

ACBNews

The Association for Clinical Biochemistry | Issue 578 | June 2011



In this issue

Ovarian
Cancer and
CA125 ...

NICE
Guidance
and a Role for the
Laboratory

ACB
Spotlight
Meetings



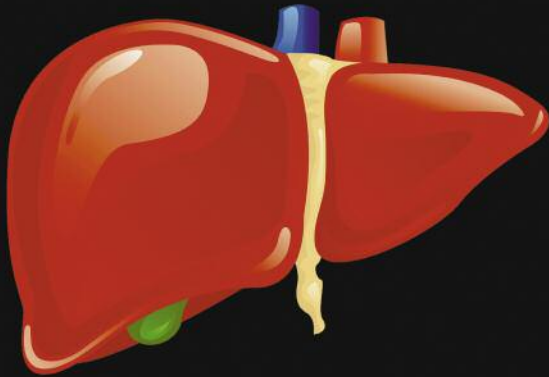
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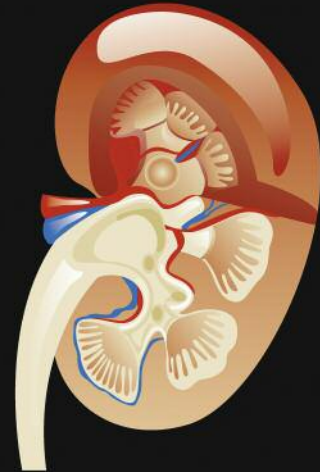
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ACB News

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Issue 578 • June 2011

General News	page 4
Practice FRCPath Style Calculations	page 10
Federation News	page 12
Council Matters	page 14
Meeting Reports	page 15
ACB News Crossword	page 23

Front cover: Sean Duffy, Chair of the NICE Guideline Development Group for Ovarian Cancer with Ian Barnes, Cathie Sturgeon and Douglas Thompson



Focus
Association for Clinical Biochemistry
National Meeting
Liverpool 2012

focus on the patient
www.focus-acb.org.uk

**The Arena
& Convention
Centre, Liverpool**
30 April - 3 May

Ovarian Cancer NICE Guidelines . . . An Opportunity to Work with Primary Care

Reported by Cathie Sturgeon

Ovarian cancer is the fifth most common cancer in women and the leading cause of death from gynaecological cancer in the UK, with an overall 5-year survival rate below 35%. Most women present with advanced disease, having had symptoms for months before presentation and additional delays often occur before specialist referral.

Recent NICE Recommendations

NICE has recently reviewed optimal means of early recognition and initial management of ovarian cancer and published guidelines that reinforce previous recommendations from the Department of Health. The NICE guidelines (www.nice.org.uk) state that

- ◆ GPs should measure serum CA125 in women with symptoms that suggest ovarian cancer.

- ◆ If CA125 is ≥ 35 kU/L, the GP should arrange an ultrasound scan of the abdomen and pelvis.
- ◆ The risk of malignancy index (RMI) score should then be calculated and all women with an RMI score >250 should be referred to a specialist multidisciplinary team.

CA125 measurement is recommended only if symptoms are frequent (e.g. more than 12 times a month is stated) and include:

- ◆ Persistent abdominal bloating or distension.
- ◆ Feeling full (early satiety) and/or loss of appetite.
- ◆ Pelvic or abdominal pain.
- ◆ Increased urinary urgency and/or frequency.

Cathie Sturgeon, with Sean Duffy, (Medical Director of the Yorkshire Cancer Network and Chair of the NICE Guideline Development Group for Ovarian Cancer) with Ian Barnes and Douglas Thompson



- ◆ Symptoms suggestive of irritable bowel symptom in women over 50 years old.

Opportunities for the Laboratory

These recommendations are definitely not an invitation to screen asymptomatic women and provide a major opportunity for us to work with primary care to ensure that:

- ◆ CA125 is requested as a diagnostic aid only for women meeting at least one of the criteria above.
- ◆ Pre-analytical criteria are met (e.g. avoiding sampling during menses).
- ◆ Patients are informed that CA125 results within the reference interval do not necessarily exclude ovarian, or other, malignancies.

Reinforcing Key Messages

- ◆ Guidance is being prepared for both GPs and laboratories to enable appropriate interpretation and implementation of the NICE guidance.
- ◆ A quick reference card relating to appropriate use of tumour markers (including CA125) will be available from Pathology Harmony (www.pathologyharmony.co.uk) this July.
- ◆ Mr Sean Duffy, chair of the NICE group that developed the ovarian cancer guidelines is speaking at the ACB Spotlight Meeting on Early Detection of Cancer (www.acb.org.uk) at the Royal College of Pathologists on July 15th, 2011. ■

Focus on Harrogate Coming Soon . . .

