto-regulation, thus demonstrating that the transcriptional programmes involving this TF complex are tightly controlled during erythroid development.

P70

Expression Profiling of Cancer Genes from a Prognostic Gene Signature by Immunocytochemistry

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Large-scale mRNA profiling of cancer has yielded many prognostic signatures, including Glinsky's 11 genes predictive of metastasis: 3 down-regulated (ANKG, CES1, FGFR2) and 8 up-regulated (BUB1, CYCB1, GBX2, HCFC1, HEC1, Ki-67, RNF2, USP22). Because such profiles are based on tissue extracts, the cellular location of individual genes is unknown. Our aim was to localise these 11 genes, using immunohistochemistry and tissue microarrays containing 50 normal tissues and 42 cancers.

Antibodies were optimised for 9 genes (not HCFC1 or HEC1). Comparing epithelial, connective, lymphoid and vascular tissues, the 3 "prognostic-when-down-regulated" genes were expressed most highly in epithelium, as was BUB1. Ki67 was highest in lymphoid tissue while CYCB1, GBX2, RNF2 and USP22 were expressed similarly across tissue types, except that vascular tissues lacked Ki-67 and CYCB1. Comparing normal tissues and cancers, "prognostic-when-down-regulated" genes, especially CES1, showed weaker staining in cancers. Of the 6 "prognostic-when-up-regulated" genes, Ki67 and RNF2 were markedly increased in cancers, GBX2 was slightly reduced in cancers and the rest were similarly expressed. All 9 proteins were expressed in one normal tissue (endometrium) and in 11 cancers, including colonic adenocarcinoma, mesothelioma and teratoma.

Translation of mRNA-derived gene signatures to immunohisto-chemical panels is thus achievable: the availability of robust antibodies is crucial. Such studies provide novel information on the cancer-cell, stromal or inflammatory-cell location of individual expressed genes and would enable swift clinical implementation of gene panels if their prognostic value were confirmed.

P71

Anillin over expression in neoplasia is associated with low level amplification of the ANLN locus and anillin protein expression activates the HIF1alpha transcriptome via SEPT9

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It has been shown that anillin mRNA expression is increased in diverse human tumours compared with normal tissue counterparts. Moreover there is a progressive increase in anillin mRNA during tumour evolution (Hall *et al* Clinical Cancer Research 2005; 11:6780-6). This poses 2 key questions: (1) what is the mechanism by which anillin over-expression occurs and (2) what are the functional consequences of anillin over-expression. One possibility is that the increased expression of anillin is due to amplification of the ANLN locus on 7p14-15. Initial support for this hypothesis was provided by consideration of comparative genomic hybridisation data in a series of breast cancer cases where in 44 consecutive grade 2/3 invasive carcinomas 9 (~20%) showed amplification of 7p. To provide further evidence for this notion probes for the ANLN locus were isolated and used in FISH experiments. A range of tumour cell lines were examined and most show low level amplification of the ANLN locus. For example, in MCF7, most cells were triploid for the ANLN locus while in Hela tetraploidy and higher order amplification were seen. To address the functional consequences of ANLN over expression we examined the effect on SEPT9 expression of altering ANLN protein expression. We find that over-expression of ANLN leads to perturbed SEPT9 protein expression with increased levels of the higher molecular weight isoforms (SEPT9_v1, 2 & 3). It is of note that these isoforms bind and stabilise HIF1alpha and promote the expression of the HIF1alpha transcriptome. This may provide a mechanism for ANLN to promote an aggressive clinical behaviour.

P72

Is Histopathology of value in Examination of Discectomy Specimens? A 'Disc'ussion

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Aims: We aimed to audit the necessity of diagnostic pathology in surgically resected intervertebral disc specimens and to ascertain the distribution of histopathologic features in the same.
Materials and Methods: All discectomy specimens reported by Neuropathology between the years 2000 and 2005 were retrieved.
Results: Of the 45 discectomy specimens (26 males and 19 female), the peak incidence of symptomatic disc prolapse was in the 5th decade. Maximum numbers occurred at L5/S1. Presence of disc tissue was confirmed in 44/45 cases (98%). A mixture of tissue other than disc material, was seen in 17/45 cases (38%). Inflammation was present in 7/45 cases (15%), vascularisation in 7/45 cases (15%) and fibrosis in 3/45(6%) cases. Other diagnosis included rheumatoid arthritis.
Conclusions: It is necessary to histologically examine disc tissue after resection for confirmation of disc tissue and to exclude other diagnosis. In the absence of disc material in the first instance, the possibility of recurrence must be considered. A range of pathology including tumour may be identified. It may also be of medicolegal relevance in cases of recurrent symptomatology where histological confirmation of disc material was not possible.

P73

A Virtual Slide Library for Histopathology

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Virtual slides allow the creation of slide libraries which have many advantages over conventional glass slide collections. They can be indexed and searched in many ways, they do not fade or break, they can be accessed from any computer with a connection to the internet, and can be easily integrated in teaching material.
An online virtual slide library has been created with over 3,000 virtual slides covering all areas of diagnostic histopathology. The slides have been scanned at 40x magnification. The library includes examples of immunohistochemical staining as well as conventional histochemical stains (for example liver cases also have associated histochemical slides available).
Metadata about each case including clinical details, diagnosis and discussion points are recorded. Every case has been coded by a consultant pathologist using MeSH (Medical Subject Heading) codes. Because these codes have a hierarchical structure, searches may be generic ("gastrointestinal neoplasia") or specific ("gastrointestinal stromal tumour").
It is hoped that the slide library will be a useful resource for pathologists in training and in practice. The slide library will be freely available online from July 2007 and can be accessed at www.virtualpathology.leeds.ac.uk.

P74

Audit of the Thames Histopathology Training School Year 1 Day Release Teaching Programme 2006-2007

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One of the aims of the Thames Histopathology Training School was 'to design innovative teaching methods'. In addition to the block teaching weeks a Day Release Teaching Programme has been established. Mapping broadly to the RCPath curriculum for stage A of specialist training, one day every other week is dedicated to learning about a specific system.

The Thames School quality assures its work-based training but no review of the Day Release Teaching Programme had been undertaken. A trainee questionnaire assessed the trainees' perception of the day release teaching.

Preliminary analysis shows that trainees' motivation to learn more about the subject varies significantly between training days and teachers. This tends to relate to the degree of interaction.

The teaching days awarded overall high grades showed high values in assessment of previous knowledge of trainees practical and theoretical relevance interactive teaching methods (particularly multi-headed slide sessions) and did not attempt to cover too much information in the limited timeframe.

The authors furthermore propose that learning would be improved by trainees writing reflective notes following each teaching day. The Thames School intends to provide feedback to the trainers and to re-audit the Programme next year.

P75

Utility of Database Server Software for Small Audit and Research Projects

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Many research projects use spreadsheet software to collect data for subsequent statistical analysis. It is not uncommon for multiple copies of the spreadsheets to be made by collaborators who must then merge their data for analysis. Data is also often passed on in this format on to other researchers. This has significant risk for data provenance, confidentiality, and security; it may also render updating data more difficult. One solution to these problems is for multiple users to access a database server; however the perception is that they are expensive, difficult to program and require extensive IT support; limiting their use to large funded multi-centre studies.

We have successfully used a commercially available database server - FileMaker Server - for research projects and audits in prostate cancer and renal pathology. This combines the ease of use of a desktop application with the advantages of a server database. The server hosts a single data file for each topic which consists of several related tables that can be used for many projects. Several researchers can enter data simultaneously from any site with an Internet connection (even at home); the server handles security and backup. Statistical programs (eg SPSS) can regularly extract data using a macro- allowing easy interim analysis and assuring that the data analysed is the most current. No other copies are held easing compliance with legal and ethical responsibilities.

P76

Liver biopsy needle size: Does it matter? A pilot study

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Background: Adequate biopsy size is important to avoid understaging chronic liver disease; recent evidence supports a minimum of 11 portal tracts should be present. We audited the biopsy specimens during a transition from 18G to the wider 16G needle.
Materials & Methods: This was a blinded retrospective analysis of 40 ultrasound guided liver biopsy specimens for chronic liver disease. Objective assessment of length, width and area was performed by scanning the H&E stained slides with a calibrated virtual slide scanner, and measuring the biopsy with virtual slide viewing software. The number of portal tracts per section was counted by one pathologist .
Results: 18G and 16G needles were used in 22 and 18 cases respectively. 16G needles yielded wider sections (0.96mm v. 0.85mm, p=0.037), although the length and area of tissue were not significantly different (p=0.716). The percentage of biopsies with >10 portal tracts increased from 23% to 44%.
Conclusions: The 16G needle resulted in significantly wider biopsy sections, and almost doubled the percentage of biopsies with>10 portal tracts. However, a larger needle caliber/different biopsy instrument would be required to achieve the recommended standard for these biopsies.

P77

An assessment of the need for examination of multiple levels from endoscopic biopsies

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Endoscopic biopsies represent a substantial proportion of the workload in most histopathology laboratories. It has been routine practice to examine multiple levels form such biopsies although this practice is not supported by any substantial evidence. Following an initial study, routine cutting of levels in our department was stopped and levels were only cut after evaluation of the initial section.
Over a period of five months the proportion of blocks from which levels have been cut has been 11.2% (429/3828). Monthly proportions range from 10.4% to 12.8%. A user survey conducted during month four of the study did not identify any problems related to endoscopic biopsies, there have been no complaints from the relevant multi-disciplinary teams and no critical incidents have been reported. Levels are most often requested from oesophageal and colonic biopsies in comparison to gastric and duodenal biopsies. The estimated time saved by technical staff is 42.7 hours/month. The time saved by medical staff has not been formally calculated.
The results support the assertion that routine examination of multiple levels from endoscopic biopsies is not necessary.

P78

Autopsy reports: how can we improve training and assessment?

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The decline in hospital consented autopsies has reduced the opportunity for trainees to gain experience of complex medical cases and the associated challenges of clinicopathological correlation and formulation of the cause of death.
The aim of the study was to assess the skills of a group of trainees (n=19) in summarising findings, providing a clinicopathological correlation and giving a cause of death in five autopsy cases. Full text reports including histology as appropriate were provided and the trainees were asked to give a summary of findings, a clinicopathological correlation and cause of death. Each component was scored by three assessors (total assessments per case = 57) and the scores were converted into grades A-D. (A – clear pass, B – bare pass, C – bare fail, D – clear fail). The grades for each case are shown in the table below.

	Case1	Case 2	Case 3	Case 4	Case 5
A	16	17	14	16	7
B	13	9	17	7	9
C	11	9	15	18	8
D	17	22	11	16	33

The results suggest that case 5 was the most challenging. Considerable interobserver variation was noted between assessors but agreement was best in categories A and D.
Further development of this approach to autopsy training would help to address current perceived deficiencies.

P79

Biomedical Scientist role extension in histopathology – perceptions of the workforce

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Biomedical Scientists (BMS) role extension is a potential answer to increasing workload in histopathology. This study aimed to investigate how participating BMS and other laboratory staff perceived role extension in terms of personal and professional benefit as well as usefulness to the service. A questionnaire using standard Likert scales was circulated to staff members to determine views about BMSs and their work. Opportunity was given for free text comments. The questionnaire was re-circulated a year later. The two data points (n = 62, 74) were analysed and compared. The study shows that histopathologists and BMSs respond positively to role extension. Value appeared to accrue to BMSs, pathologists, other staff groups and patients. Perceived benefits outweighed apparent potential detriments. Themes emerged concerning the development of role extension and how it should be progressed including comments for and against the development of an advanced practitioner grade in histopathology. In the department studied, there was consensus that BMS role extension is valuable and worthwhile. It was seen as feasible, acceptable, desirable and contributory to effective redesign of histopathology services. This study gives insight into attendant issues of role extension changing working practice in histopathology and may be useful to departments planning such development.

P80

Pathology Trainees' Views on Autopsy Following Introduction of the Human Tissue Acts

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With the introduction of recent legislation it is incumbent on the pathologist to ensure appropriate information has been provided in obtaining authorisation for autopsy. In Scotland, to assist this process, national autopsy information and authorisation paperwork has been introduced. In light of these changes we ascertained the views of histopathology trainees to autopsy.

Questionnaires were distributed to all trainees attending a training symposium in November 2006. Fifty-seven (100%) responses were received representing the views of trainees from FY2 to year 5 SpR and from 5 training centres.

Forty-five percent had not read the relevant Human Tissue Act though 79% of Scottish trainees had read the national authorisation documents. Regarding authorisation, 73% felt clinicians should seek authorisation with 9% of the view authorisation should be the responsibility of the pathologist. Hospital autopsy experience was reported as limited with few trainees achieving the RCPath recommendations though medico-legal cases appeared to be supplementing experience. Despite this only 35% expressed a desire to perform more autopsies with 48% seeking to perform fewer or none.

Overall, though many of the trainees questioned may not have read the relevant legislation, the majority are of the opinion clinicians should continue to seek consent for autopsy.

P81

The Correlation Between British Neuropathological Society (BNS) Minimal Data Set with the Leeds General Infirmary (LGI) Neuropathology Surgical Reports On CNS Tumours

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The BNS minimum data set are intended to assist histopathologists in the provision of the core data that should be included in histopathology reports of the central nervous system tumours. Standardized histopathological data are important for accurate classification and grading of tumours, and necessary for the planning of appropriate treatment for the patient. Consistency of histopathology reporting is important in communication between cancer centres. In this audit, we reviewed 100 histology reports of CNS tumours, which were reported at LGI between 21stJuly-30thOctober 2006. The reports were compared to the BNS minimum data set for reporting of CNS tumours. LGI reports provided a very good core data, such as patient details, hospital number and NHS number, in addition to date of request and reporting, the report number, the names of the pathologists and the WHO grade. However, the reports had poor records of specimen type (only 10% of reports included the type of specimen). The SNOMED code was included in 1% of reports, however; it is accessible on the CoPath software. We conclude that the main areas of weakness in the reports of LGI are the SNOMED code and specimen type. These areas could be targeted in future reports.

P82

Rapid Fixation: Does it Affect Breast Cancer Grading?

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Breast cancer grading is an important factor in determining post-operative management, and adequate fixation is essential for optimal histological assessment. The NHSBSP/RCPath guidelines recommend that mastectomy specimens are received fresh and the tumour incised prior to fixation. In this retrospective study we report the effect on grading of introducing rapid transfer of fresh specimens from a distant hospital site for incision prior to fixation. Tumour grading was assessed by 5 pathologists on 25 tumours in mastectomies before, and 19 tumours after, introduction of the rapid fixation protocol. Grading was performed blind to the treatment group, using the standard grading protocol. The tubule score, mitotic score and overall grade were significantly higher in the rapid fixation tumour group ($p<0.001$). The consistency of grading between pathologists was examined and this was poorer in the optimally fixed group; this finding is explored. The positive effect of fixation on the observed versus the expected ratio of grade 1, 2 and 3 tumours is also reported.
This study confirms the effect of rapid fixation on optimising breast cancer grading, and underlines the importance of rapid specimen transfer and handling, if pathology services are centralised to cover multiple distant operating sites.

P83

Audit of Quality of Reporting in Barrett's Oesophagus

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Histopathologists play a central role in the diagnosis of Barrett's oesophagus, an established risk factor for the development of oesophageal adenocarcinoma. In August 2005, the British Society of Gastroenterology (BSG) published its "Guidelines for the diagnosis and management of Barrett's columnar lined oesophagus". This provided recommendations for the histological categorisation of diagnostic biopsies.

This retrospective audit aimed to assess quality of reporting in cases of Barrett's oesophagus issued by histopathologists working within two teaching hospitals, and to assess whether there had been any change in reporting practices following publication of the BSG guidelines.

A total of 269 reports were assessed. Reports issued following the BSG guidelines showed improvements in both correct categorisation and reporting rates of specific histological features such as inflammation, dysplasia and malignancy. Where incorrect BSG categories were assigned, this was found to involve incorrect terminology rather than misinterpretation of diagnostic features. This affected the intermediate categories of "corroborative of an endoscopic diagnosis of CLO" and "in keeping with, but not specific for CLO". It is unclear whether these minor discrepancies are likely to have any impact on patient management. Strict adherence to guidelines is, however, likely to reduce misinterpretation of reports by clinicians.

P84

Bile Duct Cytology and the Diagnosis of Pancreatobiliary Malignancies

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OBJECTIVE: To study the efficacy of bile duct cytology in the diagnosis of pancreatobiliary malignancies. METHODS: Reports of 45 consecutive satisfactory bile duct cytology specimens over a 2 year period were audited and the results were classified into 5 groups as follows – N2 Benign, N3 Atypical, probably benign, N4 Atypical, probably malignant, N5 Malignant. The final diagnosis was based on histopathology, radiography and/or clinical follow up. A result of N2 and N3 was considered negative, and N4 and N5 positive, for the calculation of sensitivity, specificity, positive and negative predictive values. Likelihood ratios were calculated for each diagnostic category and were used for determining post-test probability of malignancy. RESULTS: The sensitivity of biliary cytology was 51% and the specificity was 85.7%. The positive predictive value was 88.9%, with the post test probability of disease given a negative test being 55.5%. The likelihood ratio for malignancy with a diagnosis of N4 was 2.28, compared to 0.69 and 0.45 for a diagnosis of N3 and N2 respectively. With a 50% pre-test probability of malignancy, a report of N4 altered the post-test probability to 70%. With a diagnosis of N2, the post-test probability was 31%. CONCLUSIONS: Brush cytology is a simple technique with a high specificity and positive predictive value for the diagnosis of pancreatobiliary malignancies. Categorising the cytomorphology will further improve the diagnostic accuracy

P85

The Comparative Environmental and Economic Impact of Hospital Based and Primary Care Phlebotomy Services

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We carried out a survey to assess the time taken, travel modes and costs for patients attending the Royal London Hospital as compared to the local primary care surgery for phlebotomy. A standard questionnaire including journey times, mode of travel and cost of travel to visit the hospital/local surgery was given to 127 patients (85 local – within a five mile radius and 42 non-local – more than five miles) over two days. No patient declined the survey. Median journey times for local patients to travel to the hospital and surgery were 46 and 10 minutes respectively ($p<0.05$). For non-local patients this time was 76 and 16 minutes. The mode of travel to the hospital and local surgery were walking (42% and 79% respectively for local and 0% and 64% for non-local patients ($p<0.05$)); car (20% and 6% ($p<0.05$) for local vs 34% and 21% for non-local) and public transport (remaining in both groups). The travel cost to the local surgery was 0 for over 90% of patients as compared with a minimum of 2 pounds for travel to the hospital in both groups ($p<0.05$). Our results show the environmental and economic impact on patients having phlebotomy done at the local hospital rather than in a primary care setting.

P86

Diagnosis of Hodgkin Lymphoma by Fine Needle Aspiration Cytology: An Audit study

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Objective: To test the accuracy of fine needle aspiration cytology (FNA) in diagnosis of Hodgkin Lymphoma (HL).
Methods: All new cases of Hodgkin lymphoma (HL) diagnosed by either FNA or biopsy, between January 2001 and February 2007, were retrieved from the archives of the Department of Cellular Pathology at Northwick Park Hospital. The diagnoses in these cases were matched with those made on corresponding FNA and lymph node biopsy.
Results and Conclusions:
18 cases were found with a diagnosis of HL made either on FNA or biopsy and having both FNA and histology available for comparison. They were 11 males and 7 females with an age range of 16 to 72 years.
15 cases were reported on FNA as suspicious/ suggestive of HL (in 3 of these cases adequate liquid base cytology material was available for immunostaining; the malignant cells in these 3 cases stained positively for CD30 and CD15). Of the 15 cases; 13 cases were proven to represent HL on biopsy, T cell rich Diffuse Large B Cell Lymphoma (DLBCL) in one case and one lymph node showed dermatopathic lymphadenopathy.
2 other cases were reported on FNA as showing large atypical lymphoid cells; suspicious of malignancy. These were proven by biopsy to be cases of HL.
One case had been reported as reactive lymphadenopathy on FNA and was showed to represent HL on biopsy.
The 16 cases reported as HL on biopsy were subclassified as: 2 nodular lymphocyte predominant, 2 lymphocyte rich classical HL, 4 mixed cellularity and 8 nodular sclerosis.
FNA cytology can play a major role in suggesting a diagnosis of HL; the patients are then triaged for an excision biopsy. However, excision biopsies provide the definitive method for diagnosing HL.

P87

D2-40 is a Sensitive and Specific Marker in Differentiating Primary Adrenal Cortical Tumours from Both Metastatic Clear Cell Renal Cell Carcinoma, and Phaeochromocytoma

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The morphological similarities between the tumour cells of clear cell renal cell carcinoma (CCRCC) and those of the adrenal cortex impose diagnostic difficulties, for example in the context of a solitary nodule in the adrenal gland in a patient with renal cell carcinoma. This problem is confounded by the variable and patchy staining seen with the established panel of antibodies utilised in this context, particularly on biopsy material. We observed that D2-40, an antibody commonly used to highlight lymphatic endothelial cells, is consistently positive in the normal adrenal cortex. We subsequently investigated its utility in distinguishing adrenal cortical cells from those of CCRCC and also from phaeochromocytoma.
D2-40 antibody was applied to tissue sections from 10 normal adrenal glands, 15 renal carcinomas (13 clear cell, 2 papillary variants), 1 metastatic CCRCC in the adrenal gland,6 adrenal cortical hyperplasias, 5 adrenal cortical adenomas, 3 adrenal cortical carcinomas, and 4 phaeochromocytomas.
D2-40 was strongly and diffusely positive in the cells of the neoplastic and non-neoplastic adrenal cortex, but did not stain any renal cell carcinomas or phaeochromocytomas. That is, 100% sensitivity and specificity on this pilot study group.

P88

Abstract withdrawn

P89

Identification of a consistent in vivo and in vitro immortality related gene expression signature in head and neck SCC.

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We previously reported evidence for divergent routes to head and neck squamous cell cancer (HNSCC) via intermediate dysplasias (Hunter et al, 2006, Cancer Res, 66, 7405). Dysplasia and carcinoma cultures can be clearly sub-grouped by gene expression profile as to those that are mortal or immortal in culture; with those cancers generating cultures with an immortal phenotype having worse prognosis.
Further microarray analysis of normal oral cultures or biopsies with immortal HNSCCs grown in vivo (xenografts/human tumour) or in culture has defined an immortal HNSCC gene expression signature which is maintained in vivo and in vitro. Conversely, several differentiation, motility and invasion markers are differentially regulated in vivo and in culture. Many genes down-regulated in our immortal HNSCCs overlap with those down-regulated in the gene expression signature of primary HNSCCs that subsequently metastasised to lymph nodes (Roepman et al., 2006 Cancer Res, 66, 2361). We found little coincidence with Roepman et al's up-regulated poor prognosis signature as those gene expression changes largely originate from the stromal component of tumour biopsies that is absent from our studies.
The overlap of the immortal HNSCC expression phenotype with other poor prognosis signatures demonstrates the usefulness of a candidate approach to new prognostic or therapeutic biomarkers in HNSCC.

P90

Beta 3 integrin null bone marrow transplantation contributes to increased tumour blood vessel density but not to tumour volume with no evidence of engraftment.

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Mice that do not express beta 3 integrin show normal developmental but increased pathological angiogenesis via an increase in expression of VEGF receptor 2 (Flk-1). Bone marrow-derived cells can contribute significantly to functional vasculature in tumour and colitis models. To investigate the effect of bone marrow beta 3 integrin in tumour growth and vasculature, C57/129 mixed background female mice were irradiated to ablate the bone marrow and transplanted with male, beta 3 null, GFP+ bone marrow. Control mice received male, wild type, GFP+ bone marrow. B16 melanoma cells were subsequently implanted subcutaneously and harvested on day 13. Although tumours in experimental and control animals were not significantly different in volume, blood vessel density was significantly increased in the tumours of animals that had received beta 3 null bone marrow. Furthermore, there was no evidence of engraftment of donor bone marrow cells into any of the B16 tumours although donor cells were readily visualised in other tissues using ISH for the Y chromosome and immunohistochemistry for green fluorescent protein.

P91

RKIP protein expression in colorectal cancer correlates with metastatic recurrence and overall survival

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RKIP inhibits the Raf and NFκB signalling pathways suppressing invasion in cell culture and metastasis in animal models.

RKIP protein expression in primary colorectal cancers (CRC) was examined in (i) a tissue microarray containing 276 samples from human tumours and normal tissues; and retrospective studies of (ii) 268 CRC patients, and (iii) 65 early-stage CRC. RKIP protein was expressed in normal epithelia but reduced in metastatic tumours. RKIP expression in primary CRC was an independent prognostic marker for survival using multivariate Cox's regression analysis (Hazard ratio 2.808, 95 % CI 1.58-4.96, p=0.0002) independent of Dukes' stage. An independent study of only early-stage CRCs confirmed that reduced RKIP protein expression predicted metastatic recurrence and reduced disease-free survival (Hazard ratio 4.5, 95% C.I 1.7-12.3, p=0.003). RKIP expression was independent of sex, age, mitotic index, and lymphatic and vascular invasion, depth of invasion and tumour site, but correlated positively with apoptotic index (p=0.024). Weak or loss of RKIP expression was the most significant and independent prognostic marker using multivariate regression equation (Hazard ratio 4.5, 95% C.I 1.7-12.3, p=0.003).

RKIP expression in primary CRC correlates with overall and disease free survival, and can be useful for identifying early stage CRC patients at risk of relapse.

P92

Abstract withdrawn

P93

An Evaluation of Mesorectal Tissue Volume Using Three Dimensional Digital Imaging

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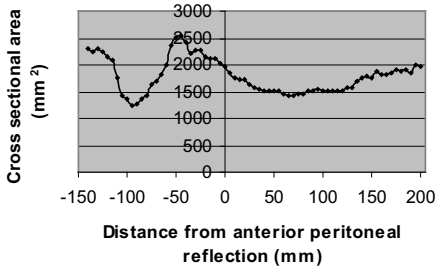
Tumour at the mesorectal circumferential resection margin (CRM) is associated with poorer outcome. Low rectal tumours (<5cm from the anal verge) have a high risk of CRM involvement due to loss of the mesorectal fat at the top of the sphincters and the type of operation. One trial (Dutch TME/SCRT) and an audit (British Columbia) reported that tumours of the upper rectum (10-15cm from the anal verge) also show increased risk of CRM involvement.
We used 3D colour digital photography on 18 rectal resections with the Minolta VI-910 and analysed the images using the Rapidform™ Basis software. Cross sectional slices were produced for every 5mm distance throughout the length of the specimen and the area was determined using the Leica Q5001W image analyzer.



A reduction in cross sectional area was confirmed in the lower rectum and was also observed in the upper rectum above the peritoneal reflection where the area reduced from a maximum of 2531mm^2 to 1428mm^2. Males and females showed the same pattern aside from a different height of the peritoneal reflection.
This data explains why tumours of the upper rectum have a higher rate of CRM involvement than tumours of the mid rectum.

P94

Quantification and Characterisation of the Mesorectal Fascia in Total Mesorectal Excisions for Rectal Cancer

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Total mesorectal excision for rectal cancer involves removal of the rectum and surrounding mesorectal fat immediately outside the plane of the mesorectal fascia (MF). We attempted to quantify how frequently the MF is identified histologically and define its characteristics.
The departmental slide archives were manually searched for all cases of primary rectal carcinoma with at least one whole mount section available. The slides were analysed to identify the length of circumferential resection margin (CRM) present and the percentage of CRM covered by MF.
25 cases were identified and included 13 abdominoperineal and 12 anterior resection specimens. 24 surgical resections were able to be retrospectively graded from the macroscopic description and included 11 with surgery in the mesorectal plane, 9 in the intramesorectal plane and 4 in the muscularis plane. MF was identified in 20 cases (80%) and varied from covering 9 to 100% of the CRM with a mean of 30% in mesorectal/intramesorectal plane excisions and 7% in muscularis plane excisions. The MF was generally observed as an intermittent fragmented layer of collagen fibres with a depth of between 0.08mm and 1.78mm. Anteriorly in the middle and upper rectum, the MF was seen to fuse with the sub-mesothelial fibrous layer.

P95

Interobserver Variation in the Diagnosis of Dysplasia in Barrett's Oesophagus

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BACKGROUND
Patients with Barrett's oesophagus undergo screening to detect dysplasia with the aim of reducing the mortality from Barrett's adenocarcinoma. A diagnosis of dysplasia, when made, may lead to extensive surgery, but there is felt to be significant variation in the histopathological diagnosis of dysplasia.
METHODS
The degree of interobserver variation in diagnosing dysplasia in Barrett's oesophagus was established by circulating conventional glass slides of 148 biopsies from patients with Barrett's oesophagus to 6 national experts in gastrointestinal pathology. The slides selected included cases of normal and reactive Barrett's mucosa, dysplasia and intramucosal carcinoma.
RESULTS
The interobserver variation of the national experts was fair to moderate, with overall agreement of 57% and overall kappa values of 0.41 (95% C.I. 0.38 - 0.45). For "indefinite probably negative" and "indefinite probably dysplastic" categories the level of agreement was only slight (kappa 0.11 and 0.07 respectively).
The frequency of diagnoses varied greatly between pathologists, with that of low grade dysplasia varying from 4.7 to 23% and that of intramucosal carcinoma varying from 2.7 to 19%.
CONCLUSION
There is significant interobserver variation in the histological diagnosis of dysplasia in Barrett's oesophagus, even amongst national experts in gastrointestinal pathology.

P96

Study of Autofluorescence Colonoscopy for the Detection and Differentiation of Colorectal Polyps

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Colorectal cancer is the second commonest cause of death in the UK. Most cancers are believed to arise within pre-existing adenomas. Although colorectal adenomas have a clear neoplastic potential, metaplastic polyps do not. Autofluorescence (AF) has been developed to enhance conventional white light (WL) endoscopy in the diagnosis of GI lesions. The aim of the study was to evaluate if AF colonoscopy can facilitate endoscopic detection and differentiation of colorectal polyps.
Patients were invited to attend for colonic assessment with both AF and WL endoscopy. AF readings, pictures and biopsies were taken of any visible pathology and of any high AF areas.
A total of 107 patients were assessed with AF and WL colonoscopy. An autofluorescence intensity ratio (AIR) was calculated for each polyp (ratio of direct polyp AF reading/background rectal AF activity).
A total of 75 polyps were detected, 54 adenomatous and 21 metaplastic polyps. Colorectal adenomas had a significantly higher AIR compared to metaplatic polyps (median [IQR]: adenoma (3.54 [2.54-5.00] vs. metaplastic (1.60 [1.30-2.24]: p=0.0001)
Our study has shown a striking visual distinction between adenomatous and metaplastic polyps using AF colonoscopy. These results suggest that AF is a promising candidate for further development and study.

P97

Autofluorescence Assessment in the Surveillance of Barrett's Oesophagus

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Barrett's oesophagus is associated with an increased risk of oesophageal adenocarcinoma. Currently patients undergo endoscopic surveillance in an attempt to detect dysplasia. Autofluorescence (AF) is a new technique which detects endogenous fluorescence in normal and diseased epithelium. Our aim is to establish if AF endoscopy is useful in detecting dysplasia.
Patients were assessed using both AF (Xillix Onco LIFE) and conventional white light (WL) endoscopy. High AF readings within the Barrett's segment were recorded and biopsied followed by standard biopsies following the Seattle protocol. The histology was blindly reported by two pathologists scoring according to the Vienna classification.
A total of 45 patients were assessed. Intestinal metaplasia was detected in 73% patients using random WL biopsies and in 62% patients biopsied with AF. Two patients had high grade dysplasia, one detected with AF biopsy and the other detected with WL. The total number of biopsies taken were 236 with WL and 68 with AF (p=0.0003). The median AI readings were 0.51 for squamous epithelium, 1.30 for intestinal metaplasia, and 3.81 for dysplasia.
AF endoscopy has a similar detection rate of intestinal metaplasia and of dysplasia as WL endoscopy with the advantage of being a faster technique with fewer biopsies needed.

P98

Assessment of Methods to Quantify Autofluorescence Intensity in Adenomatous Polyps

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Autofluorescence (AF) endoscopy has been developed to improve detection of GI lesions. It produces an intensity (AI) reading. Our aim was to quantify AI readings in relation degree of dysplasia of adenomatous polyps.
51 patients were assessed with AF colonoscopy (Xillix Onco-LIFE) with AI readings recorded of polyps, surrounding area to polyps and rectum. 38 polyps were identified, 20 confirmed histologically to be adenomatous. Five different methods were used to quantify AI reading with degree of dysplasia: AI polyp alone (P), AI polyp minus AI surrounding tissue (P-ST), AI polyp minus AI rectum (P-R), AI polyp/AI surrounding tissue ratio (P/ST) and finally AI polyp/AI rectum ratio (P/R). The five methods were tested statistically to determine if there was a significant difference for degree of dysplasia for any method.
A significant statistical difference for degree of dysplasia, using Kruskal-Wallis test, was found with P/R method (p value of 0.02). The other methods did not produce a stastically significant difference.
AI readings can be better quantified in relation to degree of dysplasia within adenomatous polyps when a ratio is used of AI polyp/AI rectum. This new AI measurement may allow autofluorescence colonoscopy to determine the degree of dysplasia within adenomatous polyps.

P99

Do Very Low Risk GISTs Represent Varying Pathological Entities?: KIT/PDGFRalpha Mutation Analysis in a Series of 12 Cases.

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We have collected 12 very low-risk GISTs in various surgical specimens. All were incidental findings. 7 were <1 cm in diameter and 5 were 1-1.7 cm. All cases show the typical phenotype of GISTs (CD117 and CD34 positivity; Desmin negativity). 3 cases were associated with large GISTs and 9 with GI tract/pancreas/liver tumours.
KIT/PDGFRalpha mutation was performed from paraffin blocks:
- Of those associated with larger GISTs, 2/3 showed identical Exon 11 status (1 Wild-Type and 1 Missense Mutation) and 1 of 3 was Wild-Type whilst the larger associated tumour showed a complex mutation.
- Of those associated with carcinomas, 6/9 were Wild-Type for KIT exon 11,1 showed a Missense mutation in KIT Exon 11 outside of the “hot spot”, 1 showed a deletion in Exon 11 and 1 showed the D842V Missense mutation in Exon 18 of PDGFR-a.
Our results suggest that very low risk GISTs represent a heterogeneous population of lesions. Some of them (carrying gene mutations) could represent true early GISTs whereas others may represent cell proliferation with no malignant potential (?ICC hyperplasia).
This material represents a useful model to clarify the developmental processes of GISTs.

P100

KIT/PDGFRalpha Mutation Analysis from EUS FNA Material from GI Tract Spindle Cell Tumours

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EUS FNA is used to collect diagnostic material from deep tumours.
We report here on 2 spindle cell tumours for which KIT/PDGFRalpha mutations screening was performed from cytology material.
Both lesions were from the gastric wall. Smears and needle washings preserved in transport medium were sent. Smears revealed spindle cells suggestive of mesenchymal tumour.
DNA was extracted from needle washings fluid for PCR and direct DNA sequencing. One tumour was found with a missense mutation in exon 11 of KIT and the other one was Wild-Type for all the exons of KIT and PDGFRalpha tested.
Both tumours were subsequently removed. Final histology showed c-kit positive GISTs.
KIT/PDFGRalpha mutation screening performed from paraffin embedded blocks showed concordant results to those from cytology material in both cases.
We demonstrate here that cytology material from EUS FNA is suitable for gene mutation analysis. This can be used to confirm the diagnosis of GIST and to predict response to Imatinib if the tumour is unresectable.
More cases are needed however to assess the value of Wild-type findings. We would like to demonstrate that these are not false negative results due to the low number of tumour cells.

P101

Recurrent Abdominal Wall Gastrointestinal Stromal Tumour Occurring Along the Surgical Tract

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We report the first case of a gastrointestinal stromal tumour (GIST) which recurred in the abdominal wall at the site of prior surgical tract, 10 years after excision of the primary tumour. Staging imaging did not reveal any other tumour.
A 48-year old man presented with an 11 cm gastric wall mass in 1996 which was diagnosed as a GIST. The tumour was completely resected. Ten years later, he presented with an abdominal wall mass at the site of the previous surgical scar. This measured 13 cm and largely involved the subcutaneous tissue with no connection to the GI tract. The overlying skin was uninvolved. Histology showed features similar to those of the gastric tumour with an admixture of spindle and epithelioid cells with mild atypia. Mitotic figures of 6-10/50HPF were identified and focal areas of necrosis were seen. The tumour cells were positive for CD117, CD34 and negative for Desmin. Mutation analysis showed large 42 base pairs insertion in Exon 11 of KIT gene starting at codon 557.
This case demonstrates the potential risk of long-term extra-intestinal recurrence of GIST, along surgical tract. It is hence essential to investigate any nodule developing at the surgical site.

P102

DNA copy number profiles of primary colorectal cancers as predictors of response to therapy

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Colorectal cancer (CRC) is a heterogeneous disease, which gives rise to different clinical behaviours, such as response to drug therapy. Therapies can be improved by matching the right combination of drugs with different biological classes of CRC.
We aimed to correlate genome wide DNA copy number status in advanced CRC with response to chemotherapy.
Thirty-two patients with advanced CRC were selected from the CAIRO study of the Dutch Colorectal Cancer Group (DCCG), based on either a good (n=17) or a poor response (n=15) to first-line combined irinotecan and capecitabine therapy. DNA copy number profiles were determined by oligonucleotide-based array CGH.
Responders showed more aberrations, especially losses ($P = 0.01$). The striking difference between the two groups were losses of 1p36 ($P = 0.05$), 18p ($P = 0.02$), and 18q ($P = 0.01$), which were more frequent in the responders.
Hierarchical cluster analysis of the array CGH data revealed two clusters. From the 17 responders, 15 were in cluster 1 ($P = 0.01$).
Advanced CRC patients with either good or poor response to systemic chemotherapy show different DNA copy number profiles. Tumours of patients with a good response to treatment had overall more chromosomal aberrations, especially losses of 1p36, 18p and 18q.

P103

Immunohistochemical Expression of pH2AX is Related to Tumour Stage, Patient Survival and Ploidy in Gastric Cancer

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DNA double strand breaks (DSB) are the most dangerous form of DNA damage. The histone protein pH2AX and the MRE11/RAD50/NBS1 (MRN) have a crucial role in immediate cellular response to DSBs. Impaired expression of pH2AX and MRN may be related to tumour progression and patient prognosis.
We investigated the expression of pH2AX, MRE11, RAD50 and NBS1 in 163 gastric adenocarcinomas (GC) using immunohisto-chemistry. Results were correlated with clinicopathological data, patient survival and expression of ATM, BRCA1, BRCA2, p53, Ki-67, MLH1, MSH2 and RAD51.
Increased expression of pH2AX was associated with poor patient survival, high tumour stage and aneuploid GC. The expression of proteins of the MRN complex correlated with each other, but none of them were associated with clinicopathological parameters or patient survival. Increased MRE11 expression was associated with diploid GC. The expression of all four proteins was higher in MLH1-positive GC. Correlations between all DSB proteins investigated including p53 were inconsistent.
Our study is the first to suggest that pH2AX expression may have a role in tumour progression and patient prognosis in GC. The relationship of DSB proteins with ploidy supports the notion that DSB repair proteins may be important in maintaining chromosomal stability. The association with MLH1 warrants further investigation into the microsatellite status at the DSB repair gene loci.

P104

CD24 is Variably Glycosylated and Stimulates Proliferation in Colorectal Cancer but it is not a Prognostic Marker

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CD24 is a cell surface protein which is thought to be an intestinal stem cell marker. In colorectal cancer (CRC), strong cytoplasmic CD24 staining has been associated with tumour progression and shortened patient survival times.
We investigated CD24 mRNA expression in 26 colorectal cell lines by Real-Time PCR. Message was detected in 24/26 cell lines with nearly a 1000 fold difference between the highest and lowest expressors. Subsequent protein analysis by Western Blot unexpectedly revealed different glycosylation patterns between cell lines with some cell lines expressing up to three different isoforms. Forced expression of cloned CD24 in HCA7 (a non-expressor) caused increase proliferation compared with empty vector.
Ten cases each of adenoma and inflamed colon together with 462 CRCs were next examined by immunohistochemistry for CD24 expression. Normal mucosa was negative but strong staining was seen in all adenomas/inflamed tissue and 76% of CRCs. In this series, there was no prognostic association.
We conclude that CD24 is upregulated in both neoplastic and non-neoplastic proliferative tissue. It may contribute to proliferation although the role of the variable isoforms is uncertain. It does not however predict clinical outcome.

P105

Investigating Epigenetic Pathways in Colorectal Cancer

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Somatic gene mutation in colorectal cancer is accompanied by gene silencing through methylation of CpG islands located within gene promoter regions. Some tumours appear to have a propensity for widespread promoter methylation – the CpG Island Methylator Phenotype (CIMP). Cancers can be subdivided into "CIMP+" and "CIMP-" BY examination of a specified panel of genes.
We investigated epigenetic changes in a series of 26 colorectal cancer cell lines. DNA from each cell line underwent bisulphite modification followed by methylation specific PCR to evaluate promoter methylation in the CIMP panel and further group of genes of interest.
The CIMP+ phenotype (methylation at ≥ 3 loci) was seen in 11/26 cell lines. As in primary tumours, 83% of cell lines with microsatellite instability were CIMP+. Methylation of MLH1 and p16 methylation was positively associated with CIMP+ status whilst APC methylation showed a negative association. Partial methylation was evident and quantitative PCR showed no significant difference between expression in cell lines showing partial and no methylation. Full methylation however was found to abrogate expression.
Thus cell lines can be used as models for investigating CIMP. Partial methylation at a locus may not significantly alter gene expression and is therefore of uncertain biological relevance.

P106

Novel and Concomitant Mutations of KRAS and BRAF in Colorectal Cancer Cell Lines

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KRAS and BRAF encode small proteins which form part of the RAS/RAF/MAP kinase cascade. Gain-of-function mutations of both genes are found in colorectal cancers and, since both activate the same signalling pathway, have been thought to be mutually exclusive.
We evaluated KRAS and BRAF mutations occur in 26 well known colorectal cancer cell lines using a direct sequencing strategy. Initially mRNA was for expressed mutations followed by in genomic DNA analysis.
In total, 21/26 cell lines had a mutation in either KRAS or BRAF. Mutations of KRAS were found in 14/26 cell lines and, unexpectedly, 4 had homozygous mutations. Mutations occurred mainly in the common codons although a novel mutation at codon 117 was found. Mutations of BRAF were found in 9/26 cell lines and all were heterozygous. Most were V600E mis-sense mutations although novel mutations in codon 529 and 581 were also detected. In addition, BRAF splice variants (hitherto undescribed) were found. Two cell lines had concomitant KRAS and BRAF mutations.
Thus KRAS/BRAF mutations occur at a wide range of residues and their frequency may be under-reportedin in colorectal cancers. The occurrence of homozygous KRAS mutations and concomitant KRAS/BRAF mutations shows that this pathway may be gene dosage dependent.

P107

The Distribution of K_V1 Voltage-gated Potassium Channel Subunits in the Human Gastrointestinal Tract

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Combinations of voltage-gated K^+ (K_V) channel subunits regulate activities of many cells. We reported K_V1 autoantibodies in dysmotility disorders (Knowles et al., 2002). Little is known of K_V1 channel distribution in gut. We investigated six K_V1 subunits in human stomach, jejunum, ileum and colon. Immunohistochemistry was performed on paraffin sections using two different sets of anti-$K_V1.1$, $K_V1.2$, $K_V1.3$, $K_V1.4$, $K_V1.5$ and $K_V1.6$ antibodies, with positive and negative controls, including peptide blocks where available. Mouse gut was used as additional validation. RT-PCR confirmed $K_V1.4$ expression. Three investigators scored sections.
Significant variation was seen in different areas ($p<0.05$-$p<0.005$). K_V1 was prominent in surface epithelial cells, gastric chief cells and enteric ganglia. $K_V1.4$ immunoreactivity was prominent in chief cells. $K_V1.1$, 1.2, 1.3, 1.4 and 1.5 immunoreactivities were similar in small bowel surface epithelium with $K_V1.6$ at lower intensity. Colonic surface enterocytes stained intensely with anti-$K_V1.1$ and $K_V1.3$. Gastric myenteric ganglia were strongly immunopositive for $K_V1.2$, 1.4 and 1.5. Small bowel and colonic submucosal and myenteric ganglia were strongly/moderately immunopositive for all K_V1 subunits. The high density of K_V1 subunits in surface epithelial cells and enteric ganglia was unexpected. Findings provide an attractive hypothesis for damage to epithelium generating a secondary autoimmune mediated neurodysfunction.

P108

Malakoplakia of the appendix: an uncommon entity at an unusual site

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Malakoplakia is an uncommon inflammatory condition usually affecting the genitourinary tract, which has been associated with infections, tumours and immunocompromised states. We report a case of malakoplakia in the appendix of a 61-year-old man with a long-standing history of ulcerative colitis. Clinically and macroscopically malakoplakia can simulate tumours or abscesses and can cause diagnostic difficulties. Histologically malakoplakia in the gastrointestinal tract (GIT) must be differentiated from Whipple's disease, other infectious and non-infectious granulomatous disorders and histiocyte storage diseases. To the best of our knowledge, this is the first case of malakoplakia of the appendix reported in association with ulcerative colitis and the sixth reported case of malakoplakia of the appendix in the literature. Although the underlying disease in our case was ulcerative colitis, the malakoplakia was limited to the appendix. The significance of this finding is not clear but we feel that this was a localised manifestation of the underlying immunosuppressive state. Ulcerative colitis and treatment with steroids may make a patient immunosuppressive and the local and systemic change in the immunity may facilitate the proliferation of the organisms and modify the phagocytic abilities of the macrophages.

P109

An Unusual Case of Small bowel Obstruction

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An unusual case of small bowel obstruction secondary to perforation by an ovarian dermoid cyst is presented. A 38 year old post-partum woman with a known right sided ovarian dermoid cyst presented with a history of small bowel obstruction which failed to settle with conservative measures. Laparotomy was undertaken, the right ovarian dermoid cyst was identified and removed and a left sided ovarian dermoid cyst was found to be adherent to the small bowel. A small bowel resection was undertaken with en-bloc resection of the left Fallopian tube and ovary. On histological evaluation, it was evident that the cyst had directly perforated the wall of the small bowl causing a polypoidal obstruction within the bowel lumen. Perforation and subsequent obstruction of the small bowel by ovarian dermoid cysts is extremely rare, but should be considered as a possible cause in those patients with known dermoid cysts presenting with obstruction. This case illustrates the importance of early surgical intervention in the management of such cysts wherever possible and also the need to be aware that complications relating to dermoid cyst disease may arise from small innocuous appearing cysts in the contralateral ovary as well as from larger well-defined lesions.

P110

Gastrointestinal Stromal Tumour of the Duodenum with Bony Metaplasia, Prominent Osteoclast-Like Giant Cells and Lymph Node Involvement

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Background: Gastrointestinal stromal tumours (GISTs) are specific, KIT or PDGFRA mutation driven mesenchymal tumours of gastrointestinal tract. Occurrence of osteoclast-like giant cells (OGCs) in GIST is extremely rare, with only two previous cases.
Case Report: A 63-year-gentleman presented with iron deficiency anaemia. An oesopahago-gastroduodenoscopy demonstrated a lesion on the 2nd part of duodenum and a biopsy obtained from this mass showed GIST. In view of the mass being very close to pancreatic duct and common bile duct terminations, a pylorus preserving pancreato-duodenectomy was performed. The tumour measured 2.5 cm in maximum dimension and was composed predominantly of spindle cells with a mitotic rate of 7 per 50 hpf. Spindle cells stained for CD117, CD34, S100 and bcl-2, and were negative for desmin and SMA. OGCs stained for CD68 and were negative for CD117. Unusual histological features that characterised this case included calcification, bony metaplasia, and prominent OGCs. Tumour was seen in two of peripancreatic lymph nodes. Morphologic and immunohistochemical findings favoured GIST of intermediate risk category. The patient is doing well after a follow up of 8 months.
Conclusion: These findings suggest that the OGCs originated from monocytes/histiocytes, and most likely developed as part of stromal reaction to the neoplasm.

P111

GLUT-1 staining pattern can help differentiate between dysplastic and invasive neoplasia of the colon

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BACKGROUND: Monosaccharide transporter proteins are responsible for transmembrane transport of monosaccharides into cells. Expression of GLUT-1 in malignant tumours is increased due to increased metabolic rate.
AIM: To study the expression of GLUT-1 in normal colonic biopsies, colonic adenomas and in biopsy specimens suspicious for adenocarcinoma on routine microscopy (confirmed as adenocarcinoma on further biopsy or resection). To assess whether GLUT-1 expression is different and whether GLUT-1 could help differentiate between normal, dysplastic and invasive colonic tissue.
METHOD: 19 normal colonic biopsies, 16 colonic adenomas and 21 biopsies showing features suspicious of invasive adenocarcinoma were randomly selected from the archive. Immunohistochemical reaction for GLUT-1 was carried out on all specimens and their staining pattern and intensity evaluated.
RESULTS: 79% of normal biopsies showed weak supranuclear staining. The remaining 21% were negative. 87% of adenomas showed weak supranuclear staining, 1 had a membranous staining pattern and 1 case showed negative staining. 43% of biopsies suspicious for carcinoma showed supranuclear staining, of variable intensity, however, in addition to this staining pattern 52% also showed moderate to strong membranous staining. 1 case was negative.
CONCLUSION:GLUT-1 staining pattern is predominantly supranuclear in normal and dysplastic colonic mucosa but often membranous in adenocarcinomas. GLUT-1 staining pattern may be helpful in differentiating dysplastic from invasive colonic neoplasia in cases difficult to classify on routine microscopy.

P112

Severe Anal Discomfort caused by a Traumatic neuroma

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Aims: Traumatic anal neuromas are a rarely documented finding in the setting of anal pain. They arise as a result of trauma or surgery and are often mistaken for scar tissue or adenomas.
Methods and Results: A 42-year-old heterosexual man affected with hemorrhoids presented with anal discomfort, presumed to be secondary to scar tissue formation. One year before his presentation to the general practitioner, he underwent to hemorrhoidopexy for prolapsed hemorrhoids. Excision of the tissue revealed a traumatic neuroma. After the removal of the neuroma, the patient's pain resolved completely.
Conclusion: Traumatic neuromas may be a cause of significant point tenderness and thickened tissue in patients with anal surgery or repair of anal lacerations. Our case shows a singular presentation with full rehabilitation following surgical excision of the neuroma.

P113

Mitochondrial DNA mutations give insight into clonalilty, lineage relationships and patch size in the human small bowel

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Introduction: Although rare, small bowel tumours cause significant morbidity and mortality. An understanding of the spread of mutations within the small bowel would give insight into normal small bowel biology and tumourigenesis.
Aims: Elucidate clonality, lineage relationships and patch size in human small bowel using mitochondrial DNA mutations.
Methods: Enzyme histochemistry and immunohistochemistry for cytochrome c oxidase (COX), succinic dehydrogenase and lineage markers was performed on frozen and paraffin embedded human small bowel mucosa. Small bowel crypts stained in this way were assessed for clonality, lineage relationships and patch size.
Results: Crypts demonstrated the phenomenon of monoclonal conversion. Paneth cells appeared have a longer lifespan compared with other cell types. Patches of COX deficient crypts were identified and patch size was assessed.
Conclusions: This study is the first to utilise mitochondrial DNA mutations to study the clonality of small bowel crypts. The results provide insight into the biology of small bowel crypts and the potential means of spread of oncogenic mutations within the small bowel.

P114

Reporting Benign Colectomies- Could We Do Better?

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Minimum datasets are used in reporting colorectal malignancies and guidelines are available for reporting inflammatory bowel disease (IBD) biopsies. However, no standards exist for reporting benign surgical resections. Here we examine the need for creating such guidelines for IBD resection specimens.
All resection specimens for IBD without cancer were identified for the years 2000 and 2005. We modified the BSG biopsy reporting guidelines to produce 12 data items for IBD resections.
The diagnosis prior to resection was uncertain in 19% of cases in 2000 and 11% in 2005. In 2000, 56% of cases were ulcerative colitis (UC), 42% Crohn's disease (CD) and 4% indeterminate colitis (IC). In 2005, 46% of cases were UC, 54% CD and there were no cases of IC.
CD average reporting scores were lower (5.7 data points (DP) in 2000 and 5.3 in 2005) than UC (7.2 DP in 2000 and 6.7 in 2005) and fewer information points were included in 2005 than in 2000.
In our study, more than 4 relevant data items were missing in most reports, some of these relating to important histological features allowing categorisation of IBD (e.g. depth of inflammation). Results suggest that guidelines on reporting IBD resections could improve the quality of reports.

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Connective Tissue Growth Factor Expression in Colorectal Cancer

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The CCN family of genes encodes extracellular matrix proteins. Cysteine rich-61 (Cyr61), Connective Tissue Growth Factor (CTGF) and NOV are involved in diverse cellular processes including wound repair, inflammation and tumour angiogenesis. Little is known about the expression or role of the CCN family of genes in colorectal cancer.
Expression of CTGF was studied in 40 cases of colorectal cancer and was compared with tumour grade, TNM stage, Dukes' stage and extra-mural vascular invasion. Staining was assessed by two observers using a semi-quantitative scoring system (0-3). There was a significant association between CTGF expression and advancing Dukes' stage ($P<0.01$), T stage ($p<0.01$) and lymph node involvement ($p<0.05$) but there was no significant association between CTGF expression and tumour grade or extramural vascular invasion. These preliminary findings suggest that CTGF may play a role in the natural history of colorectal cancer and may contribute to a more invasive/metastatic phenotype.

P118

Gene expression of the angiogenic peptides CTGF and Cyr61 in colorectal cancer

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The CCN genes encode secreted extracellular matrix proteins Cysteine rich-61 (Cyr61), Connective Tissue Growth Factor (CTGF) and Nov. They are involved in diverse cellular functions including tumour angiogenesis. Studies of these proteins in tumours have, however, produced conflicting results. The purpose of this study was to determine the expression of CTGF and Cyr61 genes in comparison to VEGF-A (a potent angiogenic factor) in hypoxic conditions in colorectal cancer cell lines (Caco-2, HT29) and in paraffin embedded tissues from colorectal cancers. The mRNA levels were quantified by real time reverse transcriptase polymerase chain reaction using primers located adjacent to the poly (A) polymerase site in the 3' UTR. Hypoxia significantly reduced CTGF mRNA expression ($p<0.01$) and induced VEGF-A mRNA expression ($p<0.01$) in HT29 and Caco-2 cell lines. Cyr61 was induced ($p<0.01$) in HT29 cell lines but significantly reduced ($p<0.01$) in Caco-2 cell lines under hypoxic conditions suggesting a complex mechanism of control. High levels of CTGF mRNA were found in 28 colorectal cancer compared with normal colon ($p<0.05$). Expression was reduced in more advanced cancers (Dukes' C versus Dukes A and B) and this may reflect a greater degree of hypoxia within more advanced tumours. Cyr61 mRNA also showed high levels of expression in cancers compared with normal tissue ($p<0.05$) with a similar pattern to CTGF. In contrast to the CCN genes, high levels of VEGF mRNA were found in all stages of tumour in keeping with previous published work. The results suggest that the CTGF and Cyr61 genes may be down-regulated by the hypoxic environment of more advances colorectal cancers.

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P120

Quality of Histopathology Reporting in Children with Coeliac Disease

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Background: Small intestinal biopsy remains the gold standard in the diagnosis of coeliac disease. It is recommended that at least 4 samples are taken to allow for patchy disease and reduce the incidence of false negatives. The aim of this study is to assess the quality of reporting of duodenal biopsies in suspected coeliac disease.
Methods: Information was collected from 87 children in whom upper GI endoscopy had been performed during 2005. We reviewed all biopsies for comparison with the original histology report.
Results: 17 cases were reported as coeliac disease, 14 with positive serology, and 16 were confirmed accurate on review. The one discrepancy was a very small biopsy with changes of either coeliac disease or duodenitis. Two further biopsies showed minor discrepancies on review. 34% of children had no coeliac serology, with one or two duodenal biopsies having been taken along with other upper GI biopsies. All of these biopsies were normal.
Discussion: Histopathology reporting of duodenal biopsies is accurate, although clinical and serological data are not always available at the time of reporting. Incidental biopsies taken during endoscopy for another reason were all normal and insufficient biopsies were taken to confidently exclude coeliac disease.

P121

Identification of biological pathways involved in colon adenoma to carcinoma progression

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Background: Colorectal adenoma to carcinoma progression is presumed to evolve through disruption of critical biological pathways. Here we aim to substantiate this hypothesis by sophisticated analysis of genome wide expression data of colorectal adenomas and carcinomas.
Materials and Methods: 37 adenomas and 31 carcinomas were analyzed using Pathway Level Analysis of Gene Expression (PLAGE). PLAGE tests differential expression of predefined gene sets between two categories. Here, gene sets from cancer progression associated biological processes were tested.
Results: Data analysis by PLAGE revealed that 7 out of 13 expression signatures were significantly differentially expressed between colorectal adenomas and carcinomas, namely chromosomal instability (Carter *et al*, 2006) - CIN25 ($p<0.0001$) and CIN70 ($p<0.0001$), proliferation (Whitfield *et al*, 2006; $p<0.0001$), cell cycle (Brentani *et al*, 2003; $p<0.0001$), differentiation (Rhodes *et al*, 2004; $p=0.0004$), metastasis (Li *et al*, 2006; $p<0.0001$), and invasion (Jechlinger *et al*, 2003; $p<0.0001$) signatures.
Conclusion & Discussion: PLAGE analysis of expression microarray data substantiates the role of disruption of critical biological pathways in colorectal adenoma to carcinoma progression and allows to identify genes within these pathways most relevant to this process.

P122

Flexible Endoscopy: Its Impact on the Biopsy Diagnosis of Oesophageal Malignancy

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Introduction: Oesophageal malignancy is increasing in incidence in the West. Oesophageal adenocarcinoma (ACa) is now more common than squamous cell carcinoma (SCC) and is often preceded by metaplastic changes in the oesophagus, including Barrett's oesophagus
Aim: To identify the changing pattern of primary oesophageal malignancy in endoscopic oesophageal biopsies following the introduction of flexible endoscopy.
Method: Flexible endoscopy (FE) was introduced in our institution in 1998. All oesophageal endoscopic biopsies between 1996 and 2001 were identified from our histopathology database using SNOMED search code of T62*. All reports were retrieved and scrutinised for diagnoses of oesophageal SCC or ACa.
Results: 872 biopsies were performed on 653 patients; 236 and 636 biopsies were performed in the 3 years before and after FE introduction respectively. 71 ACa's or SCC's were diagnosed before and 101 after FE introduction. There was an increase in the numbers of ACa's detected after FE introduction (n=66: 65%) than before (n=40: 56%) in contrast to 35 SCC's (35%) after and 31 (44%) before FE introduction. The ratio of SCC to ACa before FE was 1:1.3 and after was 1:1.9.
Conclusion: We have shown that the introduction of flexible endoscopy and increase in the numbers of biopsies was associated with increase in the numbers of diagnoses of ACa. The numbers of SCC's in these two periods remained relatively stationary.
This is could be attributed to changes in diagnostic protocols, an aging population, changing socio-economic demographics and behavioural patterns.

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Parietal Podocytes Are Present in Human Donor Kidney Biopsies of All Ages and Do not Correlate with Donor Age

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This study investigated parietal podocytes on Bowman's capsule (BC) in normal human kidney from a wide age range, to determine if their presence and extent correlate with age.
65 donor kidney biopsies, age range 11-64 years, 8-14 biopsies from each of the six decades, were stained for podocyte markers GLEPP-1 and synaptopodin. For each glomerulus, the percent of BC showing podocyte labelling was graded, as follows: 0=0%, 1=<25%, 2=25-49%, 3=50-74%, 4=75-99%, 5=100%.
Parietal podocytes were found at all age groups, in overall approximately 50% of glomeruli (range 31-72%). They were present around the vascular pole area, most commonly lining <25% of BC, and were sometimes associated with podocytic connections between the capillary tuft and BC. There was no statistical correlation between presence or grade of parietal podocytes and donor age.
In donors over 20 years of age, occasional glomeruli (<3%) showed 100% of BC lined by parietal podocytes, with contracted capillary tufts, and cystic expansion of Bowman's space with proteinaceous material containing variable numbers of detached podocytes, consistent with atubular glomeruli.
These findings indicate that parietal podocytes are present in human kidney from all age groups, and are not a direct consequence of aging. Their pathophysiological significance warrants further investigation.

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Mucinous tubular and spindle cell carcinoma of the kidney: morphologic findings in 3 cases.

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Mucinous tubular and spindle cell carcinoma of the kidney is a rarely diagnosed renal tumour included in the latest WHO histological classification of kidney tumours. It appears to have a very good prognosis: metastases were reported in only 2 cases in reports totalling 46 cases, albeit with only a few cases followed-up for more than 5 years. However, the tumour shows some morphologic features that can be misinterpreted as a sarcomatoid renal cell carcinoma, resulting in a falsely poor prognosis. We present 3 cases of this tumour, illustrating radiologic, macroscopic and microscopic features of each case. Mucinous tubular and spindle cell carcinoma should be considered when a diagnosis of an "unusual" sarcomatoid renal cell carcinoma is being entertained.

P128

Reporting of Vascular Invasion in Renal Tumours Using the 'Cardiff Nephrectomy Cut-Up Protocol'- a 5 Year Audit

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Vascular invasion is an important prognostic variable in renal cell cancer (RCC). We have previously shown that a dissection protocol that insists on complete examination of the tumour-renal sinus interface increases the yield of vascular invasion reporting in nephrectomy specimens. We now report an audit of 174 consecutive cases of radical nephrectomy for localized RCC, received between 2001 and 2006. These were cut up using the 'Cardiff nephrectomy cut-up protocol' by senior pathologists and trainees on roster.

Vascular invasion was demonstrable in 49% (total 85/174: 19/174 IVC invasion; 23/174 renal vein invasion and 43/174 microvascular invasion). This is similar to the incidence of vascular invasion in our previous series (51%) and tumour size was comparable to our previous series (median of 70mm vs. median of 74mm). Historical series have given a vascular invasion rate of no more than 40%.

This audit highlights the consistent increase in the identification of vascular invasion using the Cardiff nephrectomy cut up protocol which is maintained when rolled out to other pathologists. Our figures compare favourably with rates of vascular invasion reported in another centre that has adopted the new nephrectomy cut up protocol.

P129

Altered Growth of Bladder Cancer Cells by Tamoxifen is an ER-Independent Mechanism Upregulating Bax and Cyclin D1

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Tamoxifen, as well as inhibiting proliferation of breast cancer, can also inhibit other neoplastic cells. Bladder cancer cells possess estrogen receptors (ER) so that tamoxifen may have therapeutic benefits for patients with this cancer. This study aimed to detect any functional relationship between the expression of isoforms of ER (α and β) and the effects of tamoxifen on growth and gene expression in bladder cancer cell lines. Growth curves were prepared from 10 cell lines exposed to 10-fold increments of concentration of estradiol alone or in combination with tamoxifen. Total RNA was extracted from the 10 cell lines after exposure to 1 μM of either estradiol or tamoxifen or solvent only. It was reverse transcribed for PCR using primers specific for ERα and ERβ. Messenger RNA was also hybridised to a custom-designed DNA oligonucleotide array (MetriGenix, Gaithersburg, USA)

It was found that ER alpha was expressed in 8 cell lines, ER beta in 6 but one cell line contained neither. Tamoxifen at low doses (optimum 1 μM) had no effect on growth of two cell lines but actually stimulated growth in two. In the remaining 6 lines tamoxifen inhibited growth to varying degrees and this effect was greater than that due to simply inhibiting the effect of estradiol. Furthermore, it was unrelated to ER status. Of the 80 genes on the array, 14 were highly expressed when related to control genes and 3 of these were significantly upregulated by tamoxifen but not estradiol. Two of these, Bax and CCND1 (Cyclin D1) are involved in apoptosis and the cell cycle respectively.

We conclude that modulation of Bax and cyclin D1 expression may explain how tamoxifen influences cell growth. It also suggests that tamoxifen could be employed in the treatment of bladder cancer with fewer side effects than current regimes.

P130

Pathology and Follow-Up in Patients suffering from Hereditary Complete Complement C4 Deficiency

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Aims and Methods: Hereditary complete C4 deficiency is a very rare immunological condition that predisposes to immune complex disease and end-stage renal failure. Whether such patients should undergo renal transplantation is unknown. Clinics and pathology as well as follow-up of five transplantations in three c4-deficient patients are described.
Results The first patient lost one allograft after six years due to chronic allograft rejection. Back on dialysis, he suffered from meningitis caused by *N. menigitidis* and *Aspergillus spp.* infection. One year after a second transplantation under alemtuzumab induction, he died after the development of Kaposi's sarcoma. At present, his sister is alive and well six years after transplantation. The third patient lost his first graft after three years due to chronic allograft nephropathy and recurrence of glomerulonephritis. At this time, he lives harboring a second graft for over nine years. However, he suffered from pneumonia, a generalized varicella infection, and *H. parainfluenzae* bronchitis.
Conclusions Patients with complete C4 deficiency are at increased risk of infections after kidney transplantation. Under certain precautions and judicious use of immunosuppression good long-term results are achievable.

P131

An audit to evaluate value of positive urine cytology result

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Transitional cell carcinoma of the bladder is a significant cause of morbidity and mortality. Urine cytology is an important diagnostic tool in clinically suspicious bladder cancers.
The aim of this audit was to evaluate the effectiveness of urinary cytology in the diagnosis of bladder cancer.
A total of 73 urine cytology reports reported either as malignant or suspicious of malignancy from Dec 2002 to April 2004 were analysed. Of these, 45 cases [61%] were malignant and 28 cases [39%] were suspicious of malignancy. The follow up histology of the malignant cases was as follows: Transitional cell carcinoma [42 /45] and Hyperplasia of urothelium [2/45]. 1 case did not have a follow up histology. Of the 28 cases of suspicious malignancy, 8 cases were found to be malignant on follow up histology while 20 cases did not have a follow up histology.
The absolute sensitivity of urine cytology in detecting malignancy was 84.3% and positive predictive value was 90%.
Urine cytology is very useful in diagnosing bladder cancers as it has an excellent positive predictive value. All cases reported as suspicious of malignancy should have a follow up histology if there is a strong clinical suspicion of malignancy.

P132

Ovarian Serous Tumours of the Testis – a Report of Two Cases

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Female mullerian type neoplasms occur rarely in the testis. The most commonly reported ovarian type epithelial tumour is serous tumour of borderline malignancy (20 cases), while papillary serous carcinomas of the ovarian type are rarer tumours with less than 15 cases reported in literature. We report two cases, one each of serous tumour of borderline type and papillary serous carcinoma in the testis. The men aged 63years and 34years respectively presented with cystic lesions in the testis. Histology showed cystic tumours in both cases with papillary excrescences lined by cuboidal cells with epithelial stratification and nuclear atypia. The second tumour showed solid areas with infiltrative neoplastic cells. Both neoplasms were positive with epithelial markers (Ber –EP 4, CK 7, ESA, CEA and EMA), and were negative for mesothelial markers (calretenin, HBME -1, thrombomodulin). The main differential diagnosis is from mesothelioma of the tunica vaginalis which show a more aggressive behaviour and carcinoma of the rete tesis. Due to rarity of the lesion the management of these tumours is uncertain, however it would be reasonable to treat them like the ovarian counterparts.

P133

Monotypic Epithelioid Angiomyolipoma: a Mimic of Renal Cell Carcinoma

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Monotypic epithelioid angiomyolipoma (EAML) is a rare variant of angiomyolipoma, which belong to the family of perivascular epithelioid cell tumours (PECOMA).
Despite its marked morphological resemblance to sarcomatoid renal cell carcinoma, the immunophenotype (HMB-45 and MelanA- positive and vimentin and epithelial markers negative) is in contrast to epithelial neoplasm and parallel to the phenotypic profile of angiomyolipoma. We report a case of EAML (9.5cm mass) arising in the right kidney in a 61 year old woman in the absence of tuberous sclerosis. Histology showed poorly differentiated/ sarcomatoid carcinoma likes morphology throughout, with a high mitotic rate and necrosis. Vascular and adipocytic components were not present. The tumour cells expressed Melan A, HMB-45 and CD10. Epithelial markers (cytokeratin and EMA) were negative. CT scan seven months after the surgery showed two recurrences (4cm and 11cm) and the diagnosis of EAML was confirmed on biopsy. She died 8 months after the operation. The behaviour of EAML is unpredictable and criteria for malignancy are not well defined. This is a rare tumour which can closely mimic renal cell carcinoma, and should be included in the differential diagnosis of poorly differentiated primary renal neoplasms.

P134

How Much Prostate Have I Examined? Testing the Adequacy of Prostate Biopsies

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The ProtecT study is multicentre trial of treatments for screen-detected prostate cancer. It has been noted that the rate of prostate cancer detection varies markedly between the nine study centres. The screening and biopsy protocol is similar in all centres, but centres may vary in the skill with which biopsies are taken, and the difficulties of processing tissue from prostate needle biopsies are known to be met in different ways. Stereological considerations suggest that the total length of core examined will be an important predictor of the detection rate, and processing aims to ensure the whole core is examined histologically.

We have investigated whether the difference in prostate cancer detection rate can be explained by different processing methods making different amounts of prostate available to for examination by the histopathologist. Slides are scanned, then using the software package ImagePro Plus the area of each section is calculated and the total length of the cores present determined using a skeletonization algorithm.

Preliminary data from slides from 5 departments give a range of lengths examined from 46mm to 149mm and suggest a correlation between lengths of prostate core examined and the detection rate. In addition the area of tissue on the slide and the lengths calculated are strongly correlated. This suggests that area (a simple measurement) may be a good proxy for length when auditing biopsies.

P135

Spontaneous regression of a metastatic transitional cell carcinoma to the lung following removal of the primary tumour and cessation of immunosuppression

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We present a case of spontaneous regression of a metastatic transitional cell carcinoma (TCC) to the lung occurring in an allograft renal transplant after surgical removal of the primary tumour and discontinuation of the immunosuppressive therapy.

A 45 years old gentleman of Indian origin previously diagnosed with polycystic kidney disease underwent a cadaveric renal transplantation. This was preceded by 13 months of haemodialysis. He was on a combined immunosuppressive therapy composed of azathioprime, prednisolone and cyclosporine. Sixteen years later, he developed frank haematuria associated with raised creatinine level. His CT scan revealed a 9x10cm mass in transplanted renal pelvis together with multiple soft tissue nodules within the lungs consistent with metastatic deposits. These nodules were not biopsied. A transplant nephrectomy was done and the immunosuppressive therapy was discontinued. He was put back on haemodialysis. Histological examination revealed a G3 pT1 TCC which was invading into the renal parenchyma. He was followed up by repeated CT scan which showed complete spontaneous regression of his lung deposits over a period of 12 months.

The spontaneous regression of the metastatic deposits may be explained by the reduction of tumour bulk on one side and the increased efficiency of the immune system to overcome the residual metastatic nodules on the other side. To our knowledge this is the first such case to be reported.

P136

The role of human papillomavirus in the development of transitional cell carcinoma in renal transplant patients

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Objective: We investigated the role of human papilloma virus (HPV) in the development of transitional cell carcinoma (TCC) arising in renal transplant recipients.

Methods: Genomic DNA was extracted from 10μm paraffin embedded sections of 5 TCCs arising in 5 renal transplant recipients using the QIAamp DNA mini kit (Qiagen Cat No. 51304) according to manufacturers' instructions. *β-Globin PCR* was performed to test DNA adequacy. Samples were tested for the presence of HPV DNA by broad spectrum HPV PCR method using non-biotinylated SPF10 primers (SPF1A, SPF1B, SPF1C, SPF1D, SPF2B, SPF2D) which amplify a short 65bp fragment. Positive bands were identified on a 3% gel. Positive samples underwent a second HPV PCR and were amplified using biotinylated SPF10 primer set, which amplifies the same 65bp region of the L1 open reading frame. INNO-LiPA line probe assay (Innogenetics) was then performed to genotype the samples which uses a reverse hybridization principle.

Results

4 out of 5 TCCs examined were positive for HPV. The high risk HPV16 was detected in 3 cases whereas in the fourth case an unclassifiable HPV genotype was present. In all DNA samples *β-Globin* amplification was successful.

Conclusion: Our results indicate that HPV and in particular HPV16 may play an aetiological role in the development of TCC in the renal transplant patients.

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Abstract withdrawn

P138

Necrobiotic Granuloma Associated with Endometrial Carcinoma: a Case Report

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BACKGROUND: Uterine granulomas are very rare. Granulomatous inflammation is a well recognized sequel of prior surgery in many anatomic sites, especially in the male and female genitourinary system. They are either focal or diffuse, related to previous biopsy or surgery, usually represent local reaction without an obvious cause. The coexistence of endometrial carcinoma and necrobiotic granulomas is a very rare clinical entity. The case being reported here is unique and to our best knowledge it is the first ever reported case of this type
CASE: A 65 years old postmenopausal presented with history of postmenopausal bleeding. She had history of same kind of bleeding episode three years back for which diagnostic hysteroscopy and polypectomy was done and histology report revealed mild atypical hyperplasia of polyp. Hysteroscopic polypectomy was done and endometrial biopsy was taken this time again. The histology report showed atypical hyperplasia of endometrial polyp with no element of malignancy. There was extensive necrobiotic granuloma with Langhan's type giant cells in the endometrium. Subsequent histological examination of uterus after hysterectomy disclosed a well differentiated endometrioid endometrial carcinoma and the necrobiotic granuloma.
CONCLUSION: Uterine granulomas are rare and their association with uterine carcinoma is even more rare. They are usually related to infection or previous surgery, representing idiopathic reaction and do not require further action. But, they warrant careful assessment to exclude infection or systemic granulomatous diseases.

P139

An Audit of Placental Histology Reports

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AIMS/OBJECTIVES: To know different indications of placental histology and to correlate different histological findings with different clinical indications.
BACKGROUND: Macroscopic and histological examination of the placenta has an important role in delineating the cause of obstetric and neonatal pathologies. The working party report of Royal College of Obstetricians & Gynaecologists and Royal College of Pathologists has recommended placental examination for a number of indications. Following are the major indications of placental examination, early neonatal sepsis, congenital anomalies, preterm labour, twin pregnancy, severe pre- Eclampsia, intrauterine growth restriction and macroscopic placental abnormalities. There is little information available on the extent to which these guidelines are being followed and quality of reports in different institutions.
MATERIAL & METHODS: A retrospective audit of maternal notes and placental histology reports of 84 patients, whose placenta were sent for histological examination. Data was collected on a proforma and results were analysed by using simple statistical methods.
RESULTS: Out of 84 placental histology reports 35 % were submitted due to twin deliveries, 20% due to intrauterine growth restriction and remaining were sent for histology due to, Preterm delivery (8%), pre-Eclampsia and HELLP Syndrome(7%), Two vessels in umbilical cord (7%), congenital anomalies(2.3%) and 17% due to other miscellaneous causes.

Microscopic examination of majority (70%) of placentas submitted due to twin pregnancy revealed normal histology while in intrauterine growth restriction group, 23% and 29% histology reports showed small placental infarctions and Perivillous fibrin depositions respectively. All placental histology reports in preterm labour, congenital abnormality, two vessels in the umbilical cord and miscellaneous group were normal and 83% of histology reports revealed normal placental tissue in pre-Eclampsia & HELLP syndrome.
CONCLUSION: It is apparent from the results of this audit that most of the histology reports were normal and except in intrauterine restriction group, there was little correlation between clinical indication and histology reports. Placental histology costs good amount of money to NHS and there should be very clear indication of its histology. Awareness of this deficiency, standardization of diagnostic criteria and increased knowledge in placental pathology may improve the quality of diagnosis and correlation with clinical indications in this area.

P140

Molecular Genetic Analysis of Ovarian Clear Cell Adenocarcinomas Reveals Novel Pathobiological Insights

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Ovarian clear cell adenocarcinomas (OCCA) account for approximately 5% of all ovarian malignancies. Compared to other epithelial ovarian cancer subtypes, they are generally associated with a poorer prognosis and are relatively resistant to platinum-based chemotherapy. Hence, there is a need to improve our understanding of its pathobiology in order to optimise currently available treatments and develop new therapeutic strategies. To delineate the molecular genetic features of OCCA, we performed tiling-path array comparative genomic hybridisation (aCGH), using 32,000 BACs with a resolution of ~50kb, on DNA extracted from 12 OCCA cell lines. Common regions of copy number change (>30% frequency) included gains of 1p13.1-p12, 8q12.1-q12.3, 8q24.21-q24.3, 20q13.13-q13.33 and losses of 13q11-q12.11, 13q32.2-q34, 15q12-q22.31, 18q, and 19p13.2. Commonly amplified regions included 1p13.1 (*VCTN1*), 8q24.21 (*MYC*), 19q12 (*CCNE1*), whilst high levels of amplification were observed in 3q21.3 (*MCM2*), 8q24.13-24.22 (*MYC*), 8q11.21-q11.23 (*SNAI2*), 11q13.3-q13.4 (*FOLR1*), and 19q12 (*CCNE1*). Interestingly, MCM2 overexpression is associated with platinum-resistance in ovarian cancer, and the *VTCN1* gene, within the recurrently amplified 1p13.1 region, codes for an inhibitor of T cell-activation, which is also upregulated in clear cell renal carcinomas. Recurrent regions of loss harbouring putative tumour suppressor genes included 13q11-q12.11 (*LATS* and *SAP18*), 13q32.2-q34 (*ING1*) and 19p13.2 (*MBD3L1*). We are currently validating these copy number changes in a larger series of OCCA tumours. This study provides the first characterisation of the molecular genetic profiles of OCCA, and reveals novel insights into the molecular pathogenesis of this tumour type.

P141

Hypoxia and Angiogenesis in Endometrioid Endometrial Carcinogenesis

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Background: Hypoxia-inducible factor 1α (HIF-1α) plays an essential role in the adaptive response of cells to hypoxia, triggering biological events associated with aggressive tumour behaviour.
Aim: To explore the expression of hypoxia related proteins in normal, premalignant and malignant endometrial lesions representing the morphologically well defined stepwise model of human endometrioid endometrial carcinogenesis
Materials and Methods: Expression of HIF-1α and proteins in the HIF-1α pathway (Glut-1, CAIX, VEGF) in paraffin-embedded specimens of normal (n=17), premalignant (n=17) and endometrioid endometrial carcinoma (n=39) was explored by immunohistochemistry, in relation to microvessel density (MVD).
Results: HIF-1α overexpression was absent in inactive endometrium but present in hyperplasia (61%) and carcinoma (87%), with increasing expression in a perinecrotic fashion pointing to underlying hypoxia. No membranous expression of Glut-1 and CAIX was noticed in inactive endometrium, in contrast with expression in hyperplasia (Glut-1 0%, CAIX 61%, only focal and diffuse) and carcinoma (Glut-1 94.6%, CAIX 92%, both mostly perinecrotically). Diffuse HIF-1α was accompanied by activation of downstream targets. VEGF was significantly highly expressed in hyperplasias and carcinomas compared to inactive endometrium. MVD was higher in hyperplasias and carcinomas than in normal endometrium ($p<0.001$).
Conclusion: HIF-1α and its downstream genes are increasingly expressed from normal through premalignant to endometrioid adenocarcinoma of the endometrium, paralleled by activation of its downstream genes and increased angiogenesis. This underlines the potential importance of hypoxia and its key regulator HIF-1α in endometrial carcinogenesis.

P142

Progressive Derailment of Cell Cycle Regulators in Endometrial Carcinogenesis

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Background: Derailments of the control mechanisms of the cell cycle can initiate carcinogenesis, and play a role in progression to cancer.
Aim: To explore the expression of cell cycle proteins in normal, premalignant and malignant endometrial lesions representing the morphologically well defined stepwise model of human endometrial carcinogenesis
Materials and Methods: Observational study. Paraffin-embedded specimens from inactive endometrium (n=17), endometrial hyperplasia (n=23) and endometrioid endometrial carcinoma (n=39) were stained immunohistochemically for cyclin A, cyclin B1, cyclin D1, cyclin E, cdk2, p16, p21, p27, p53 and Ki-67(MIB-1)). Differences in expression between the tissues, and correlation with classical prognostic factors for the carcinomas were analysed.
Results: Expression of cyclin A and MIB-1 gradually increased from normal through hyperplasia to carcinoma, indicating that proliferation increases over the carcinogenetic spectrum. Cyclins B1 and D1, and p16, p53, and cdk2 gradually increased from normal through hyperplasia to carcinoma, indicating their potential importance in both early and late carcinogenesis. Cyclin E and p21 especially increased and p27 decreased from hyperplasia to carcinoma, underlining their role in late carcinogenesis.
In cancers, expression of p53, cyclin A and MIB-1 was positively correlated to grade, and cyclin A was positively correlated with cdk2, p21, MIB-1, cyclin E and p53.
Conclusion: During (endometrioid) endometrial carcinogenesis, there is increasing proliferation paralleled by progressive derailment of cyclin B1, cyclin D1, cyclin E, p16, p21, p27, p53, and cdk2, indicating the importance of these cell cycle regulators in endometrial carcinogenesis.

P143

p16 is Consistently Expressed in Endometrial Tubal Metaplasia

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Background: Cell cycle proteins and HIF-1α with downstream factors are often abberrantly expressed in (pre)neoplastic tissue.
Methods: Paraffin-embedded specimens of inactive endometrium with TM (n=15), ovarian inclusion cysts (n=6), cervix with TM (tubal metaplasia) (n=3), Fallopian tubes (n=7), cycling endometrium (n=9) and a ciliated cell tumour of the ovary were stained for p16 and LhS28. 39 Endometrioid endometrial carcinomas and 5 serous endometrial carcinomas were stained for p16. Additionaly, inactive endometrium (n=15) was immunohistochemically stained for p21, p27, p53, cyclin A, cyclin D1, cyclin E, HIF-1α, CAIX, Glut-1 and MIB-1.
Results: A mosaic pattern of expression of p16 was seen throughout in all cases of endometrial TM (15/15), in 2/6 of the ovarian inclusion cysts with TM, in all (3/3) cervical TM and focal in 5/7 of Fallopian tube cases. Mosaic expression was also seen in a ciliated cell tumour of the ovary and in 18/39 of endometrioid endometrial carcinomas, and diffuse p16 expression was seen in 5/5 serous carcinomas. In comparison with normal endometrium, TM areas in the endometrium showed significantly increased expression of HIF-1α, cyclin E, p21 and cyclin A, and decreased expression of p27. Membranous expression of CAIX and Glut-1 was only seen in TM areas, pointing to functional HIF-1α.
Conclusion: As p16 is consistently expressed in TM, less and only patchy expressed in the nomal Fallopian tube, is paralleled by aberrant expression of cell cycle proteins, HIF-1α, CAIX and Glut-1 and resembles the pattern of p16 expression frequently seen in endometrial carcinomas, we propose endometrial TM to be a potential premalignant endometrial lesion.

P144

The Invasive Front in Endometrial Carcinoma: Higher Proliferation and Associated Derailment of Cell Cycle Regulators

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Objective: To explore whether expression of proliferation and hypoxia-related proteins differs in the central parts and the invasive front in endometrial carcinomas.
Methods: Proliferation associated proteins Ki67 and cyclin A, cell cycle regulators p16, p21, p53, cyclin D1, cyclin E, and cdk2, and Hypoxia Inducible Factor 1α and its downstream factors Glucose transporter 1, Carboanhydrase IX, and Vascular Endothelial Growth factor, were immunohistochemically stained in paraffin-embedded specimens from endometrioid (n=33), mucinous (n=1) and serous (n=5) endometrial carcinomas. The percentages of positive cells at the invasive front and central tumour parts were scored and compared.
Results: Ki67 ($p<0.001$), cyclin E ($p=0.018$), p16 ($p=0.003$) and cdk2 (0.001) were higher expressed at the invasive front than centrally (Wilcoxon Signed Ranks test). Higher expression of these antigens at the invasive front was seen in 31/38 cases for Ki67, in 16/39 cases for cyclin E, in 15/39 cases for cdk2, and in 11/39 cases for p16. The other cell cycle proteins and the hypoxia related factors did not show significant differences in expression between the central parts and the invasive front.
Conclusion: Endometrial carcinomas clearly show an invasive front that is characterized by higher proliferation and progressive derailment of the cell cycle regulators cyclin E, p16 and cdk2, but not by an increased hypoxic response.

P145

Tubulo-Squamous Polyp: Report of 10 Cases of a Hitherto Uncharacterised Vaginal Polyp

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We report 10 cases of a distinct vaginal polyp which has hitherto not been characterized. The polyps occurred in women aged 39 to 78 years. Most were in the upper vagina. Histologically all were composed of well circumscribed expansile nests of epithelial cells embedded in a hypocellular fibrous stroma. The epithelial elements were predominantly squamous in type but small tubules were present at the periphery of some of the nests.. In three cases, a few tubules unassociated with squamous elements were present. In 3 of 4 cases tested, the cells lining the tubules were positive with prostatic acid phosphatase and in two of four with prostate specific antigen. The histological features of this polyp, which we term “tubulo-squamous polyp of the vagina”, are constant and distinctive and differ from other polyps and from mixed tumour of the vagina. Possible theories of histogenesis include a Mullerian origin, derivation from mesonephric remnants or derivation from urogenital sinus-derived epithelium. Positive staining in some cases with prostatic acid phosphatase and prostate specific antigen raises the possibility of ectopic prostatic tissue, although the overall appearance is different from that entity, or derivation from paraurethral Skene’s glands, the female equivalent of prostatic glands in the male.

P146

Endometrial Hyperplasia Involving Endometrial Polyps: Report of a Series and Discussion of the Significance in an Endometrial Biopsy

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Endometrial polyps are a common cause of abnormal uterine bleeding. Rarely a hyperplasia, either complex or atypical, is identified within a polyp in a biopsy or polypectomy specimen. It is not known whether the hyperplasia is likely to be confined to the polyp or also involve non-polypoid endometrium. We identified 32 cases in which endometrial hyperplasia was present within a polyp. This comprised 3.1% of all endometrial polyps (total number 1031) diagnosed during the study period. We traced any follow-up pathology specimens in order to evaluate the status of the surrounding endometrium. The hyperplasias were complex (n=23) or atypical (n = 9) in type. In 14 of 27 (52%) cases in which non-polypoid endometrium was available for histological evaluation, either on the original biopsy or in follow-up specimen, hyperplasia involved the non-polypoid endometrium and in 3 further cases, hyperplasia was present in a polyp in follow-up specimens. Patients with atypical hyperplasia were slightly more likely to have hyperplasia in the surrounding endometrium than those with complex hyperplasia. We illustrate that the risk of endometrial hyperplasia in a polyp concurrently involving non-polypoid endometrium is significant. We suggest a strategy for the management of patients with hyperplasia identified within an endometrial polyp.

P147

Uterine Tumour Resembling Ovarian Sex Cord Tumour (UTROSCT) is an Immunohistochemically Polyphenotypic Neoplasm Which Exhibits Coexpression of Epithelial, Myoid and Sex Cord Markers

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Four UTROSCTs are described and a detailed immunohistochemical analysis undertaken. The tumours ranged from 0.8 to 19.5 cm. Three were well circumscribed intramural lesions and the other a pedunculated mass attached to the uterine serosa. The tumours were variably composed of solid, corded, trabecular , nested, glandular and retiform arrangements.. Three were diffusely positive with AE1/3 and all with epithelial membrane antigen. Three , 4 and 1 case respectively stained with desmin, smooth muscle actin and h-caldesmon. Two, 4, 1 and 2 respectively were positive with α inhibin, calretinin, melan A and CD99. All were chromogranin negative and exhibited diffuse staining with CD56. All were positive with oestrogen and progesterone receptor, vimentin and WT1. Three were androgen receptor positive and all CD10 and HMB45 negative. UTROSCT exhibits a polyphenotypic immunophenotype with coexpression of epithelial, myoid and sex cord markers and hormone receptors. CD56 positivity is evidence of true sex cord differentiation since it has recently been shown that ovarian sex cord-stromal tumours stain with this marker. However, epithelial membrane antigen positivity is against a true sex cord tumour. The polyphenotypic immunophenotype is useful in diagnosis. UTROSCT is most likely derived from an uncommitted cell with the capacity for multidirectional differentiation.

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Histopathological Reporting of Vulval Cancer Specimens

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Introduction Careful reporting of vulval cancer specimens is important because it defines the staging, determines patient management and provides prognostic information.
Aims To identify how closely reporting of vulval cancer specimens adhered to guidelines set out in the national minimum dataset.
Method All cases of vulval cancer reported between 01/01/2000 and 31/12/2005 were retrospectively identified and the histology reports compared with the National Minimum Dataset (the gold standard).
Results 167 specimens were identified. Only 14% of vulvectomies had complete data. The maximum horizontal tumour dimension was not reported in 32% of specimens and the minimum tumour free deep soft tissue margin was not reported in 34% of specimens. Many of the other variables were also missing from a proportion of reports. Vulval biopsies were particularly poorly reported compared to vulvectomy specimens. Following the introduction of the National Minimum Dataset there was a general improvement in the reporting of information required
Conclusions The reporting of vulval cancer specimens was frequently incomplete. A computerised reporting system for vulvectomies, compliant with the National Minimum Dataset is to be started and a local dataset for the reporting of vulval cancer in vulval biopsies has been developed in order to improve completeness of reporting.

P150

Kikuchi-Fujimoto Disease of the Uterine Cervix - an unusual clinico-pathologic presentation

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An asymptomatic 29 year old female was referred for further investigation after a routine cervical smear revealed mild to moderate dyskariosis. The cervical biopsy showed warty CIN-1 and 2 with moderate inflammation. The cervical LLETZ showed extensive ulceration with focal CIN-1 and 2 and koilocytosis. There were dense lympho-histiocytic inflammatory aggregates with areas of necrosis and abundant karryorhectic nuclear debris in the subepithelial stroma. Plasma cells and neutrophils were scanty. Immunohistochemistry revealed predominance of T cells. Admixed with these were many CD68 positive histiocytes and plasmacytoid monocytes. The initial differential diagnosis included peripheral T cell lymphoma, granulocytic sarcoma, a vasculitic process, and a very unusual manifestation of Kikuchi's disease. The infiltrate was negative for leukaemia markers (MPO). Full blood count with peripheral film, bone marrow biopsy, chlamydia serology and a CT scan of the thorax, abdomen and pelvis were normal. On T cell receptor gene rearrangement the T cell population was polyclonal. A final diagnosis of Kikuchi-Fujimoto disease was offered and the patient was kept on close follow up. Six years later she is well and free of disease.
This to the best of our knowledge is the first report of Kikuchi- Fujimoto disease of the uterine cervix.

P151

The Histopathological Reporting of Radical Hysterectomy Specimens for Cervical Cancer- An Audit of Practice at the University Hospital of Wales, Cardiff

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Radical hysterectomy and pelvic node dissection is the preferred treatment for early-stage cervical carcinoma. The Royal College of Pathologists published a minimum dataset in 2001 to ensure reporting of items with prognostic significance for patients. Our audit assessed adherence to reporting of dataset items between Jan 1st 2004 and 31st June 2006. This included size of tumour, site, presence of parametrial disease, involvement of the vaginal cuff, depth of invasion, lymph node metastases, histological type and grade. 121 hysterectomy specimens were identified from the pathology department database at UHW using the 'hysterectomy for cancer ' Snomed code. Endometrial malignancy, metastases from other sites and pelvic exenteration specimens were excluded leaving 38 cases, of which 28 contained remaining carcinoma after cervical biopsy. Results of comparative analysis revealed 42% of reports lacked a macroscopic size for the tumour; 50% failed to indicate whether the vaginal cuff was present; microscopic depth of invasion was not stated in 14%, and 32% did not mention parametrial margins. All reports gave details of lymph node metastases and histological type and grade of malignancy. These findings suggest development and implementation of a departmental proforma for reporting of these specimens may be necessary to improve standards.

P152

Urine cytology in the diagnosis and staging of cervical neoplasia

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Background: Urine cytology is mainly used in the screening of urothelial neoplasms. Evaluation of bladder mucosa typically by either cystoscopy or urine cytology is important in the staging of cervical cancer. In addition, voided urine specimens may incidentally detect cervical dysplasia due to vaginal contamination.
Aim: We describe 5 cases of positive urine cytology in which the primary diagnosis was cervical neoplasia.
Methods: All urine samples from November 2005 to November 2006 were reviewed.
Results: 253 urine cytology specimens were received over a 12 month period and 5 positive cases for cervical neoplasia were identified. Of these 5 positive cases, 3 were catheterised specimens sent as part of a staging procedure for known cervical cancer (1 adenosquamous carcinoma and 2 endocervical adenocarcinomas). The 2 remaining samples were voided specimens sent to exclude primary urothelial neoplasms. One had borderline nuclear atypia of squamous cells with confirmed CIN 1 on biopsy and the other had severe dyskaryosis with confirmed squamous cell carcinoma on cervical biopsy.
Conclusion: These 5 cases illustrate that urine cytology is a useful adjunct in the staging of cervical carcinoma and the primary diagnosis of cervical neoplasia.

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Audit of regional thyroid cancer incidence in Liverpool

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Thyroid cancer, although relatively rare, is most likely to develop in women of reproductive age. The commonest type of thyroid cancer is described as "differentiated"; this accounts for 90% of cases. This is sub-divided into two forms: papillary and follicular adenocarcinoma, which account for 80% and 10% of cases, respectively. Five per cent of patients have medullary cancer, which is sometimes familial and can be associated with other endocrine malignancies. Finally, there are two rare types which occur in the elderly. About 1% of patients have lymphoma of the thyroid, which presents as a rapidly expanding mass and is usually diagnosed on the basis of the patient's history, together with a tissue diagnosis.

Thyroid cancer is a relatively uncommon cancer; in the Northern and Yorkshire region there are around 120 cases annually. The prognosis for thyroid cancers is generally good, with middle aged adults with differentiated thyroid carcinoma showing a 10 year survival rate of 80-90%, overall.

We audited, 196 thyroid cancer cases presented at MDT meetings during the year 2003-2006 at Liverpool, and compared the incidence rates and type of cancer statistics with the data obtained from Mersey and Cheshire cancer network website.

P156

Co-expression of EGFR and Cyclin-D1 Predicts Radiocurability of T2N0 Squamous Carcinoma of the Larynx

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Modulators of the cell cycle are considered important in carcinogenesis and may influence the response to radiotherapy. Previous studies on potential interactions between tumour biomarkers have produced inconsistent results due to a mixture of primary sites, stages and treatment modalities.

This study has examined the immunocytochemical expression of Ki-67, epidermal growth factor receptor (EGFR), cyclin D1 and retinoblastoma protein in diagnostic biopsy material, in relation to primary site recurrence rates of T2N0 laryngeal carcinomas in 50 patients treated with a standard radical radiotherapeutic protocol.

Five carcinomas showed loss of retinoblastoma protein expression and the median indices of immunocytochemical markers were 50% for Ki-67, 21% for cyclin D1 and 47% for EGFR. There was a positive correlation between the expression of EGFR and that of cyclin D1 ($p=0.03$). On univariate analysis, only Ki-67 expression showed a trend for association with tumour recurrence but this was not significant. Multiple logistic regression analysis with categorical modelling indicated that a combination of high EGFR expression and high cyclin-D1 expression was associated with a high risk of tumour recurrence at the primary site (odds ratio 5.32, 95% CI 0.41).

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Expression of IL-8 and IL-8 receptors on neuroendocrine tumours of pancreas

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Introduction: IL-8 is a chemokine that play role in acute inflammation, angiogenesis and tumour growth through its two receptors IL-8RA and IL-8RB. Recent studies suggest that IL8 may play a role in the growth of neuroendocrine tumours (NTP). The *aim* of our study was to examine the expression of IL8 and IL8 receptors NTP.
Materials and methods: expression of IL-8 and IL-8 receptors was examined in 52 surgically resected specimens of different tumour grades of NTP. Immunohistochemical analysis was performed by using three step indirect method. The presence and intensity of staining was scored.
Results: IL-8 was expressed in 11/52 (21%) cases of NTP. The inflammatory cells of tumour stroma expressed IL-8. The expression of IL-8RA was 63.4% (33/52) and IL-8RB was 92% (48/52). The expression of all antigens was mainly cytoplasmic. Nine out of 52 tumours co-expressed all 3 antigens and 30/52 tumours co-expressed both receptors.
Conclusion: This is the first *in vivo* study of IL-8 and its receptors in NTP. The results show that IL-8, IL-8RA and IL-8 RB were over expressed. Which suggest the role of IL-8 and receptors in the growth of NTP. The simultaneous presence of IL-8 and receptors suggests an autocrine signalling.

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Differential Expression of Estrogen and Progesterone Receptor Isoforms in Pancreatic Neoplasms

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The potential role of estrogen (ER) and progesterone (PR) receptor isoforms in pancreatic neoplasms has been debated for many years, and the expression pattern of the ER beta (β) isoforms remains especially enigmatic.
The expression of ERα, ERβ1, ERβ2 and PR (total and B isoform) was analyzed by immunohistochemistry. Paraffin-embedded tissue blocks from 19 patients with pancreatic neoplasms, diagnosed at the Department of Histopathology at St. James's University Hospital, Leeds, were labeled using specific monoclonal antibodies. The tumours included mucinous cystadenoma (MCA), serous cystadenoma, ductal adenocarcinoma, solid pseudopapillary tumour (SPT), intraductal papillary mucinous neoplasm, and neuroendocrine tumours. The sections were reviewed and the immunoreactivity of the tumours to ERα, ERβ1and 2, PRs was scored.
All tumours showed strong immunoreactivity for ERβ1 and 2 but were ERα negative. Significant positive correlation was found between ERβ1 and ERβ2, whose expression did not depend on age or gender of patients. Total PR was moderately expressed in SPT and MCA and negative in the remaining tumours. PRB was positive in two out of the four MCA. We conclude that pancreatic tumours strongly express ERβ1 and ERβ2, which may have therapeutic implications for these tumours.

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Abstract withdrawn

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Liver Biopsies for Metastatic Disease- the Aberdeen Experience.

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Introduction: The liver is the second most common site for metastatic spread, after the lymph nodes. Because of its rich blood supply and unique humoral factors that promote cell growth it provides an ideal environment for the metastasis to establish itself. Liver biopsies are often used to confirm metastasis from a known primary and in many instances to identify the primary site if this is unclear clinically and thereby help in prompting further investigations or appropriate therapy as the case may be.
Methods: All specimens of liver tissue including core biopsies, hepatic resections and frozen sections undertaken for liver metastasis during the year 2006 were analysed. A standard panel which included CK7, CK20, CEA, CDX2, TTF1, ER, PSA, AE1/3 and CAM5.2 was employed to determine the primary site for adenocarcinomas. Selected markers were used for other tumours based on tumour morphology and clinical suspicion. The clinical impression, specimen size, immunophenotype and final diagnosis were then documented.
Results: Out of a total of 196 liver specimens 65 cases with metastasis were analysed which included 52 liver core biopsies, 9 hepatic resections and 4 frozen sections. The histological types of tumour were as follows: Adenocarcinomas 39, Hepatocellular carcinomas 5, Small cell carcinomas 4, Transitional cell carcinomas 4, Neuroendocrine carcinomas 3, Poorly differentiated carcinomas 3, Lymphomas 3, Squamous cell carcinomas 2, GIST 1, and Hurthle cell tumour (Thyroid) 1. Among adenocarcinomas, the primary tumours were accurately localised in the colon or rectum in 80% of cases using a combination of immunohistochemistry and tumour morphology. Likewise, only 50% of the remaining adenocarcinomas were accurately localised to the pancreas/biliary system/stomach.
Conclusions: Adenocarinoma constituted the majority (58%) of the metastasis while primary hepatocellular carcinomas (8%), small cell carcinomas (6%) and transitional cell carcinomas of bladder (6 %) represented the remaining bulk of the tumours. CK20+/CK7- /CDX2+ metastasis indicated a colorectal origin with considerable accuracy. The same is true of CK20+/CK7+ /CDX2- metastasis, which indicated upper GIT(pancreas/biliary system/stomach) localisation but there is, however, a need for markers which could establish pancreas, biliary system or stomach as primary sites more specifically.

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Does Liver Fibrosis Regress in Autoimmune Chronic Hepatitis?

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Introduction: Liver fibrosis is a feature of autoimmune chronic hepatitis (AICH); 40% of patients develop liver cirrhosis in the long term. Although fibrosis is thought to be "irreversible" there is some evidence that this might regress in AICH-related fibrosis.
Aim: To determine whether there is histological resolution of liver fibrosis in patients with AICH.
Method: Patients with a diagnosis of AICH were identified from our database using SNOMED search criteria (T56* and D4700). Patients with AICH who had multiple liver biopsies between January 1997 and December 2006 were identified. Each biopsy was re-reviewed to confirm histological grade using the modified Knodell scoring system.
Results: 28 (24F: 4M) patients with multiple biopsies were identified; one patient (F) was excluded due to an inadequate second biopsy. These patients had two (n=19), three (n=5) and four (n=3) biopsies over 10 year period. The median time from initial to final biopsy was 30 months (range=8-62).
17 (63%) patients showed an improvement in the stage of fibrosis [by 1 stage (n=9), 2 stages (n=2), 3 stages (n=2) and 4 stages (n=4)] within this time.
Six (22%) patients showed deterioration in the grade of fibrosis (by 1 stage (n=3), 2 stages (n=1) and 3 stages (n=2)).
Four (15%) patients showed neither improvement or deterioration.
The median change in the staging of fibrosis showed improvement by half a stage.
Conclusion: There is improvement in the stage of liver fibrosis in a significant proportion of AICH patients. Progression may be related to other coincident risk factors.

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Lymphomatous Polyposis of the Gallbladder

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Lymphomatous polyposis of the gastrointestinal tract is caused by mantle cell lymphoma. It is an uncommon disorder producing a nodular cobblestone like appearance of the mucosa and can occur anywhere from the oesophagus to the rectum. Involvement of the gallbladder, however, has not been previously described in the English literature.
We report the case of a 76 year old man who had tonsillar mantle cell lymphoma diagnosed in 2003. Three years later he presented with central abdominal pain, nausea and jaundice. On ERCP gritty calculi were seen in the common bile duct and a cholecystectomy was performed.
Macroscopically, gallbladder was studded with multiple mucosal nodules of 2-3mm size giving a cobble-stone like appearance. No gallstones were present.
Microscopically, a nodular lymphoid infiltrate with occasional germinal centres was seen occupying the mucosa. No lympho-epithelial lesions were seen.
Differential diagnoses of follicular cholecystitis and lymphoma were considered. Immunohistochemistry showed CD79a, CD5 and Cyclin D1 positivity thus confirming a diagnosis of mantle cell lymphoma.
This case indicates that lymphomatous polyposis can sometimes affect the gallbladder. Care is required to distinguish this from follicular cholecystitis.

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Peer review of lymphoma reporting: a practical and palatable alternative to EQA

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Geography dictates the shape of clinical services in the north and east of Scotland. To address quality and consistency of lymphoma reporting, interested pathologists from Highland, Grampian, Tayside and Fife met monthly to review around a multi-headed microscope our new diagnoses of lymphoma. Between April 2004 and March 2007 we reviewed 823 cases - 81% were mature B-cell neoplasms, 9% Hodgkin lymphoma, 9% T-cell tumours; the remainder were rarities. There were no errors impacting on patient care. We agreed which cases were difficult. Areas of debate included grading follicular lymphomas and differentiating nodular lymphocyte predominant Hodgkin lymphoma from T-cell rich B-cell lymphoma. Cutaneous lymphomas, cases with unexpected immunoprofiles and T-cell lymphomas were challenging.
Consultants and trainees valued the educational experience of the reviews; accuracy, consistency and confidence were enhanced by participation. We have maintained this process consistently over three years and remain supportive of it. It has enabled us to expand our lymphoma practice and improve perceived quality of our individual and collective skills. The regional review process is educational, non-threatening, yet demanding and challenging. Unlike EQA, review deals with real cases thus having tangible benefits for patients concerned and for the security with which they are treated.

P166

Cyclin D1 expression and light chain in situ hybridisation in multiple myeloma using resin embedded bone marrow trephine specimens

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Cyclin D1 is over-expressed in 25-40% of cases of multiple myeloma. The prognostic significance of that feature is unclear. This study examined the relationship between immunocytochemical staining of cyclin D1 in methyl methacrylate resin embedded bone marrow trephines and overall survival in 93 sequential myeloma cases. Minimum follow up after diagnosis was two years. Staining was carried out with an automated stainer using a rabbit monoclonal antibody, marked by avidin biotin peroxidase. Survival was assessed using a Kaplan Meir Curve. Comparison of immunocytochemical and in situ hybridisation of immunoglobulin light chains was performed. Both were carried out on methyl methacrylate sections, the former by standard means, the latter using a commercially available kit with minor modifications.
Positive cyclin D1 staining was found in 37 cases (40%), ranging from focal weak to generalised strong staining. There was no discernible advantage or disadvantage in crude survival in patients whose tumour cells demonstrated over-expression of cyclin D1 over the two year follow up. Despite this, this study demonstrates that reliable cyclin D1 staining can be achieved in standard conditions using resin sections. Further, in situ hybridisation for light chain RNA, with small changes to established protocols, was demonstrated in resin embedded material

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Acute Myeloid Leukaemia Mimicking Inflammatory Bowel Disease: a Hospital Post Mortem Case Report

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We describe an unusual case of a 73-year-old man presenting with a 6 week history of diarrhoea.

A colonoscopy showed active proctocolitis and biopsies reported features in keeping with idiopathic inflammatory bowel disease. Special stains for micro-organisms were negative, and stool cultures were negative. A course of steroids were given with no symptomatic improvement. Initial investigations also revealed myelodysplastic syndrome (refractory anaemia with excess blast) but no definite evidence of leukaemia. The patient gradually deteriorated and died from septicaemia and renal failure.

A full hospital post mortem, with consent for histology and education/research, was requested to establish the cause of diarrhoea.

Post mortem revealed florid ulceration of the colon extending from the rectum to terminal ileum associated with haemorrhage. The spleen was “beefy” and the kidneys pale.

Histology demonstrated an extensive infiltrate of immature myeloid cells throughout the colon, confirmed by immunohistochemistry, involving all of the organs sampled. Review of the earlier colonic biopsies revealed a similar immature myeloid infiltrate.

This case describes an unusual presentation of acute myeloid leukaemia and highlights the importance of full clinical details being available to the reporting histopathologist, the educational benefits of hospital post mortems and of clinico-pathological correlation for both pathologists and clinicians.

P168

Post-transplant Lymphoproliferative Disorders (PTLDs) in Renal Allograft Recipients: An Autopsy Based Study

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PTLDs continue to be a major complication after solid organ transplantation. We retrospectively examined all autopsies performed on renal transplant recipients for the presence of PTLD, its clinicopathologic features and association with Ebstein-Barr virus (EBV). A total of 91 renal transplant autopsies were performed over a 23 year period of which six had PTLD. Patients ranged in age from 29-53 years, all were males, and fever was the commonest clinical feature. Organ specific symptoms were present in three cases: dysuria, abdominal distension and malena. Three cases presented in the first year post-transplant, of which one occurred as early as three months. Gastrointestinal tract and liver were the most commonly affected, though involvement of uncommon sites (prostate, urinary bladder and heart) was seen in one case each. The graft kidney itself was not involved in any case. All cases of PTLD in this series were monomorphic and included four B cell (monoclonal), one T cell and one null cell phenotype. Four cases were positive for EBV while 3 had concomitant CMV infection.
Monomorphic PTLD can occur earlier than is traditionally believed in transplant recipients. Gastrointestinal tract and liver were the commonest sites of involvement.

P169

Unusual presentation of Haematological Malignancies – Three Cases with Primary Presentation in the Liver

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We report three patients with an uncommon haematological malignancy who presented with alteration in liver structure/function.
The first patient, a 35 year old male with a 6 week history of fatigue, weight loss, night sweats, bruising and epistaxis. Examination revealed hepatosplenomegaly. A liver biopsy showed a sinusoidal malignant lymphoid infiltrate. The lymphoid cells showed a natural killer (NK) cell immunoprofile (CD56, CD2 and TIA positive) and did not show gamma-delta receptor rearrangement. A marrow and peripheral blood showed an NK cell infiltrate. The features being consistent with involvement of liver by a primary NK cell leukaemia.

The second patient, a 16 year old male, presented with fever, hepatosplenomegaly and leg oedema. The liver biopsy showed a malignant sinusoidal lymphoid infiltrate with an immunophenotype consistent with a hepatosplenic T-cell lymphoma, gamma delta type.
The third patient, a 60 year old male, presented with deranged liver function tests and elevated ferritin with a clinical query to exclude haemochromatosis. A liver biopsy showed a sinusoidal infiltrate composed predominantly of plasma cells with the morphology and immunophenotype entirely in keeping with a leukemic infiltrate by a plasma cell myeloma. A subsequent bone marrow biopsy confirmed an IgD/lambda restricted plasma cell myeloma.

P170

An Unusual case of Cyclin D1 positive T cell lymphoma with an (11:14) translocation.

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Overexpression of cyclin D1 is commonly observed in human cancers. Perhaps the best known association is with mantle cell lymphoma in which there is an (11:14) translocation.

We describe an unusual case of high grade T cell lymphoma, presenting as rapidly enlarging, painless lymphadenopathy in an 80 year old female. She died 13 months after presentation having relapsed after chemotherapy.

The lymph node showed diffuse effacement by blastic lymphoid cells with the following immunoprofile-
CD3, CD4, CD5- strong membrane positivity.
cyclin D1- strong diffuse nuclear staining.
CD2- diffuse, weak membrane positivity.
CD7- focal weak membrane positivity.
Bcl2- moderate cytoplasmic staining in approximately 60% of the tumour cells.
CD20, CD79a, BOB1, MUM1, OCT2, CD10, CD23, CD8, Bcl6, CD56, CD30 and TIA- negative.

Molecular genetics investigations confirmed upregulation of cyclin D1 and also an (11:14) translocation. There was definite T cell clonality with gamma and beta clones but no convincing evidence of B cell gene rearrangement.

This would appear to be the first time cyclin D1 expression and an (11:14) translocation has been implicated in the pathogenesis of human T cell lymphoreticular malignancy.

P171

Review of Pathology of Mantle Cell Lymphoma in the West of Scotland

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Mantle cell lymphoma (MCL) accounts for 3-6% of non-Hodgkin lymphomas (NHL) and may present difficulty in diagnosis.

We reviewed the clinical presentation, morphology and immunophenotype of 72 MCL (3% of all NHL in West of Scotland) reported over a 7-year period. The median age at presentation was 67 (range 37-88). The presenting site was lymph node (40%), bone marrow (23%), Waldeyer's ring (18%), GIT (11%), lacrimal gland (4%), and spleen (3%). The morphological patterns were: diffuse (40%), nodular and mantle zone (30%) and mixed (30%). Eleven cases (15%) had a blastoid morphology, 8 of which had a mitotic count >20/10HPF. On paraffin immunocytochemistry, CD5 was positive in 89% of cases while Cyclin D1 was positive in 96%. Nine cases (12%) had an aberrant immunophenotype displaying positivity for bcl-6, CD10 or CD23 and required assessment of t(11;14) status by FISH for confirmation of diagnosis. Eight of 9 cases with a MIB-1 proliferation index of >50% were recognized as blastoid variant. In 9 cases, an incorrect diagnosis was made at the referring hospital.

Conclusions: There is wide variation in presentation and morphology of MCL, which may be confused with other lymphomas or reactive conditions. Immunocytochemical panels should always include Cyclin D1 as well as CD5. FISH should be used for confirmation of diagnosis in atypical cases. Recognition of blastoid variant is difficult and MIB1 proliferation index is likely to be a more reliable prognostic marker.

P172

West of Scotland. Audit of Clinical Usefulness of ZAP 70 and Cytogenetic Status in Chronic Lymphocytic Leukaemia.

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Zap 70 status and cytogenetic analysis determine prognosis in Chronic Lymphocytic Leukaemia (CLL). Since 2004 we have assessed ZAP70 status on formalin fixed lymphopreps made from peripheral blood of patients with CLL. Fresh cells were also subjected to analysis for 13q14, 11q22 and 17p13 deletion and trisomy 12 by fluorescence in-situ hybridisation (FISH). We have collected clinical data from 87 of 108 patients tested between January 2004 and August 2006. The median age was 59.7. The median time from diagnosis to first treatment was 67 and 33 months for the ZAP70 negative and positive groups respectively ($p<0.02$). There were no deaths in the ZAP negative group compared to 25% at 100 months for the positive group ($p<0.03$). Doubling time was significantly shorter in the ZAP 70 positive group ($p<0.005$). ZAP70 status did not correlate with peripheral white cell count or the presence of autoimmune complications. The number of cases with cytogenetic abnormalities detected by FISH was small with no statistically significant differences in time to first treatment. However, combining ZAP70 status and cytogenetic profile did yield four progressively worse prognostic groups (ZAP70-FISH-, ZAP70+ FISH-, ZAP70+11q del, ZAP70+17pdel $p=0.006$), which if confirmed could be useful for treatment planning.

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Immunohistochemical Study of Plasmacytoid Dendritic Cells in Lymph Nodes Draining Breast Cancer by BDCA2 and CD123 Antibodies

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Background. Plasmacytoid dendritic cells (PDC) are a distinct subset of antigen presenting cells which are major producers of Interferon type-1 and contribute to development of immune response. These cells are known as "plasmacytoid monocytes, PM" in tissue sections. They are found in groups in paracoretex of reactive lymph nodes (LN), close to high endothelial venules (HEV). PM are characterised by their bright expression of CD123 (IL-3 alpha-chain receptor); an important cytokine for PM survival, proliferation and differentiation) and by their specific expression, in frozen section, of an antibody reactive with blood dendritic cells (BDCA2).
Methods. We examined PM in frozen sections of 40 axillary LN draining breast carcinoma by using two antibodies, namely BDCA2 and CD123. The antigen localisation was performed using biotinylated detection system.
Results. PM stained strongly for BDCA-2 and CD123 in frozen sections of all LN; they were found scattered discretely in LN paracortex and in groups, close to HEV. A few PM were found in subcapsular LN sinus.
Conclusions. **1.** Identification of PM in LN paracortex, discretely and in groups close to HEV, confirms previous data on the localisation of these cells in reactive lymph nodes. **2.** PM were observed in LN subcapsular sinus; this may suggest that some PM migrate to LNs through the afferent lymphatics. **3.** Consistent demonstration of PM in LN draining breast cancer suggests a possible role for PM in mounting an immune response towards cancer cells **4.** BDCA-2 was found to be highly specific to PM; this can facilitate the use of this antibody to isolate a pure population of PM in flowcytometric studies.

P174

An unusual case of EBV driven lymphoproliferative disorder of the conjunctiva which mimicked a high grade lymphoma

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Conjunctival lymphoid masses or nodules are known to occur with EBV infection and are mostly polyclonal.

We report a case of monoclonal B cell infiltrate in the conjunctiva mimicking diffuse large B cell lymphoma which spontaneously regressed.

A 20-year-old young man with no history of immunosuppression, presented with a swelling in his left lower eye lid and cervical lymphadenopathy. An incisional biopsy of the conjunctival mass showed sheets of transformed blasts that were CD45 and CD20 positive and lambda light chain restricted but CD10, CD3, CD5, BCL6 and cyclin D1 negative. The cells were EBER positive and the proliferation fraction was 80-90%. Molecular genetic analysis revealed a clonal rearrangement of the immunoglobulin heavy chain gene.

The morphology, immunohistochemistry and molecular findings strongly suggested a diagnosis of diffuse large B cell lymphoma. However the EBV positivity and clinical setting were unusual. Two weeks post-diagnosis and without further intervention, the mass and lymph nodes completely regressed. Further enquiries revealed a recent history of infectious mononucleosis.

This case highlights the need to exercise caution when dealing with lymphoid proliferations at unusual sites in young individuals.

P175

A rare case of divergent differentiation in post transplant lymphoproliferative disorder.

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Post transplant lymphoproliferative disorder (PTLD) comprises a heterogeneous group of lymphoid proliferations. Although morphological overlaps are known, sequential and combined B and T cell PTLD is a rarity. We report such a case in a renal transplant recipient.

A 36-year-old male, a cadaveric renal transplant recipient with stable graft function, presented with bilateral cervical lymphadenopathy. The lymph node biopsy revealed transformed blasts with an anaplastic morphology which were CD2, CD30, EMA and EBER positive. B cell markers were negative. A diagnosis of EBV related anaplastic T cell PTLD was made. He received 8 cycles of chemotherapy along with reduction in immunosuppression. He had a good response to the treatment but later presented with recurrent cervical lymphadenopathy. A second biopsy showed a plasmablastic EBV positive PTLD with CD2, CD38 and CD138 positivity although a small residuum of the original T cell tumour remained. Molecular analysis confirmed the presence of a T cell clone but no definite B cell clone was identified.

This case demonstrates a very unusual EBV driven mixed lymphoid neoplasm in a renal transplant patient. It highlights that PTLD can simultaneously infect different lineages. Re-biopsy of recurrences may help in the management.

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In-situ Mantle Cell Lymphoma - a Report of Two Cases

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Mantle cell lymphoma (MCL) is a small cell lymphoma which is thought to develop from peripheral B lymphocytes that reside normally in the inner mantle zone of reactive lymphoid follicles. Early neoplastic clones of MCL would therefore be expected to be seen confined to the mantle zone compartment of the lymphoid follicles. We describe two such cases of in-situ MCL.

One patient was a man in his seventies who developed bilateral cervical lymphadenopathy. Biopsies of a lymph node showed florid reactive hyperplasia; reactive germinal centres were enlarged, irregular and surrounded by mildly expanded mantle zones, and the mantle zone B lymphoid cells expressed Cyclin D1.

The other patient was a man in his forties who had been initially diagnosed to have follicular lymphoma, stage 4B, six years prior to the current presentation. He recently developed generalised lymphadenopathy and had a cervical lymph node biopsy. This showed grade 1 follicular lymphoma with mildly expanded residual mantle zones. The mantle zone lymphoid cells expressed Cyclin D1. The original lymph node biopsy did not show any staining for Cyclin D1.

In both biopsies, definite CD5 expression on mantle cells positive for Cyclin D1 was not seen. It is likely that these cases represent early MCL where the initial lymphomagenic events have not been followed by other genetic changes. It also suggests that cases of MCL early in the evolution are mostly CD5 negative.

Our findings also confirm that early development of MCL starts in the mantle zone of lymphoid follicles; such events can be identified by immunostaining for Cyclin D1.

P177

Quality Assurance in Paediatric Histopathology: Comparison of Three International Programs

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Aims: Diagnostic skills are paramount in clinical and surgical pathology. Very few slide survey programs are intended worldwide for pediatric pathologists Aim was to compare three main slide survey programs.

Methods: Three international slide survey programs (BRIPPA, RCPAP, and SPP) were compared with reference to the following parameters: circulations/year, slides/year, membership requirement, pediatric pathology requirement, overseas open, CPA accreditation, CPD/CME credits, slides discussion meeting, fixed organizer, annual report issue, improvement meetings, digital images option, and substandard performance letter.

Results: Data collection indicates that a quality assurance scheme should have at least two circulations per year for a total of 26 slides per year and requirement for membership or substantial pediatric pathology workload. However, it could be open to overseas participants and provide CPA accreditation, CPD/CME credits, and regular slides discussion. Scheme improvement meetings and annual report issues are important. Virtual microscopy and substandard performance letter remain an option.

Conclusion: Uniformity for standards to set up a quality assurance program at national level is an important task. Digital image option is probably underscored in pediatric pathology EQA schemes.

P178

Brachmann-De Lange Syndrome in a Fetus Whose Mother Presented with a Diffuse Large B Cell Lymphoma

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Aims: Brachmann De Lange Syndrome (BDLS, MIM 122470) is a rare multiple congenital anomaly/mental retardation syndrome characterized by fetal growth restriction (FGR), limb reduction, and distinctive facial and skull features (low frontal hairline, synophrys, anteverted nostrils, long philtrum, down turned corners of the mouth, micro- and retrognathia, low-set ears and micro-/brachicephaly) as well as a significant psychological developmental delay. We report the unique recurrence of BDLS in a mother harboring a large B cell lymphoma.
Methods and Results: A 22 weeks gestation fetus with BDLS showing FGR, brachicephaly, micro-/retrognathia, and monolateral single bone of the forearm in a woman harboring diffuse large B cell lymphoma. Detailed family history was negative for malformations, syndromes, congenital anomalies or psychiatric disorders. BDLS gene sequencing showed no mutations.
Conlusion: To the best of our knowledge, this is the first case occurring simultaneously with a hematological neoplastic disease of the mother. A proposed classification system for BDLS include a *classic* type with characteristic facial and skull changes, a *mild* type where similar changes may develop with time or may be partially expressed, and a third type including *phenocopies*, where phenotypic changes are casually related to chromosomal aneuploidies or teratogenic exposures.

P179

Fatal Circumstances of Human Herpesvirus 6 Infection: Transcriptosome Analysis Results

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Aims: Human herpesvirus type 6 (HHV-6), a T-lymphotropic DNA virus commonly associated with exanthema subitum in 1-2 years-old children, has also been associated with sudden death and short-term mortality. Its authentic contribution to death is still debated and anecdotal evidence only has been provided. We evaluated the contributing role of HHV-6 in death of four children (4-months-, 3-years-, 6-years-, and 11-years-old).
Methods: In all patients, death was initially associated with HHV-6. We used serum immunoassay, nested polymerase-chain-reaction (PCR) amplification of the viral genome, immunohistochemistry, transcriptosome analysis, and transmission electron microscopy (TEM).
Results: HHV-6 DNA sequences were amplified in all four index cases and HHV-6 viral proteins were also detected by immunohistochemistry, but transcriptosome analysis and TEM failed to demonstrate either viral RNA replication or virus particles, respectively.
Conclusion: On the basis of our data, we suggest more prudence in diagnosing HHV-6 infection as cause of death. The presence of HHV-6 in serum is necessary, but not sufficient to identifying it as cause of death. Conventional PCR results have to be confirmed by both transcriptosome analysis and TEM. A review of the methods for diagnosing HHV-6, their advantages and disadvantages or limitations is provided.

P180

Quality of Histopathology Reporting in Paediatric Tumours Home and Away

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There is a national shortage of paediatric pathologists which has resulted in a vacancy in a large teaching hospital. Consequently, some tumours are reported locally (soft tissue, bone tumours and lymphomas) whilst others are sent away for reporting (nephroblastoma, neuroblastoma). The aim of this audit is to establish whether the lack of a paediatric pathologist affects the quality of histopathology reports.
The study included all malignant tumours from children from the past five years. Slides were reviewed and all reports were analysed according to National Minimum Datasets, current trial protocols or local guidelines as appropriate. The proportion of cases sent away and the time taken to issue reports was also assessed.
The overall quality of paediatric tumour reporting was excellent, with full compliance with reporting guidelines in 85% of cases; the remaining had only minor omissions. Cases sent away had a longer turnaround time than those reported locally in terms of issuing a final report. However, preliminary reports were telephoned to prevent delay. A small number of the cases sent away had absent or incomplete supplementary reports.
This study shows high quality pathology reporting for paediatric tumours. Cases sent away wait longer for final reports and occasional reports are incomplete.

P181

Is Beta-catenin Expressed in Congenital Mesoblastic Nephroma?

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Introduction: Congenital mesoblastic nephroma (CMN) has two main subtypes, the classical & cellular variants, which may represent different diseases. The cellular variant may be a form of infantile fibrosarcoma since it shares the ETV6-NTRK3 fusion product. It has been suggested that the classical subtype may be a variant of renal aggressive fibromatosis due to its histological appearances. Aggressive fibromatoses in adults at other anatomical sites are beta-catenin positive but this has not been examined in CMN subtypes. Subtyping, including immunohistochemistry & molecular data, in other paediatric tumours has resulted in more accurate diagnosis leading to improved stratification & therapeutics.
Methods: Histopathological features of a series of mesoblastic nephromas at GOSH were collated. Diagnosis was made on a combination of light microscopic appearances and molecular techniques (RT-PCR) for t(12;15) translocations involving the ETV6/NTRK3 fusion product.
Results: There were 12 cases of CMN comprising 3 classical, 4 cellular & 5 mixed types. None of these subtypes showed positive immunostaining for beta-catenin.
Conclusion: Compared with positive control (aggressive fibromatosis, desmoid type) all CMN subtypes were beta-catenin negative suggesting that the beta-catenin/APC/Wnt pathway is not involved in the pathogenesis of CMN. In particular this negative finding suggests that classical CMN ("infantile fibromatosis of the renal sinus") is a different entity from other fibromatoses.

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Abstract withdrawn

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Gaucher Disease (GD) & Haemophagocytic Lymphohistiocytosis (HLH): Chicken or Egg?

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Introduction: HLH is an immunological disorder, with a range of known (perforin, MUNC 13-4, syntaxin 11) & unknown mutations with high mortality. Gaucher disease (glucocerebrosidase deficiency) is a sphingolipid storage disorder. This patient presented with both disorders raising the possibility of two different primary disease processes. The alternatives are that haemophagocytosis is secondary in this case or that these disorders are associated.
Case: The patient was born at 35w to non-consanguinous parents & had respiratory distress aged 1h. She had widespread petechiae, retinal haemorrhages, hepatosplenomegaly & jaundice.
She had clinical criteria as well as positive genetic testing (MUNC 13-4 mutation) for HLH. She had diffuse white matter abnormality on MRI. Fibroblast culture showed low glucocerebrosidase activity. She died aged 2.5m following respiratory deterioration.
Pathology: Postmortem examination showed an enlarged heart, ascites & hepatosplenomegaly. Electron microscopy showed atypical storage material in the liver & spleen with more typical filamentous storage material seen in the lungs. Unusually, despite the MRI abnormality, there was no EM evidence of storage in the CNS.
Conclusion: This patient was a compound heterozygote with one known (L444P) and one unknown GD mutation. MUNC expression was absent on western blotting & she had clinical signs of HLH. Our hypothesis is that there may be a higher incidence of HLH and/or immunological disorders in Gaucher disease. If a subgroup of GD patients has an immune defect related to HLH mutations (eg MUNC) these patients are likely to have a worse phenotype compared with GD or HLH alone.

P184

Virological Investigations in Sudden Unexpected Deaths in Infancy (SUDI): Review of >500 Autopsies

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Introduction: Previous studies have implicated viral infections in the pathogenesis of sudden unexpected death in infancy (SUDI), and routine virological investigations are recommended by current SUDI autopsy protocols. The aim of this study is to determine the role of post-mortem virology in establishing a cause of death.
Method: A retrospective review of 546 SUDI autopsies, as part of a larger series of >1,500 consecutive paediatric autopsies performed over a 10-year period, 1996 to 2005, in a single specialist centre.
Results: Virological tests were performed as part of the post-mortem examination in 490 (90%) of the 546 SUDI autopsies, comprising 4,639 individual virological tests, of which 79% were performed on lung tissue samples. Diagnostic methods included immunofluorescence assays (98% of cases), cell culture (61%), rapid culture techniques such as the DEAFF test for CMV (55%), PCR (13%), electron microscopy (10%), and others. Virus was identified in only 18 cases (4%), viz. five cases of enterovirus, four of RSV, three of HSV and CMV, and one of adenovirus, influenza virus and HIV. In seven of the 18 cases the death was classified as due to viral infection, whilst of the remaining 11 cases, death was due to bacterial infection in five, a non-infective cause in one or unexplained in five. Virus was identified in 33% of deaths due to probable viral infections, but also in 6% of SUDI due to bacterial infections, and in 2% of SUDI due to known non-infective causes and unexplained SUDI.
Discussion: Virus is identified in only a small proportion of SUDI and contributed to the final cause of death in < 2%. Routine virological analysis at autopsy appears to be of limited benefit in SUDI for the purposes of determining a cause of death.

P185

Role of Post-Mortem Bacteriological Investigations in SUDI: 10-Year Experience from a Single Specialist Centre

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Introduction: Infections are recognised to be a leading cause of death in infants who die suddenly and unexpectedly (SUDI), and most SUDI autopsy protocols recommend routine microbiological sampling. This study evaluates the role of post-mortem bacteriology in SUDI.
Method: A retrospective review of 546 SUDI autopsies (7 to 365 days of age), as part of a larger review of >1,500 paediatric autopsies over a 10-year period. Isolates were classified as non-pathogens or pathogens, and the latter divided into Group 1 (usually associated with an identifiable focus of infection) or Group 2 (pathogens known to cause septicaemia without an obvious focus of infection: groups A and B beta-haemolytic streptococcus, pneumococcus, meningococcus, Escherichia coli and Staphylococcus aureus). SUDI was categorised into unexplained SUDI, explained SUDI with histological evidence of infection (infection group) or explained SUDI due to non-infective causes.
Results: Of 2,079 bacteriological episodes overall, 27% were sterile. Positive cultures yielded 2,871 separate isolates, 32% showing pure growth, the majority mixed growth. There were no significant differences in the proportion of non-pathogenic and Group 1 pathogenic isolates between the three SUDI categories, but there were significantly more Group 2 pathogens in the bacterial infection group (24%) than in unexplained SUDI (19%, P = 0.03) and explained non-infective SUDI (11%, P = <0.0001).
Discussion: Group 2 pathogens are isolated in >10% of explained SUDI due to non-infective causes; however, these data suggest that, on the basis of the frequency of Group 2 pathogens, 2-8% of SUDI deaths are likely to be due to septicaemia / bacteraemia with no histologically identifiable focus of infection.

P186

Effect of Post-Mortem Interval on Bacteriological Yield in Sudden Unexpected Death in Infancy (SUDI)

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It has been hypothesised that post-mortem translocation, the migration of micro-organisms from mucosal surfaces into the body after death, leads to polymicrobial growth in post-mortem samples (rather than pure growth of a single species) and is detected more frequently with an increased post-mortem interval (PMI). As a consequence, it is suggested that post-mortem translocation is not commonly found if cultures are taken relatively soon after death or if the body is stored appropriately at low temperatures. The aim of this study is to evaluate the association between PMI and bacteriological yield in SUDI post-mortems.
Methods: A retrospective review of 546 SUDI autopsies (7 to 365 days of age), as part of a larger review of >1,500 paediatric autopsies over a 10-year period, 1996 to 2005.
Results: Overall there were 2,079 bacteriological episodes. The mean PMI was 2.7 days (median 2 days). The proportion of sterile cultures increased from 17% for samples taken within 24 hours of death to 33% if taken five or more days after death, and mixed culture isolates decreased from 61% to 46% respectively (chi-square 27.21, df = 10, P = 0.0024).
Discussion: The findings of this study show that a PMI of several days' duration is not associated with an increase in mixed growths or with a decrease in sterile cultures, as would be expected with post-mortem translocation. Indeed, the opposite trend is observed, suggesting that a longer PMI may result in death of micro-organisms. However, these data do not allow assessment of the possibility of significant post-mortem translocation occurring within the first few hours after death.

P187

Bacteriological Yield According to Sample Site in Sudden Unexpected Death in Infancy

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Introduction: The Kennedy autopsy protocol for sudden unexpected death in infancy (SUDI) currently recommends that at least three sites are routinely sampled for bacteriology: blood culture (BC), CSF and the respiratory tract. The aim of this study is to compare the bacteriological yield from these sites (and additionally from the spleen), taken as part of the local SUDI autopsy protocol in a single specialist centre (BC, CSF, lung and spleen).
Methods: A retrospective review of 546 SUDI autopsies (7 to 365 days of age), as part of a larger review of >1,500 paediatric autopsies over a 10-year period, 1996 to 2005.
Results: Bacteriology was performed in 93% of all SUDI included in this analysis, of which BC's were performed in 96%, CSF cultures in 94%, lung cultures in 90%, and spleen cultures in 84%. There was marked variation in both sterile and mixed growth episodes between the four different culture sites. There were significantly more sterile CSF cultures (75%) than BC's (33%), lung cultures (3.9%) and spleen cultures (14%), and significantly more mixed growth episodes in lung cultures (78%) than BC's (41%), CSF cultures (4.3%) and spleen cultures (49%). In addition, there were differences in the proportion of specific pathogenic isolates, with significantly more episodes of Staphylococcus aureus in lung (31% of all positive lung culture episodes) than in BC or spleen (20% and 19% respectively) or CSF (5%), whilst the isolation of beta-haemolytic streptococcus group B was similar for all four sites (5-7%).
Discussion: There is marked variation in sterile and mixed growth episodes, and in isolation of specific pathogenic organisms, between different culture sites.

P188

Neuroleptic Treatment Worsens Cognitive Function and Alzheimer-type Pathology in Dementia Patients

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We analysed the effect of neuroleptic treatment on memory functions and the expression of disease-related proteins in Alzheimer's disease (AD) patients. The cognitive status of the patients had been assessed not more than 6 months prior to death using the CAMDEX. After necropsy, diagnoses were confirmed using the CERAD protocol and the Braak staging. Quantitative immunohistochemistry was used to measure hyperphosphorylated tau, PHF tau, and beta-amyloid in the CA1 and CA2/3 regions of the hippocampus.

The cognitive scores of neuroleptic treated patients in the early stages of AD were significantly lower than those of controls. A similar effect was seen for the recent memory and learning memory scores. The remote memory and attention scores were not significantly different between the two groups.

The treatment had no effect on the expression of hyperphosphorylated tau in the hippocampus. In contrast, the expression of PHF tau in the CA2/3 region (but not in CA1) was significantly higher in the neuroleptic group than in the matched controls. We found no difference in beta-amyloid deposition.

We conclude that the worsening of memory functions induced by neuroleptic therapy in demented patients is associated with increased amounts of AD-type tau pathology in the hippocampus.

P189

Lewy pathology in the olfactory pathways of subjects with dementia is associated with anosmia

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A loss of smell (anosmia) is an early symptom in patients who develop dementia, including Alzheimer's disease (AD) and Dementia with Lewy bodies (DLB). The use of a smell test has been proposed as an early diagnostic procedure and distinguishes those with early DLB from those with early AD. The present study aimed to examine the relationship between anosmia and the presence of Lewy body pathology in the olfactory pathways.
Participants in the Oxford Project to Investigate Memory and Ageing were tested for basic olfactory function during life (n = 214). Tissue was taken from 5 areas of the olfactory pathway; the Olfactory Tract/Bulb, the insertion of the Olfactory Tract, the orbito-frontal cortex, the *hippocampus* and the *amygdala*. Lewy bodies were detected using immunohistochemistry to alpha-synuclein. Results show that the quantity of Lewy Body pathology in the olfactory system varied, but may follow a particular pattern of development. The presence of Lewy pathology in the cortical olfactory pathway is particularly associated with anosmia, and is further support towards the use of a smell test to aid diagnosis of neurodegenerative diseases.

P190

Screening of EGFR abnormalities in paediatric high-grade gliomas reveals the presence of vIII deletion mutations

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Adult high grade glioma (HGG) patients have a differential response to therapeutic strategies targeting the epidermal growth factor receptor (EGFR), with a variety of factors reported to be predictive for treatment efficacy. EGFR is thought to play a less important role in paediatric HGG, although extensive data is lacking. We have retrospectively studied EGFR overexpression, amplification, and mutation in a total of 76 FFPE paediatric HGG specimens. Gene amplification was detected by CISH in 18% cases, with a corresponding overexpression of the wild-type receptor protein by immunohistochemistry. These cases had a shorter median overall survival time than those without amplification/overexpression ($p<0.05$, log-rank test). None of the 76 samples contained mutations in either the extracellular (exons 2-8) or the tyrosine kinase domains (exons 18-21) of EGFR. By contrast, the exon 2-7 deletion mutation vIII was detected by RT-PCR and direct sequencing in 6/33 (18%) of samples from which RNA was available, including cases of glioblastoma multiforme, anaplastic oligodendroglioma and gliosarcoma. This was further evaluated by immunohistochemistry using an antibody specific for the EGFRvIII mutant protein. These data identify EGFR gene amplification and mutation in cases of paediatric HGG, and provide a rationale for the use of anti-EGFR therapies in these patients.

P191

Loss of heterozygosity of chromosomes 1p and 19q in oligodendroglial tumours - results of a British pilot study.

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Introduction: LOH 1p and 19q predict improved response to chemotherapy, radiotherapy and prolonged overall survival in oligodendroglial tumours, and so help guide patient management. Clinical demand for LOH screening is increasing. Much of the evidence comes from centres outside Britain. We set up a pilot study to investigate whether these findings applied to our Wessex population, UK, and to assess the feasibility of introducing the test to our laboratory.
Methods: This study was a retrospective analysis of archival tumour biopsy tissue from Southampton General Hospital. Allelic loss was assessed by PCR in tumour DNA/constitutional DNA pairs using microsatellite markers on chromosomes 1p and 19q. PCR and progression free survival (PFS) data were obtained for 20 patients.
Results: LOH 1p was detected in 12/17 conclusive cases (71%). PFS ranged from 4 to 135 months. PFS overall was longer in those with LOH 1p than in those without ($p=0.004$). A larger sample size is needed to test the clinical value of LOH 19q in our population.
Conclusion: Our findings support current evidence that LOH 1p is prognostically useful. It is feasible to establish the technique in clinical practice and we recommended it as part of standard pre-treatment work-up of oligodendroglial tumours.

P192

Angiomatous meningioma with stromal amianthoid fibre deposition: case report of a rare pathological entity

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Aggregations of giant collagen fibrils, termed amianthoid fibres, have been identified in a variety of tissues, both reactive and neoplastic, and are characterised by the presence of individual collagen fibrils that are six to ten times the width of those seen in native collagen.
Amianthoid fibre deposition within meningeal tumours are exceedingly rare with very small numbers cited in the literature, the majority of such cases referring to the aggressive (WHO grade 2) clear cell variant of meningioma. Only a single case of amianthoid deposition in benign meningiomas is previously reported.
We describe a case of an intracranial angiomatous meningioma with intrastromal amianthoid fibre deposition in a 67-year-old male who presented with left superior quadrantanopia. Histology revealed a vascular lesion composed of numerous multi-calibre blood vessels with admixed sheets of meningothelial cells. Within the tumour, multiple acellular eosinophilic structures were seen. These structures stained with trichrome but were negative for congo red, reticulin and smooth muscle actin. Electron microscopy confirmed the meningothelial nature of the tumour and the presence of numerous abnormal large collagen fibrils identified as amianthoid fibres. This report represents the first described case of amianthoid deposition in an angiomatous meningioma. The pathological significance is, as yet, unknown.

P193

Muscle Biopsy Audit: is Muscle Biopsy Size a Good Indicator of Adequacy?

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Aim and Methods
We examined 81 muscle biopsies performed in a tertiary referral centre to investigate whether the size of the muscle biopsy is a good indicator of the adequacy of the muscle biopsy. Then we assessed the adequacy of the clinical information supplied by the clinicians.
Results
Although the final adequacy of the muscle biopsies as assessed by the reporting pathologist was 94%, adequacy dropped to 81% when we assessed it against the criterion of whether at least one dimension of the biopsy was more than 10 mm. When we changed the criterion again to adequacy with all dimensions at more than 10mm, only 17% of biopsies could be classed as adequate.
All the important clinical history features we examined in this study were mentioned in only 5% of the cases.
Conclusion
The recommended size of a muscle biopsy, which is generally regarded $10mm^3$ should perhaps be considered as a target, rather than an absolute requirement, since there was no clear relationship between the muscle biopsy size and the final diagnostic adequacy of the specimen. Muscle biopsies also suffer from the common pathological specimen problem namely the supply of inadequate clinical information.

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Abstract withdrawn

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Abstract withdrawn

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Analysis of Structural Abnormalities in FGFR3 Mutant Mouse Brains Using 7T Magnetic Resonance Imaging

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Mutations in Fibroblast Growth Factor Receptor 3 (FGFR3) cause CNS abnormalities that accompany severe dwarfism, Thanatophoric Dysplasia. Macrocephaly and the hypoplastic hippocampus, as well as severe limitations in motor and intellectual development have been reported in the patients. We previously generated the Fgfr3 gain-of-function mouse models by conditionally knocking-in the corresponding mutations. The aim of this study is to analyse the brain structure of Fgfr3 mutant mice by MRI using the 7 Tesla experimental MRI scanner, in order to establish the relevance of the mouse models to the brain pathology observed in human TD. By T2 high-resolution scans and Diffusion Tensor Imaging, we have identified that the hippocampus of Nestin:Fgfr3+/K644E mutant mice was severely malformed at postnatal day 7.5, similar to observations in human TD. In addition, the volume of the hippocampus was increased by 4.1% in the mutant in comparison to wild type littermate. Cortical thickness was increased in the mutant by 8.5%, 44.4%, and 16.1% in S1, V1, and A1 area, in comparison to corresponding regions of the wild type, respectively. Investigation of the role of FGF signalling in progenitor behaviour is likely to provide significant insights into the molecular mechanisms of human brain malformation syndromes and cognition.

P197

Regulation of Cell Cycle Parameters by FGFR3 in the Developing Mouse Cerebral Cortex

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The kinase domain mutation in Fibroblast Growth Factor Receptor 3 (FGFR3) is known to cause macrocephaly in Thanatophoric Dysplasia patients. We previously showed that mice carrying the corresponding mutation in Fgfr3 (EIIa;Fgfr3+/K644E, "mutant") have enlarged brains owing to an increase in cell proliferation and a decrease in apoptosis, indicating the role of Fgfr3 in controlling cortical progenitor numbers (Inglis-Broadgate et al, 2005). Fgfr3 is expressed in the embryonic cerebral cortex in a rostromedial-low caudolateral-high gradient. The increased activity of the mutant Fgfr3 protein may exaggerate the cell proliferative effect in the caudal regions. In order to address this, we have performed in vivo BrdU labelling study at each developmental stage during E11.5-E13.5. In accordance to the expression gradient of Fgfr3, the difference in proliferation between the Fgfr3 mutant and wild type cortices was the greatest in the caudal cortex (41% and 46% increase in the mutant, at E12.5 and E13.5, respectively) (Thomson et al., 2006). Finally, a cumulative BrdU labelling study analysing 8 points at 1.5 hour interval between 0.5-11 hours of labelling revealed that the total cell cycle length was 1.4 hour shorter in the caudal region of the Fgfr3 mutant cortex compared with the wild type at E12.5.

P198

Effect of FGFR3 Thanatophoric Dysplasia Mutations in Areal Patterning of the Cerebral Cortex

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Patterning of the cerebral cortex is a complex process that ensures the correct positions of the cortical areas. The aim of this study is to determine the role of Fibroblast Growth Factor Receptor 3 (FGFR3), a receptor for FGF8, in regulation of cortical patterning. We performed Cytochrome C Oxidase histochemistry to analyse the cortical areas of Nestin;Fgfr3+/K644E and Foxg1;Fgfr3+/K644M gain-of-function mutant mice, models for human Thanatophoric Dysplasia (TD). We quantitatively analysed the location of S1 using the posteromedial barrel subfield (PMBSF) as a reference point. Statistically significant rostral and medial shifts were observed in the mutant cortex in comparison to wild-type controls. A previous report showed that a rostral over-expression of FGF8 caudally shifted the cortical areas. Therefore, our results indicate that Fgfr3 antagonizes the effect of FGF8 in vivo. In addition, in situ hybridization of key transcription factors for protomap formation, including COUP-TF1, showed that its gradient was up-regulated in the rostral region at embryonic day 12.5 (E12.5) and E14.5. These results indicated that alteration of Fgfr3 activity was able to regulate the cortical area patterning by regulation of protomap formation. The study strongly indicates that the mechanism of the CNS structural abnormalities in TD involves a patterning defect.

P199

Review of Primary Central Nervous System Lymphomas in a Regional Neuropathology Service

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Diagnosing primary central nervous system lymphoma (PCNSL) in neurosurgical biopsies may present a challenge. Routine practice in our centre is for haematopathology review of all PCNSL and suspected diagnoses. We present a review of this practice and detail on PCNSL sub-types.

From the reporting archives all PCNSL diagnosed between January 2001 and December 2006 and cases referred for opinion to confirm/ exclude PCNSL were identified. These were then reviewed and the neuropathology opinion, haematopathology opinion and subtype recorded.

Forty-two cases were identified of which 40 were referred for haematopathology opinion. In total, 38 PCNSL were diagnosed with a mean age at presentation of 60 years (range 42 to 80). Of these, 91% were diffuse large B-cell lymphomas (DLBCL) with a 100% concordance in opinion between neuropathology and haematopathology; though haematopathology provided additional information on sub-type with 90% displaying a non-germinal centre immunophenotype. Four (10%) referred cases resulted in a changed diagnosis. All were reactive, non-diagnostic or low-grade lymphoma on review.

This review demonstrates the majority of PCNSL in this service are DLBCL, non-germinal centre phenotype. Furthermore, haematopathology review is not necessary where the diagnosis is DLBCL though is of value in assessment of low-grade lymphomas and/ or reactive lymphoid infiltrates.

P200

Pilomyxoid Astrocytoma Presenting with CSF Rhinorrhea in a 15-year-old: a Case Report

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Pilomyxoid astrocytomas (PMA) are rare tumours of infancy typically presenting with focal neurological symptoms or endocrine dysfunction. They are histologically distinct from pilocytic astrocytomas (PA) and have a more aggressive clinical course. We report a PMA in a 15-year-old presenting with CSF rhinorrhoea.

A 15-year-old male presented following 2 weeks of headache, nausea and vomiting. Provocation testing demonstrated clear fluid from his left nostril. Retinoscopy showed features of chronically raised intracranial pressure. He underwent an anterior cranial fossa repair during which biopsies of dura and temporal lobe were taken.

Sections showed fragments of tumour with appearances typical of PMA, namely loosely cohesive cells with a bipolar cytology suspended in a myxoid matrix. Occasional eosinophilic granular bodies were present. Scattered mitotic figures were seen. There was no evidence of endothelial hyperplasia or of necrosis.

Previous reports of PMA document these as tumours of infancy with, to the best of our knowledge, only two reports of patients over 7 years of age. This case confirms the occurrence of these tumours outwith the infant population. The more aggressive behaviour of PMA when compared to PA justifies increased vigilance for this entity amongst tumours of the hypothalamic/ chiasmatic region in all age groups.

P201

Gastrointestinal Stromal Tumours and WT1

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WT1 was first identified as a tumour suppressor gene involved in the development of Wilms' tumor. It is also well known for its application in the diagnosis of ovarian serous carcinoma and desmoplastic small round cell tumours. Recently, oncogenic properties of WT1 have been demonstrated in various hematological malignancies and solid tumors.

We recently came across a case of a gastrointestinal stromal tumour (GIST) staining positively with WT1. We further evaluated this by staining other GISTs selected at random for verification purposes. To our knowledge, the detection of WT1 in GISTs has not been realised with no such cases reported in the literature. WT1 protein is a promising tumour antigen for cancer immunotherapy against leukaemias and various kinds of solid tumours, including lung and breast cancer. The gene plays an essential role in the growth of solid tumours and performs an oncogenic rather than a tumour suppressor gene function, making it suitable as a therapeutic target. This, together with the ability to predict prognosis thus will immunohistochemical detection of WT1 in tumour cells an essential part of routine practice.

P202

ERα and ERβ Expression in Soft Tissue Neoplasms: An Immunohistochemical Study

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Relative distribution of oestrogen receptors (ERs) has been implicated in carcinogenesis of different tissues. However, little is known about hormone receptor expression, in particular ERβ, in soft tissue neoplasms.
This retrospective study aimed to evaluate the expression of ERα and ERβ isoforms (β1 and β2) in a range of soft tissue tumours. A computerised search between 2000 and 2006 was performed at the Department of Histopathology in Leeds. The tumours were stained with specific, well-validated, antibodies to ERα, ERβ1 and ERβ2. Percentage of positive cells and intensity of staining were analysed and a final Allred score (0 to 8) calculated.
ERα was negative in the majority of tumours showing only focal weak expression in solitary fibrous tumours. ERβ1 and ERβ2 were more widely expressed. In adipocytic lesions, benign tumours expressed less ERβ1 and ERβ2 as compared with Liposarcoma. Both ERβ1 and ERβ2 isoforms were expressed in Ewing's sarcoma, Fibrous histiocytoma, Fibromatosis, Haemangioma, Angiosarcoma, GIST and Carcinosarcoma. High Allred scores tended to correlate with better differentiation.
In conclusion, ERβ is widely expressed in soft tissue neoplasms as compared with ERα which might relate to phenotypic behaviour. This study forms the basis of a large tissue microarray analysis of soft tissue neoplasms.

P203

Matrix Metalloproteinase Expression in Soft Tissue Neoplasms: An Immunohistochemical Study.

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Matrix metalloproteinase (MMP) expression correlates with biological aggression in a wide range of epithelial tumours. Few studies have analysed the Immunohistochemical expression of MMPs in benign and malignant soft tissue neoplasms.
We conducted a retrospective study to evaluate the expression of MMPs and their inhibitors (TIMPs) in a cohort of fibrous, fibrohistiocytic and vascular lesions. A Snomed search was performed from 2000 to 2006 at the Department of Histopathology in Leeds. The tumours were evaluated with commercial antibodies to MMP1, 2, 3, 7, 11, TIMP 1 and 2. A semi-quantitative assessment of percentage of positive cells and intensity of staining was undertaken.
The results revealed MMP1 expression in all tumours, however, the intensity of staining was more pronounced in the malignant lesions. MMP2 and MMP9 showed no expression in benign fibrous/fibrohistiocytic lesions but were expressed in high grade pleomorphic sarcomas. Interestingly expression of TIMP 1 and 2 was noted in both benign and malignant sarcomas. Angiosarcomas expressed MMP1 and MMP9, with reduced or negative expression in haemangiomas.
In conclusion, MMP1, MMP2 and MMP9 show increased expression in malignant soft tissue neoplasms when compared with their benign counterparts, suggesting they play an important role in the malignant potential of a tumour.

P204

Lipoma arborescence of the ankle joint with ganglion formation

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Lipoma arborescens is a villous lipomatous proliferation of the synovial membrane. It is a rare condition that usually is found in the knee, but it has been reported in other joints, including the wrist and ankle. It may present de novo but it has also been associated with degenerative joint disease, chronic rheumatoid arthritis, or posttraumatic conditions. It typically presents as a painless swelling of the knee accompanied by intermittent effusions. Laboratory tests are normal. The condition is characterized by marked villous proliferation of the synovial membrane and hyperplasia of the subsynovial fat, mainly in the suprapatellar pouch.
A 50 year old male presented with a soft tissue lump in right ankle within tendon sheath of peroneus brevis muscle. The histological appearances were that of villous lipomatous proliferation of the synovium with ganglion formation.
We describe this interesting case of Lipoma arborescence of the ankle joint with ganglionic degeneration and present the review of literature.

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Abstract withdrawn

P206

Malignant Melanoma – Audit of minimum dataset use and value to clinicians in a large UK teaching hospital

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Introduction. Melanoma reports were audited against the minimum dataset produced by the Royal College of Pathologists for quality assessment. Clinicians were asked to evaluate each of the minimum dataset points.
Method. Minimum dataset points were scored either present or absent from a cohort of reports, compiled from the first 6 months of 2001 (n=54) and 2006(n=62). These represent reporting before and after the release of the minimum dataset. In a questionnaire, thirty clinicians were asked to score the dataset points according to importance in patient management (scored 1-5, ascending importance).
Results. Improvement in the quality of reports was evident, with 11 of 15 dataset points more frequently reported and some up to 60% more often (microsatellites & accurate margin assessment). Data from the questionnaire revealed that clinicians value the majority of dataset points highly (importance score > 4). Only mitotic rate and presence of co-existant naevus failed to achieve an average importance score of 3 (2.9&1.9 respectively).
Conclusion. Quality of reporting of melanoma cases in this centre has improved. The majority of dataset points are valued by clinicians.

P207

Evaluation of diagnostic values of EMA and Ber-Ep4 in distinction between BCC and SCC of the skin

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Objective: Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are two common tumors of the skin. In some cases distinction between BCC and SCC can be difficult. This study aims to clarify this uncertainty through immunohistochemistry. Epithelial membrane antigen (EMA) and Ber-Ep4 are the two immunohistochemical markers on which we focus in differentiating skin BCC from SCC.
Materials and Methods: Archived paraffin – embedded tissue samples of BCC (n=40) and SCC (n=40) were stained immunohistochemically using Ber-Ep4 and EMA antibodies.
Results: 37 (92.5%) of the BCC samples stained positive for Ber-Ep4 but 2.5% of SCC group showed positive staining. The majority of SCC group (37 of 40) expressed EMA, while 5% of BCC samples showed positive staining.
Conclusion: Distinction of BCC and SCC of the skin can be readily achieved through Ber-Ep4 and EMA immunohistochemical markers. Regarding potential false positive and false negative results through immunostaining techniques, we recommend the use of these two antibodies together.

P208

A Histopathological Study of 10 Cases of Nephrogenic Fibrosing Dermopathy – a Recently Described Entity

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Nephrogenic fibrosing dermopathy is a rare and recently described skin disorder occurring in association with renal disease. Its pathogenesis remains unclear. It is characterized clinically by large areas of indurated skin with fibrotic nodules and plaques. The histological features mimic scleromyxoedema and include an increase in dermal cellularity of CD34 positive spindle cells and increased dermal mucin. None of the recent publications regarding this disease entity have yet focused on its variable histology.
We reviewed 10 cases (6 females: 4 males) of NFD histologically (age range 37-73 years). Each patient had a history of chronic renal failure. In 5 cases, there was a dense proliferation of spindle cells whereas in the remainder, the degree of cellularity was less marked. In 6 cases, the predominant cellularity of the lesion was located in the dermis whereas, in 2 cases there was subcutis involvement only. The remaining 2 cases showed comparable cellularity in the dermis and subcutis. Only 5 cases showed an increase in dermal mucin staining with Alcian blue.
This study demonstrates that the histological features of NFD are variable in relation to the degree and location of spindle cells and in the presence of mucin. Therefore, clinical pathological correlation is paramount.

P209

Late Metastasis from a Porocarcinoma

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A frail ninety year old man presented with increasing shortness of breath and weight loss and was found to have a large left sided pleural effusion. He had a history of a skin nodule excised from the right lower leg 15 years earlier which had been diagnosed as metastatic adenocarcinoma.

The pleural fluid contained small clusters of atypical cells with vacuolated cytoplasm. Immunocytochemistry showed positive staining with the epithelial markers Ber EP4 and ERA. There was also focal weak positivity for CEA. Other markers including CK5/6, TTF-1, CK7 and CK20 were negative. The appearances were regarded as metastatic carcinoma but the cells were felt to be somewhat smaller and less pleomorphic than those typically seen in metastatic adenocarcinoma. Despite extensive investigations no primary tumour was identified to explain the malignant pleural effusion. The patient subsequently died and post-mortem authorisation was not obtained.

The original skin lesion was reviewed by the dermatopathologists who diagnosed a porocarcinoma - malignant tumour of eccrine origin. Morphologically the tumour consisted of infiltrative nests and strands of epithelial cells with variable cytological atypia, mitotic activity and showing intercellular duct formation. The immunohistochemical profile was identical to that of the atypical groups seen in the pleural fluid, with positive staining for Ber EP4, ERA and CEA.

It is postulated that the malignant cells in the pleural cavity represent a late metastasis from this malignant skin appendage tumour. We report this case as a reminder that these lesions can present many years later with late metastasis.

P210

Angiogenesis transcript profiling identifies distinct tumour signatures in non-melanoma skin cancers

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Non-melanoma skin cancer (NMSC) is the commonest group of malignancies in Caucasian populations. Approximately 80% of NMSC are basal cell carcinoma (BCC) and 20% are squamous cell carcinoma (SCC). Both tumours are capable of metastatic spread. Tumour angiogenesis is essential for tumour growth and spread and appears to play an important role both at the transition from in situ to invasive growth and at a late stage in the metastatic process. The aim of this study was to identify genes involved in angiogenesis, comparing normal and tumour tissue samples from NMSC.

Eleven samples of NMSC and the corresponding normal adjacent skin samples were examined to assess the expression of 84 key genes involved in modulating angiogenesis.

A total of 30/84 genes were found to be up- and/or down-regulated in all tumour samples when compared with adjacent normal skin. A number of gene transcripts were differentially expressed between SCC and BCC.

We have established that BCC and SCC exhibit a distinct pattern of angiogenic gene expression when compared with adjacent normal tissue and with each other. Angiogenic transcript profiling may be a clinically useful predictor of tumour progression. In addition these biomarkers are potential targets of agents aimed at anti-metastatic therapeutics.

P211

Optimal DNA Extraction is Required to Ensure Efficient Routine Diagnostic Clonality Assessment

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PCR clonality assessment is routinely used in the diagnosis of lymphoproliferative disorders within our reference laboratory for the All Wales Lymphoma Panel. However, the addition of Biomed 2 protocols has shown a need for high quality and quantifiable DNA: tissue fixation and processing can reduce DNA fragment size affecting the efficiency of Biomed 2 PCR reactions. We compared an in-house DNA extraction method with the Qiagen EZ1 robot on excess material from 21 diverse prospective diagnostic samples by control gene PCR (Biomed 2) for fragment size then by traditional and Biomed 2 IGH and TCRG analysis. Biomed 2 analysis was only possible on those samples with at least 300bp DNA present. Quantitation of the EZ1 DNA also enabled the Biomed 2 protocol to be precisely followed.

Statistical analysis showed that 18 out of the 21 EZ1 DNA extractions had the same or improved size distribution and quality. In addition, IGH and TCRG PCR data showed a marked improvement in definitive clonality/polyclonality assessment with the EZ1 DNA.

We conclude that the Qiagen EZ1 Robot methodology provides a rapid, automated, user-friendly, reproducible and optimal method of DNA extraction for clonality assessment for use in routine diagnosis.

P212

Analysis of the "Toxic" mRNA That Cause Type 1 Myotonic Dystrophy

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Type 1 myotonic dystrophy (DM1) is caused by the expansion of a tandemly repeated CUG trinucleotide within a host mRNA. The protein is unaffected and most, perhaps even all, the symptoms of DM1 are caused by the CUG repeat-containing "toxic" mRNA. Using a novel small RNA detection method developed in our laboratory, we have found that the CUG repeat within an mRNA is fragmented into a regular array of much smaller RNA. This only occurs when the CUG repeat is of a length characteristic of those that cause DM1. Characterisation of the normal cellular turnover of CUG-repeat-containing mRNA is crucial to understanding DM1. Our ability to detect the fragments gives us a new way of doing this and to identify factors involved in regulating toxic mRNA abundance. For example, we have found that reducing the expression of muscleblind-like 1 - a protein known to interact with CUG repeat RNA and to have a major role in DM1 - reduces the accumulation of the CUG RNA fragments. We are also developing a PCR-based method for amplifying the small RNA fragments that will be essential for their detection in minute clinical samples. Such an assay could ultimately also find diagnostic use.

P213

Colorectal Cancer Gene Expression Profiles Are Dependent Upon Tissue Ischaemic Time and Tissue Handling Protocols

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Successful gene expression studies using surgical samples require purification of intact, high quality RNA. Streamlining of tissue collection, storage and RNA isolation methods is therefore essential. Although poor preservation of RNA might be anticipated with time from surgery, formal assessment of the effects of time and method of tissue handling are rarely given prominence.

In this study we have used Affymetrix gene expression analysis to examine the gene expression profile in colorectal cancer samples taken endoscopically to determine the effect of delay in freezing samples and also the effect of RNAlater™, a RNA stabilisation reagent, on the profiles obtained. Our findings demonstrate that the expression profile of excised tissue remains constant for 15 minutes. Thereafter, there are substantial changes in the expression profile, with expression of some genes increasing whilst that of others declines. Further, if tissues are either snap frozen or placed in RNAlater™ immediately upon removal from the patient, significantly different profiles are obtained.

Our findings indicate that gene expression profiles vary with time and with the mode of tissue preservation and that to interpret or compare gene expression microarray studies the effects of time and tissue handling protocols must be taken into account.

P214

Development of Protocols to Allow the Simultaneous Demonstration of Origin, Phenotype and Function of Cells in Paraffin Sections Within a Phyllodes Tumour Xenograft

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Introduction: We have developed a number of techniques to identify transplanted cells and assess their phenotype in a variety of experimental models relevant to transplantation and cancer research.
Methods: A fibroblast culture established from a benign phyllodes tumour developed a rapidly dividing sub-clone after 6 passages. The two cell populations were genotyped confirming that the they were from the same individual. Both populations of cells were injected into the mammary fat pad of a nude mouse and a high grade tumour developed. Immunohistochemistry using a panel of markers (Ki67, PDGF β, cytokeratin, c-myc, p53, CAM 5.2, Vimentin, S100 and β Catenin) when combined with mouse and human pan-centromeric FISH probes showed that the tumour was human with epithelial phenotype with distinct mouse stromal elements. Array CGH confirmed that the genetic changes within the xenograft were similar to those in the malignant sub-clone in vitro.
Conclusions: Fibroblasts from a benign phyllodes tumour can undergo mesenchymal to epithelial transformation in vitro, resulting in tumourigenicity in vivo. Immunohistochemistry combined with mouse and human pan-centromeric fluorescence in situ hybridisation is a simple method for determining the origin and phenotype of cells within a tumour xenograft.

P215

Abstract withdrawn

P216

Raman Microscopy for the Chemometric Analysis of Tumour Cells

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Raman spectroscopy is recognized as a tool for chemometric analysis of biological materials due to the high information content relating to specific physical and chemical qualities of the sample. Thirty cells belonging to two different prostatic cell lines, PNT1A (immortalized normal prostate cell line) and LNCaP (malignant) cell line derived from prostate metastases), were mapped using Raman microscopy. A range of spectral preprocessing methods (partial least-squares discriminant analyses (PLSDAs), principal component analyses (PCAs), and adjacent band ratios (ABRs)) were compared for input into linear discriminant analysis to model and classify the two cell lines. PLSDA and ABR were able to correctly classify 100% of cells into benign and malignant groups, while PLSDA correctly classified a greater proportion of individual spectra. PCA used to image the distribution of various bio-chemicals inside each cell and confirm differences in composition distribution between benign and malignant cell lines. This study has demonstrated that PLSDAs and ABRs of Raman data can identify subtle differences between benign and malignant prostatic cells in vitro.

P217

Reproducibility of image analysis in virtual microscopy

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Virtual microscopy is revolutionising pathology by producing diagnostic quality images of an entire slide. This provides enormous opportunities for automated analysis, particularly tissue microarray (TMA) analysis. However quantitative analysis of TMA virtual slides must produce consistent intra/inter-scanner results.
This study aims to assess the reproducibility of morphologic, densitometric and texture data on different slide scanners. A single TMA showing samples of gastric lesions and immunohistochemically stained for Cyclin B1 was scanned 5 times on two Aperio CS Scanscopes. The same ten tissue cores were selected from each scan and a series of geometric, densitometric and textural measurements made to compare reproducibility on sequential scans on different instruments.
Measurements showed that intra-machine scans produce consistent densitometric results with a coefficient of variation of 0.039 (machine 1) and 0.013 (machine 2) for mean grey level of positively stained tissue. A comparison of tissue cores scanned on different instruments shows subtle differences in visual appearance of the images. This was confirmed by quantitative evaluation of immunomarker labelling: e.g. a 4% difference was observed between the number of positively stained pixels between machines on a single core and a 32.4% difference in total mean density in positively stained areas.
Consistent results are essential for the quantitative evaluation of TMAs. This study has shown that sequential scans from a single instrument are reproducible. However, there are obvious differences in the quantitative evaluation of TMAs from different instruments and it may be necessary to develop suitable internal control slides to standardise results.

P218

Quantifying tumour-infiltrating lymphocyte subsets by colour image histogramming

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Background: efficient counting of T and B lymphocyte subsets and other immune cell populations infiltrating archival tumour tissue samples would facilitate research into the roles of such cells in human cancer. We have developed such a method using colour image histogramming*.
Methods: sixteen invasive breast carcinomas were immunoperoxidase stained for CD3, CD4, CD8, and CD20. For each stained section ten x40 digital images at the tumour edge were acquired. The number of pixels in each image matching a cuboid of the L*a*b* colour space corresponding to the immunoperoxidase signal was counted with 'color range' and 'histogram' tools (Adobe Photoshop 7). Pixel counts were converted to cell counts per mm^2 using calibration factors calculated for one, two, three or all 10 available images for each case and antibody combination.
Results: between-case and between-antibody variation in the number of labelled pixels per immuno-stained cell made individual calibration for each case and antibody combination essential. Calibration based on two representative fields containing the largest numbers of labelled pixels yielded cell counts minimally higher (+5.3%) than counts based on 10-field calibration, with 95% confidence limits -14.7 - +25.3%. As TIL density may vary up to 100-fold between cases, this accuracy and precision will generally be acceptable.
Conclusion: the approach described is sufficiently accurate, precise and efficient to quantify the density of TIL sub-populations in breast cancer using commonly available software. A program to automate batch processing of pixel counting using software utilities in the public domain is being developed.

*Journal of Immunological Methods, 2007;321:32-40.

P219

Episcopic Microscopy, Reconstruct and OsiriX: Tools for 3D Vision

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Background: Histology is inherently two dimensional. Visualising tissue structures in 3D can be informative, but technical challenges are non-trivial. A particular limitation is the problem of registering images of serial sections. Episcopic microscopy is a novel technique[1,2] which solves the registration problem by imaging embedded tissue exposed on the block face after each section has been cut, generating a stack of perfectly registered images.

Methods: two blocks of nipple tissue were examined by episcopic microscopy to investigate duct structure in the papilla. Image data was visualised using two open-source (public domain) programs: Reconstruct[3] (for PCs) and OsiriX[4] (for Mac OS X).

Results: episcopic microscopy generated large quantities of perfectly registered image data, completely solving the registration problem. Substantially more structural detail was captured in a 'second generation' episcopic microscopy set-up. 3D analysis in Reconstruct allowed the ducts to be visualised as a 3D model and the OsiriX viewer also allowed interactive visualisation of structural data.

Conclusions: episcopic microscopy is a recently established tehnique with considerable potential for application to the investigation of 3D structure in the field of pathology. Recent software in the public domain including Reconstruct and OsiriX make available capabilities comparable to those of expensive commercial software, allowing large 3D data sets to be investigated in a resource-efficient manner.

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P220

The Effects of Various Forms of Fixation On the Quality of Messenger RNA Extracted from Paraffin Embedded Tissue

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Background Alcohol based fixatives are thought superior to formalin for the preservation of messenger RNA (mRNA) in tissue. However, there has been little formal comparison. The aim of the study was to compare the quality of mRNA extracted from frozen, formalin fixed and alcohol fixed human tissue from the same specimen.
Materials and methods Human colon was obtained from colorectal carcinoma specimens, snap frozen or fixed for 24 hours in formalin or alcohol fixative and embedded in paraffin wax. RNA was extracted using the RecoverAll Kit (Ambion) and integrity assessed by Taqman Real Time PCR and the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH).
Results and Conclusions RNA isolated from frozen tissue gave a mean Ct value of 21. This was significantly lower than all the other groups tested. Methacarn and Umfix gave mean Ct values of between 23 and 28 as did tissue collected in RNAlater and subjected to the embedding procedure. These were significantly lower than both formalin fixed material and material fixed in Finefix. Our data support the superior retrieval of RNA from most alcohol based fixatives, but also demonstrate that real time PCR is possible from formalin fixed material.

Abstracts

Invited Speakers

S1

Introduction to Mesenchymal Induction of Epithelium in Development, Tissue Remodelling and Cancer

{P} B Gusterson, T Stein
Section of Pathology and Gene Regulation, Glasgow University, Glasgow, United Kingdom

The inductive effects of the mesenchye in tissue differentiation during embryonic development are well established through tissue recombination experiments. In the post natal developing mammary gland it is clear that individual cellular components of the connective tissue and local cytokine production are major contributors to branching morphogenesis and migration. By analysing the genes expressed at key time points in puberty, pregnancy and involution it is possible to identify novel regulators and physiological processes that can predict survival ad metastasis in breast cancer cohorts, indicating that carcinomas are utilising these common pathways of tissue remodelling. This is really Willis re-invented some 50 years on albeit with more functional understanding.

S2

Stromal Recruitment in Cancer

{P} M Alison
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The stromal microenvironment provides support for tumour growth. Inflammatory cells, e.g. macrophages and T cells, can act as tumour promoters through the secretion of cytokines, particularly TNFα activating the NFκB pathway in tumour cells, leading to oxidative stress, cell proliferation and evasion of apoptosis, expanding the tumour mass. Additionally, tumour stroma comprises vascular networks, fibroblastic and myofibroblastic cells, and extracellular matrix components upon which tumour expansion critically depends.

In wounding, end-stage fibrotic disease and tumour desmoplasia, fibroblasts and myofibroblasts can be derived from local mesenchyme and circulating fibrocytes, but we have often observed that a significant proportion (25-30%) are of bone marrow (BM) origin. Expanding peritumoural vascular networks are in part due to the sprouting of existing capillaries (angiogenesis), but also due to the recruitment of BM-derived endothelial progenitor cells (EPCs). Mesenchymal stem cells (MSCs) from BM can preferentially home to certain tumours, and transduced with the IFNγ gene are able to prolong host survival. Likewise, MSCs transduced with a truncated soluble Flk-1 gene, have been shown to slow tumour growth by retarding new vessel development. Thus, the tumour-BM axis is proving a promising new portal through which to direct anti-stromal and anti-angiogenic therapies.

S3

Evidence for functional immune responses against tumour antigens

{P} JJ Going
Uniiversity of Glasgow, Glasgow, United Kingdom

Neoplastic transformation is often seen as driven by events purely internal to the cancer cell, such as oncogenic mutation and loss of tumour suppressor gene function, but interactions with the cellular microenvironment are equally important and include avoidance of innate and adaptive immunosurveillance. That immune mechanisms can prevent emergence of neoplasia is established by the increased incidence of neoplasia in animal models and immunosuppressed people, although the cancer spectrum in immunosuppressed individuals does not closely match spontaneous human cancers (mainly carcinomas).

Innate and adaptive cellular effectors of tumour cell killing potentially include NK and γδ T cells; macrophages; and MHC class I restricted CD8+ cytotoxic T cells (a mechanism potentially subverted by loss of MHC class I from tumour cells or Treg cells). Humoral mechanisms may involve antibody-directed cellular cytotoxicity and complement-mediated cell lysis. B cells may also participate as antigen-presenting cells and some antibodies may have pro-inflammatory effects or in some situations may block more effective anti-tumour effector mechanisms.

While there are relatively few tumour-specific antigens, a larger group of less specific tumour-associated antigens and potential immune targets include oncofetal antigens, oncogene-associated antigens, viral antigens, and others less well characterised.

While tumour cells can provoke significant immune responses, it is clear that immune control of tumour growth is often ineffective. Despite the supposition that cell-mediated immunity is generally more important than humoral anti-tumour immunity, some of the most successful immunologically-based anti-tumour therapies of recent years have exploited humanised monoclonal antibodies, e.g. Herceptin (directed against the erbB2 oncogene); and Rituximab (directed against CD20).

S4

Forensic histopathology – is it different?

{P} S Leadbeatter
Cardiff University, Wales Institute for Forensic Medicine, Cardiff, United Kingdom

This presentation will attempt to destroy any canard that histopathology forms no part of the armamentarium of a forensic pathologist, seeking to demonstrate that the microscopic appearances of organs may do more than bear upon the cause of death and, in so doing, create problems of primacy and procedure.

S5

Medication is Meant to Help, not Harm

{P} J Clark
University of Glasgow, Glasgow, United Kingdom

Drugs in one form or another feature in a significant proportion of forensic post mortem examinations. Principally this will be in deaths from a suicidal overdose of medication and in those from abused substances.
A much smaller number will be the result of complications of normally prescribed medication, either an unexpected severe side effect, or a dose related effect because of increased blood levels developing for whatever reason, including drug interactions.
Some of these deaths will be obvious for what they are – antibiotic related toxic epidermal necrolysis, intracranial haemorrhage from excess warfarin, or reported prescription and drug administration errors, but others will be much more subtle and may be missed if not considered.

S6

Intra-cerebral haemorrhage - Trauma, stress and other factors

{P} C Smith
University of Edinburgh, Edinburgh, United Kingdom

Intra-cerebral haemorrhage is a not uncommon finding in the brain of cases of sudden death. The causes of intra-cerebral haemorrhage are numerous and the accurate diagnosis may have a bearing on subsequent investigations relating to the cause of death.

Intra-cranial haemorrhages can be described as extradural, subdural, subarachnoid and intra-cerebral. Intra-cerebral haemorrhages may not be apparent externally although they may give rise to subarachnoid haemorrhage if the bleeding enters the ventricular system. On coronal sectioning it is important to note the location and size of the lesion, describe the consistency and any other pathological lesions.

Important causes of single focal lesions include hypertension, trauma, cerebral amyloid angiopathy and vascular malformation. Multiple lesions are more typical of trauma and particularly diffuse vascular injury. Petechial haemorrhages can be caused by a number of pathologies including fat emboli, infections, and ADEM.
The role of stress in initiating a hypertensive bleed in certain situations will be discussed with reference to the established literature.

S7

Cardiac Disease and Medico-legal Issues

{P} N Cary
Forensic Pathology Services, Abingdon, Oxford, United Kingdom

Cardiac diseases particularly those associated with cardiomegaly, myocardial fibrosis and / or coronary atherosclerosis are associated with a risk of sudden dysrhythmic death. Although the precipitating factors are often unclear, in a small but important proportion “stress” whether emotional, physical or a combination may promote dysrhythmia. This is likely through the effects of adrenaline and a rise in pulse rate / blood pressure.

A role for stress has been established through casework and also through the study of populations exposed to earthquakes.
When stress is the result of actions of a third party the issue of criminal liability arises. In analysing such cases three aspects are fundamental:-
1 The temporal coincidence of the proposed stressful event and first collapse /sudden death
2 The lawfulness or otherwise of the stressful event
3 The condition of the deceased’s heart prior to the event

A thorough pathological examination of the heart and a good history of the deceased’s pre-morbid status are essential to prove that the deceased’s cardiac condition was not already deteriorating acutely prior to the event and also to establish the likely timing of the terminal event. Forensic pathological findings both positive and negative are relevant to the issue of lawfulness.

S8

Cancer and plasticity of the inflammatory response in tumour development and progression

{P} F Balkwill
Barts & The London, Queen Mary's School of Medicine & Dentistry, London, United Kingdom

The connection between inflammation and cancer is now well accepted and provides an framework for studying the interplay between malignant cells and the other cells that are important in the tumour mass. Until recently the field has been driven by the hypothesis that **extrinsic** inflammatory pathways promote or, in some cases, initiate cancer. However there is now evidence for an **intrinsic** inflammation pathway, activated by genetic events that cause neoplasia.
Through these intrinsic and extrinsic pathways, it appears that cancer-related inflammation is a general and essential pathological process in malignant disease, with common and defined players at different stages of cancer development and cancer progression.
The study of cancer-related inflammation provides us with novel approaches to cancer treatment; therapies that compliment those targeting the malignant cell or that attempt to boost specific immunity.

S9

New Entities and New Twists on Old Entities

{P} J Meis-Kindblom
Royal Orthopaedic Hospital NHS Foundation and Trust, University of Birmingham School of Medicine, Division of Cancer Studies, Birmingham, West Midlands, United Kingdom

Clear cell sarcoma of tendons and aponeuroses (CCS) is a well-defined clinicopathologic entity described by Enzinger in 1965. It displays distinct melanocytic differentiation but is unrelated to cutaneous melanoma clinically and genetically. A reciprocal t(12;22)(q13;q12) translocation and resulting *EWS/ATF1* fusion transcript are characteristic of CCS; however, they are not pathognomonic since they have now been found in angiomatoid (malignant) fibrous histiocytoma (A(M)FH). To date, only 6 cases of primary CCS of bone have been reported; a purported 7th case of "polyphenotypic round cell sarcoma" has been suggested to be a primary CCS of bone based on molecular genetic studies, but is undoubtedly a rare example of A(M)FH of bone. We have documented the occurrence of a clinically aggressive primary CCS of bone using molecular genetic techniques. The occurrence of classical soft tissue tumours (STT) in bone, whilst rare, is not totally unexpected. Thus, CCS and A(M)FH are yet two additional STT that may rarely arise in bone. Other examples include sclerosing epithelioid fibrosarcoma, solitary fibrous tumour, ossifying fibromyxoid tumour, extraskeletal myxoid chondrosarcoma, IMT, embryonal rhabdomyosarcoma, myxoid liposarcoma and synovial sarcoma. The clinical behaviour of these primary bone tumours does not necessarily parallel that of their more common soft tissue counterparts.

S10

Reactive and Pseudomalignant Lesions of Soft Tissue

{P} R Reid
Western Infirmary, Glasgow, United Kingdom

As in all branches of diagnostic pathology the distinction between malignant tumours and their benign, often non-neoplastic mimics is of much importance. Errors in this area are easy to make and are a source of significant litigation, usually because of over- rather than under-diagnosis of malignancy. These lesions are difficult to diagnose unless the pathologist is familiar with them, because their often rapid clinical growth is mirrored by brisk mitotic activity. All have, at least focally, a distinctive tissue culture-like architecture of proliferating fibroblasts or myofibroblasts.
Nodular fasciitis has recently been described within joints and within peripheral nerve. Like many other lesions traditionally regarded as reactive, reports of karyotypic abnormalities suggesting a neoplasm, have been published. Proliferative fasciitis and proliferative myositis are characterised by large ganglion-like cells and may suggest malignancy, especially in children where the lesions are highly cellular. Fracture callus and myositis ossificans circumscripta remains an important differential from the diagnosis of soft tissue osteosarcoma. Myositis ossificans and fibro-osseous pseudotumour of digits are essential the same process, although the zoning phenomenon is less well formed in the latter. Myositis ossificans progressiva resembles the circumscribed form histologically but patients develop progressive truncal ossification with respiratory failure. Aneurysmal bone cyst, traditionally regarded as a reactive lesion but now thought to be a tumour has now been described in soft tissue.

S11

Paediatric Soft Tissue Sarcomas – a Paradigm of the Role of the Pathologist in Oncology

{P} AG Howatson
Royal Hospital for Sick Children, Glasgow, United Kingdom

The development of an integrated approach utilising morphology, immunohistochemistry and molecular diagnostics has resulted in a more objective approach to diagnosis of paediatric "small blue cell" sarcomas.

Problem cases remain however. Undifferentiated tumours are not uncommon in paediatric practice and, in many instances, remain refractory to current diagnostic techniques. Increased experience with immunohistochemistry has identified a number of staining reactions e.g. CD99 positivity in rhabdomyosarcoma and small cell variant synovial sarcoma which have, on occasion, led to misdiagnosis. Identification of tumour specific chromosomal translocations has retrieved accurate diagnosis in many of these cases and, with the development of RT-PCR and FISH, we are no longer dependent on classical cytogenetics.

These molecular diagnostic techniques are not infallible. Difficulties remain with tumours such as translocation negative alveolar rhabdomyosarcoma and site specific rhabdomyosarcomas which have aggressive clinical behaviour but neither alveolar morphology nor translocations.

Patient and tumour specific treatment protocols to ensure the best possible outcome in individual cases are now a driving force in paediatric oncology. Where immunocytochemistry and molecular diagnostics assist diagnosis and prognostication, the cases are relatively straightforward. However, in a minority, the responsibility remains with classical histological assessment.

This presentation will review the integrated diagnostic approach to paediatric soft tissue sarcomas and highlight areas of diagnostic confusion and difficulty.

S12

Gastrointestinal stromal tumours (GIST) - an update

{P} L-G Kindblom
Dept of Musculoskeletal Pathology, Royal Orthopaedic Hospital NHS Foundation Trust and Dept of Pathology, Division of Cancer Studies, University of Birmingham, Birmingham, United Kingdom

For a long time GIST remained a largely enigmatic tumour with unknown differentiation (causing a confusing nomenclature), that lacked definite diagnostic criteria, caused problems in prognostication and had a dismal outcome in malignant cases. Over the last years GIST has (for a relatively uncommon disease) received an unprecedented attention from the medical community as well as the media and the general public. The reason for this is a dramatic and unusually illustrative breakthrough involving the understanding of its line of differentiation (interstitial cells of Cajal, ICC), identification of powerful diagnostic (KIT receptor expression) and prognostic (consensus risk scoring systems) markers, identification of the pathogenetic mechanisms (activating KIT and PDGFRA mutations) and most importantly the development of a novel, highly effective, targeted molecular treatment (imatinib mesylate). GIST now nicely illustrates the new and important roles for pathologists that include, in addition to correct diagnosis, identification of new prognostic markers, prediction of treatment response (with mutation analysis) and identification of new targets for molecular treatment.
This presentation, based on our own population-based studies and others' experience, will try to give an update on recent developments in the diagnosis (including pitfalls), prognostication and treatment of GIST.

S13

The clinicopathological significance of molecular abnormalities in medulloblastoma - a paradigm for the diagnosis and management of childhood brain tumours.

{P} D Ellison
St Jude's Children's Research Hospital, Memphis, Tennessee, United States

It is certain that molecular analysis will increasingly supplement histopathology as part of the diagnostic evaluation of tumours. However, an often bewildering array of molecular data is now available for correlation with clinical and pathological variables and raises issues about how molecular assays should be optimally formulated both for use as diagnostic, prognostic or predictive tumour markers and in the interests of patient and society as a whole. Currently, the medulloblastoma presents the best example of this paradigm in childhood brain tumours; recent studies provide insights into its development that impact on clinical behaviour and histopathological phenotype. In particular, molecular variants of medulloblastoma caused by disruption of developmental signalling pathways, such as the Wnt and Shh pathways, appear to have distinct genotypes, morphologies and behaviours. Despite these advances, it is also clear that, for a tumour that is relatively rare and for which we are still uncovering new histopathological variants with prognostic significance, finding the appropriate combinations of histopathological and molecular assessments will require the careful implementation of appropriate clinical studies.

S14

Stem cells and the brain: a potential for repair?

{P} R Franklin
University of Cambridge, Cambridge, United Kingdom

The adult CNS contains an abundant and widespread population of stem/precursors cells that are highly efficient at replacing myelin sheaths lost in demyelinating diseases such as multiple sclerosis. However, this regenerative process (called remyelination) is inconsistent and its failure leads to irreversible axonal loss. Since remyelination can occur its therapeutic enhancement therefore represents not only an important but also a feasible clinical objective. Identifying potential targets will depend on a detailed understanding of the cellular and molecular mechanisms of remyelination. This talk will review 1) the nature of the cell or cells that respond to demyelination and generate new oligodendrocytes, identifying current areas of uncertainty and addressing the role of adult CNS stem and progenitor cells, 2) intrinsic factors regulating precursor differentiation and 3) how an environment favourable to remyelination is generated, and will introduce the concept of a matrix of signalling events critical for the successful completion of remyelination.

S15

Basal-like carcinomas: from pathology to mouse-models and beyond

{P} JS Reis-Filho
The Breakthrough Breast Cancer Research Centre, Institute of Cancer Research, London, United Kingdom

Basal-like breast carcinomas (BLCs) are a subgroup of aggressive and chemotherapy resistant breast cancers characterised by lack of hormone receptors and by the expression of genes preferentially expressed in basal/ myoepithelial cells. Our group has demonstrated that these tumours are of high histological grade, have pushing borders, brisk lymphocytic infiltrate, high proliferation rates, central necrosis/scaring and presence of homologous metaplastic elements. Given the morphological similarities between sporadic BLCs and tumours arising in BRCA1 mutation carriers, we investigated whether the latter would have a basal-like phenotype. In fact, 70-80% of all tumours arising in BRCA1 mutation carriers showed expression of at least one basal marker. Interestingly, approximately 2/3 of both BRCA1 familial cancers and sporadic BLCs showed overexpression of EGFR. Owing to the reported efficacy of EGFR tyrosine kinase inhibitors in tumours harbouring either EGFR activating mutations or gene amplification, I investigated whether one of these mechanisms would drive EGFR expression in BLCs. Although EGFR activating mutations were exceedingly rare in BLCs, EGFR gene amplification was found in 1/3 of cases with EGFR overexpression. Furthermore, using microarray based comparative genomic hybridisation I have defined the smallest region of amplification in EGFR amplified cancers, which encompasses LANCL2, SEC61G and EGFR, the latter being the likeliest amplicon driver. Given the similarities between sporadic BLCs and tumours arising in BRCA1 mutation carriers, our group investigated whether BRCA1 gene or its pathway would be inactivated in sporadic BLCs. We observed that BRCA1 expression levels were significantly lower in basal-like grade III invasive ductal carcinomas when compared to grade and histological type matched tumours and hypothesised that this finding would be due to BRCA1 gene promoter methylation. Surprisingly, both sporadic invasive ductal carcinomas with and without basal-like phenotype showed a low prevalence of BRCA1 gene promoter methylation. We therefore investigated alternative epigenetic mechanisms of BRCA1 pathway inactivation and found that sporadic invasive ductal carcinomas with basal-like phenotype expressed ID4, a negative regulator of BRCA1, at significantly higher levels than controls. This may account for the low levels of BRCA1 expression in sporadic BLCs of ductal morphology. On the other hand, BRCA1 gene promoter was methylated in 63% of metaplastic breast carcinomas. Interestingly, >90% of metaplastic cancers show a basal-like phenotype and 64% display p53 nuclear overexpression. Consistent with this, pathological analysis of tumours arising in the conditional mouse model BLG-Cre;Brca1F22-24/F22-24;p53+/- revealed that 78% were of basal-like phenotype and 88% showed homologous metaplastic elements. Taken together, these results suggest that BRCA1 pathway dysfunction is paramount for the biology of BLCs. Targeting defects in the BRCA1 pathway with crosslinking agents or PARP inhibitors or inhibiting EGFR pathway with specific tyrosine kinase inhibitors may provide novel therapeutic strategies for the management of BLCs.

S16

The Enigma of trophoblast – a 24 year perspective

{P} M Wells
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When inundated with numerous specimens of products of conception as the consequence of miscarriage, it is all too easy for histopathologists to forget that the biology of trophoblast and the events of early placental implantation continue to fascinate because of the inherently invasive properties of the non-villous (extravillous) trophoblast. However, unlike the invasion of a malignant tumour the invasion of trophoblast is controlled. The interaction of growth factors, receptors and cytokines at the crucial materno-fetal interface of the placental bed is complex; TGF-β, for example, inhibits extravillous trophoblast cell growth and invasion. Non-villous trophoblast expresses a unique class 1 HLA antigen (HLA G) which is not expressed by villous trophoblast. The failure of adequate conversion of maternal uteroplacental arteries is a major pathogenetic phenomenon of important disorders of pregnancy including pre-eclampsia. However, it is in the field of gestational trophoblastic disease that diagnostic acumen is most called for. There are several problematic areas that give rise to diagnostic error; e.g. the diagnosis of early complete mole as partial mole, the overdiagnosis of hydatidiform mole in tubal pregnancy and the diagnosis of placental site non-villous trophoblast as placental site trophoblastic tumour or choriocarcinoma, particularly if associated with atypia as frequently observed in complete mole. The chorionic villi of early diploid complete mole show characteristic features of villous profile, stromal mucin and stromal nuclear debris. The distinction between diploid complete mole and triploid partial mole can also be facilitated by ploidy analysis (the one field of diagnostic histopathology in which it is routinely applied) and immunohistochemistry for the product of the paternally imprinted, maternally expressed gene $p57^{kip2}$. Persistent trophoblastic disease (PTD) is a clinical not a histopathological diagnosis and the role of the histopathologist once a diagnosis of PTD has been made is limited. Invasive mole and choriocarcinoma are encompassed by PTD. Tumours of the non-villous trophoblast are placental site trophoblastic tumour and the more recently recognised epithelioid trophoblastic tumour.

S17

Sperm Centriole Abnormalities are Causative for Intracytoplasmic Sperm Injection (ICSI) Fertilization Failure

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Fertilization failure in human after assisted reproduction technique with ICSI (Intracytoplasmic Sperm Injection) may be due to different dysfunctions affecting the spermatozoon. Because the mature oocyte is devoid of centrioles, an impaired capacity to promote the growth of microtubule (MT) arrays from the sperm centrosome may preclude pronuclear opposition required for syngamy resulting in developmental arrest of the embryo.
Native ejaculate with motile sperm evidence (50%) from a 40-years old healthy man with a history of 2 unsuccessful homologous ICSI cycles, was examined for ultrastructural abnormalities.
A significant number (80% of examined) of abnormal spermatozoa with an aberrant acrosomal complex, head deformations, and multiple centrosome lesions was observed.
In eight spermatozoa out of 11 with optimally visible centrosomes (73%), the transversal centriole sections revealed a distinct loss of the MT-triplets or their reduction to a MT-doublet, and a coupled additional smaller centriole structure was evidenced. In the longitudinal centrosome sections overlong MT protruding laterally the spermatid neck were displayed.
The spectrum and relatively high incidence of the observed centriolar aberrations suggest the causative sperm defect responsible for the early embryo development failure. At present no help could be offered to couples affected by totally impaired centrosome function.

S18

The drug pipeline and development of new predictive biomarkers

{P} D McHale
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Despite the development of many technologies offering the promise of personalised medicines most drugs are currently being developed in the same way as they were 30 years ago. This has led to an industry struggling to find targets and therapies that offer significant medical benefits over current therapies.

In an effort to change this paradigm many companies are investing heavily in the identification of biomarkers that can be used in drug development to improve decision making and ultimately be used to predict drug response. Although these predictive markers are generally associated with personalised medicine they are more commonly used to predict population clinical outcome e.g. mean change in HbA1c as a surrogate for diabetic complication rates. This talk will discuss the evolution of biomarkers from disease understanding and target identification through surrogate clinical endpoint to predictive test for personalised medicine and the challenges of getting these biomarkers accepted into clinical practice.

S19

The Kidney in Systemic Disease

{P} P Furness
University Hospitals of Leicester, Leicester, United Kingdom

The kidney can be involved in a large proportion of human diseases; it is therefore necessary to be selective. Some important conditions will be covered by other speakers.
The impact of monoclonal proteins on the kidney is extremely variable. Beyond the well-known "myeloma cast nephropathy" and amyloidosis, monoclonal paraproteinaemia can cause a Fanconi-like tubular disorder, glomerular monoclonal immunoglobulin deposition disease (light and/or heavy chain nephropathy) and the various glomerular consequences of cryoglobulinaemia and macroglobulinaemia. Monoclonal proteins also have a strong association with the recently defined entities fibrillary glomerulopathy and immunotactoid glomerulopathy. Presentation clinically and histologically can therefore be extremely variable, and some of these disorders require only trace quantities of paraprotein in the bloodstream to generate serious renal effects. When this happens, the clinical definition of "myeloma" can become problematic.
The variety of impact which systemic lupus erythematosus can have on the kidney is rather better known. The WHO classification of lupus nephritis always suffered from poor reproducibility, and has recently been replaced by a new international consensus classification, the ISN/RPS classification, which will be described. Evidence of improved reproducibility is now available, but there are areas where the old and new classifications have significant differences in their application. Knowledge of these differences is important when extrapolating between the two systems
Numerous infectious diseases can impact on renal function. HIV infection is one which can generate a wide variety of changes in the kidney, some of which will be discussed.

S20

Post Mortem Renal Pathology – What You Can and Can't Tell from An Autopsy Kidney

{P} ISD Roberts
John Radcliffe Hospital, Oxford, United Kingdom

Macroscopic examination of post-mortem kidney is sensitive in the diagnosis of chronic renal diseases. The pattern of scarring can distinguish common aetiologies including hypertensive renovascular disease, atheroembolic disease and reflux nephropathy. In general, cortical thickness correlates with renal function, an exception being diabetic nephropathy, in which cortical thickness may be preserved in the presence of severe renal failure. Gross changes show less specificity in the diagnosis of acute renal injury, for which histology is usually necessary.

Histological diagnosis and quantification of chronic damage is reliable in post-mortem kidney. However, renal tubules undergo rapid autolysis, confounding the diagnosis of acute tubular necrosis (ATN). Identification of necrotic cells within the lumen of well-preserved medullary collecting ducts is a useful marker of ante-mortem ATN. Intratubular neutrophils suggest ascending infective nephritis. Post-mortem bacterial overgrowth may be seen without prior infection, but large numbers of intravascular bacteria suggest ante-mortem septicaemia.

Several conditions commonly seen at autopsy can only be diagnosed histologically, such as diabetic nephropathy, vasculitis and thrombotic microangiopathy. Many antigens are well preserved for several days post-mortem, enabling the characterisation of glomerular immune deposits and tubular casts, such as myoglobin. Electron microscopy is less useful post-mortem, as ultrastructural morphology deteriorates within hours of death.

S21

How to diagnose glomerular disease

{P} B Young
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[2]*University of Glasgow, Glasgow, United Kingdom*

This talk is intended to give an outline of an approach to renal biopsies for non-specialist renal pathologists. Many people are put off renal pathology because it seems esoteric and polysyllabic. However there are some simple rules that can be applied to make the entire process a lot simpler.

Rule one – clinical presentation ≠ histological appearance ≠ diagnosis – that is to say many different diseases have similar clinical presentations and overlapping or similar histological appearances

Rule two – the glomerulus has a limited range of responses to insult – increase in cellularity, increase in stroma, changes to the basement membrane

Rule three – work out the pattern of the glomerular changes and then combine that information with immunofluoresence/immunohistochemistry, electron microscopy and clinical history to reach a definitive diagnosis if possible

Using a few examples of common and important renal diseases we will apply these rules and demonstrate how they can simplify the diagnostic process.

S22

Pathology: what does it mean to you?

{P} NA Wright
London Research Institute, Cancer Research UK and Institute of Cell and Molecular Science, Barts and the London, London, United Kingdom

Should anyone ask me where my primary professional allegiance lies, I would have to say in surgical pathology. I was trained as a surgical pathologist. I have practised surgical pathology most of my professional life. I also believe in the concept of *academic* surgical pathology, accepting that I am probably in a minority among my professorial colleagues. Why should this be? Well, just suppose we were trying to distinguish a Spitz naevus from a spitzoid malignant melanoma: who taught us to disregard the significance of Kamino bodies, to hunt for deeply-sited mitoses and pigment and to look very carefully for evidence of epidermal invasion? In short, our predecessors who examined these lesions, and through painstaking clinico-pathological correlation and follow-up, established these criteria. *This* is academic surgical pathology, and most of us merely apply these hard-won maxims to our own practice. It is very easy to think of many other examples, and current academic surgical pathologists are adding to these all the time. I therefore fail to see how any can deny the existence of an academic surgical pathology.

But I would go further. I would propose that it is surgical pathology that provides the basis of most, if not all, of the research topics that so-called academic pathologists work on: in my view, any research that does not derive from or be applicable eventually to surgical pathology is, for pathologists, a sterile exercise. A harsh view? We shall see. I shall argue strongly for surgical pathology as the foundation of our discipline, and our common origins, a proposal which, again in my view, we ignore at our peril.

S23

Pathology in Colorectal Cancer Screening

{P} F Carey
Ninewells Hospital, Dundee, United Kingdom

Population testing for faecal occult blood (FOB) has been shown to decrease mortality from colorectal cancer. Pilot programmes have demonstrated the feasibility of delivery and national programmes are underway in Scotland and England. The programme will have a significant impact on colonoscopy and pathology services. The experience to date is that approximately 2% of the population accepting screening will be FOB positive. Of these 10% will have cancer and 30% adenomas. Significantly, about 20% of cancers in the 1st (prevalence) round of screening were polypoid early stage malignancies. The main immediate challenges for pathology will be in coping with increased workload, difficulties in diagnosing early cancer (danger of overdiagnosis) and accurate reporting of adenomas to identify and screen individuals at high risk of subsequent neoplastic disease. National datasets are under development to aid in this process and guidance will be made available to standardise reporting of potentially useful items such as villousness and high grade (severe) dysplasia in adenomas.

Screening has a major effect in diagnosing a higher proportion of cancers at an early stage. There is need for a concerted effort to refine pathological and biological markers of aggressive behaviour in such tumours.

S24

Pathology guided management of colorectal cancer

{P} P Quirke
Leeds University, Leeds, United Kingdom

Pathologists are important in the management of CRC and continue to be critical in determining treatment and improving outcomes. Much has been done but we need to improve our performance further to ensure the maximum benefit to patients.
Our contributions are direct and indirect.
Direct contributions relate to identifying node positive and high risk stage II cases. Indirect contributions are in grading the plane and thus the quality of surgery, auditing the accuracy of MRI and determining the effect of therapy.
In the near future we will also play an increasing role in determining the need for resection when diagnosing early cancer from the NHS bowel cancer screening programme.
Evidence of improving pathologist performance, the impact of the NHS multidisciplinary team Pelican programme on CRC pathology and the residual areas of poor performance will be given. The latest evidence on the importance of the quality of surgery will be presented and discussed.
It is essential that pathologists recognise the importance of their role and understand the need for high quality performance in day to day practice.

S25

Dysplasia-related Pitfalls in the Upper Gastro-intestinal Tract

{P} NA Shepherd
Gloucestershire Royal Hospital, Gloucester, United Kingdom

A review of the author's personal second opinion practice shows that the assessment of dysplasia provides particular diagnostic consternation for practising pathologists. This especially applies to dysplasia in Barrett's oesophagus. It is worth emphasising that, in all current management guidelines in GI practice, dysplasia is classified according to Riddell-type systems. This certainly serves to reduce inter-observer variation but, more importantly, such systems more accurately guide individual patient management.
It is the experience of international GI pathologists that a major pitfall of dysplasia diagnosis is its overcalling. This is surprising as pathologists have an excellent "get out" when they are uncertain as to whether there is or is not dysplasia. GI pathologists and international guidelines encourage the use of "Indefinite for dysplasia" category whereas non-specialist pathologists seem reluctant to use this useful category. The causes of overcalling are a legion: in Barrett's oesophagus they are primarily inflammation causing reactive epithelial hyperplasia, the juxtaposition of intestinal mucosa in patchwork epithelium, reactive changes akin to reactive gastritis and, after therapy, surface squamous re-epithelialisation, disallowing the pathologist an assessment of surface maturation.
The assessment of dysplasia, throughout the gastrointestinal tract, primarily requires routine histopathological techniques. There has been exhaustive research into "biomarkers" but standard histopathological assessment remains the gold standard for the diagnosis of dysplasia in the oesophagus and stomach and the prime driver for patient management.

S26

Pitfalls in the Diagnosis of Inflammatory Bowel Disease

{P} RH Riddell
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There are numerous traps for the unwary, that include:
Does the patient have IBD? (Unrecognized IBD)
Biopsies from the region of the ileocecal valve are normally chronically inflamed. Those from the distal rectum can normally have architectural distortion while some never have distorted architecture. There is a sometimes an overlap of IBD; these are now called IBD unclassified (IBDU).
Histological features that can be pitfalls to the unwary.
These include mimics of *aphthoid ulcers, the presence of rectal sparing, and atypical presentations –especially in children, and other mimics of UC* especially *diverticular colitis*. *Microscopic/lymphocytic/collagenous colitis* can all be seen in patients with established UC, and may sometimes evolve into them. *Allergic colitis* can have architectural distortion and an excess of eosinophils with eosinophilic crypt abscesses. *Chronic infection* including amebiasis, TB, resistant C. difficile can all have features of chroncicity mimicking IBD.
Upper gastrointestinal disease. This usually raises the question of Crohn's Disease, especially in the paediatric population, and is the presence of overt gastric or duodenal disease (or both) in Helicobacter negative patients. However this can also be seen, especially in children with severe colitis of other causes including ulcerative colitis, but resolves with the colitis or with colecomy.

S27

How to do it (Lung Pathology)

{P} B Corrin
Brompton Hospital, Imperial College, London, United Kingdom

The elucidation of focal lung lesions is similar in its approach to that employed with other organs, namely is the lesion inflammatory, neoplastic or hamartomatous? And as in other organs the elucidation of diffuse disease requires a good knowledge of normal structure. It is recommended that you examine each of the lung components in turn and ensure that none of these is overlooked. In the lung it is essential to know the microanatomy of the acinus and the position of the various non-alveolar structures - principally the conductive airways, the pulmonary arteries and the pulmonary veins: each of these should be examined in turn, remembering that the arteries accompany the airways in the centres of the acini and the capillary blood drains into veins that are situated at the periphery of the lung lobule.
The lung lobule is imprecisely defined by interlobular septa whereas the acinus (of which there are 2-5 per lobule) has no peripheral border but is defined as that portion of the lung supplied by one terminal bronchiole. This last term refers to the last of the purely conductive (or membranous) bronchioles. Beyond the terminal bronchiole there are about three generations of bronchioles that both conduct gas and participate in gas exchange by virtue of alveoli opening directly off them. These are the respiratory bronchioles. They lead into alveolar ducts beyond which are the alveolar sacs, off which most alveoli open.

S28

Why does glioma invade the brain and how can we prevent this?

{P} G Pilkington
University of Portsmouth, Portsmouth, United Kingdom

Intrinsic brain tumours are most commonly derived from glial cell or glial progenitor cell lineage and generically known as glioma. Although neoplastic glia rarely metastasize to form extraneural tumours, paradoxically, one of their most prominent biological features is that of local invasion of the contiguous brain. This invasion may take several forms including leptomeningeal and CSF spread along the neuroaxis, pseudo-invasion along the vascular basal laminae, "Roman Army" spread and diffuse, infiltrative invasion by single cells, often as much as several centimetres from the edge of the main tumour mass. Such diffuse local spread constitutes a major obstacle for effective therapy of these tumours. Not only is it impossible for neurosurgeons to accurately determine how far these "guerrilla cells" have migrated, but, during migration, neoplastic glia arrest from the cell cycle, rendering them refactory to radiotherapy. Moreover, although the blood-brain barrier (B-BB) is disrupted in the major tumour zone, allowing certain therapeutic agents access to the glioma these guerrilla cells, having migrated away from the tumour, are invested in areas of intact B-BB. The mechanisms underlying glioma invasion are complex and include interaction between growth factors, cell adhesion molecules, extracellular matrix and proteases. Our group has, for the past two decades, concentrated on elucidating these mechanisms and developing strategies to overcome this therapeutic obstacle. Currently we are investigating the interaction between the lymphocyte homing receptor (CD44) and the poliovirus receptor (CD155), which are closely apposed on the glioma cell surface and play a key role in invasion. In addition, interplay between two further cell surface molecules, GD3 and NG2, which confer invasive and proliferative properties respectively on neoplastic glia, is being studied and these molecules may constitute possible therapeutic targets. Here, both saporin immuno-toxin ablation and genetic modification of acetylation pathways are being used as proof of principle. We are also investigating the specific migratory properties of tumour stem cells isolated from malignant glioma biopsies by use of sophisticated microscopic techniques. Finally, we have shown that certain tricyclic drugs which cross the B-BB are effective at eliciting mitochondrially-mediated apoptosis in neoplastic, but not non-neoplastic, brain cells. Thus the invasive cell populations may be targeted and selectively destroyed.

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