The ACB Annual National Meeting took place at the end of May in the International Conference Centre in Harrogate, Yorkshire. Yet again this meeting had excellent science with a mix of high quality formal sessions as well as an impressive array of posters and oral communications.

ACB News will be reporting on various aspects of the meeting in the months ahead.

If you had an ACB Bursary to attend the meeting please do contact the Editor to discuss which aspect of the meeting you would like to report on. ■



Dr Rossa Chiu from Hong Kong gave the Professors' Prize Lecture looking at non-invasive prenatal diagnosis

ACB Scientific Scholarships

Once again we are seeking applications for an ACB Scientific Scholarship from members of the ACB. Funding of up to £5000 is available to fund or partially fund a research project. Sums of less than £5000 may be offered to successful applicants who apply for the maximum grant. In the past few years we have had a number of very high quality applications with some leading to a publication in a peer-reviewed journal. It is becoming increasingly difficult to decide which projects to fund but this can only be good for the profession.

The application form is much simpler than most grant applications and since applications are restricted to ACB Members you will have a greater chance of success than with most applications of this type. Whether the funding is required to support an MRCPATH Part 2 project or a pilot study is not important, what is important is that the study is scientifically sound. Preference will however be given to junior members and this year for the first time we will be asking how the funding will help the applicants career progression.

Application forms are available on the ACB website along with some advice on how to write a good application. Alternatively, contact either the Director, Robert Hill (email: director.scientificaffairs@acb.org.uk) or Chris Chaloner, the Deputy Director of Scientific Affairs (email: director.scientificaffairs@acb.org.uk).

Please note the closing date for applications is 1st August 2011. We look forward to receiving your applications. ■

MHRA Warning on Statstrip Glucose Meters

The MHRA has issued a Medical Device Alert that relates to the Nova Biomedical Statstrip glucose meter. Details on this can be accessed at the following link: www.mhra.gov.uk/Publications/Safetywarnings/MedicalDeviceAlerts/CON117373 ■

ACB South West and Wessex Summer Meeting

June 30th 2011

Bristol Royal Infirmary

Preliminary programme:

- ◆ Cardiac Imaging
- ◆ High Sensitivity Troponin
- ◆ Genetic Testing for Familial Hypercholesterolaemia
- ◆ Genotype-Phenotype Relationships in Familial Hypercholesterolaemia
- ◆ HbA1c
- ◆ Modernising Scientific Careers
- ◆ Demand Management

Registration costs £25 for ACB Members, £10 for formal pre-registrant Clinical Scientist Trainees, £15 for retired Members and £40 for non-Members. To register please email vicky.clough@nhs.net

Sudoku

This month's puzzle

				T	H	S		
	R	C		S			T	M
I			S					E
Y				R				T
H					M			C
S	Y			C		I	E	
	T	I	H					

Last month's solution

T	R	C	S	H	M	E	I	Y
H	E	M	T	Y	I	S	R	C
Y	I	S	E	C	R	T	M	H
I	M	H	R	E	S	Y	C	T
E	T	R	Y	I	C	M	H	S
S	C	Y	M	T	H	I	E	R
R	S	E	H	M	Y	C	T	I
M	H	I	C	S	T	R	Y	E
C	Y	T	I	R	E	H	S	M

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Life needs answers

Call for Entries for the National Handbook for Laboratory Medicine (NHLM)

Dr Robert Hill, ACB Director of Scientific Affairs

The NHLM is a Department of Health (DOH) initiative to provide test based information to health professionals. The ACB has been commissioned to produce this multi-disciplinary knowledge repository.

Just as 'lab tests on line' provides the public with information about laboratory tests, so the NHLM will provide health professionals with high quality information that has been peer reviewed and professionally edited. It will be a national resource accessible from any Trust's information systems.

The first few entries have already been written. A template and examples are available. A typical entry for a single analyte is approximately 2000 words long and contains easily-researched material.

Why not stake your claim as an author for

your favourite analyte or supervise a trainee to reach a high level of knowledge about part of our analytical repertoire? For example, the University of Birmingham has accepted the principle of a single handbook entry being acceptable as a dissertation in partial fulfillment of the West Midlands Training Course MSc degree.

On application you will be given an information pack and your application will be considered by the ACB's commissioning body, the Clinical Sciences Review Committee (CSRC). If successful you will be assigned an editor and your progress will be supported by a project administrator.

To receive your information pack, send an email to enquiries@acb.org.uk with a subject header 'NHLM enquiry'. ■



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ACB Spotlight Series

A series of one-day meetings addressing hot topics in Clinical Science to be held at the Royal College of Pathologists, 2 Carlton House Terrace, London SW1Y 5AF

Friday 15th July 2011 10:00-16:30

Early Detection of Cancer

- ◆ Challenges and opportunities in prostate and ovarian cancer
- ◆ NICE guidelines for ovarian cancer
- ◆ Update on prostate cancer
- ◆ Quality care: a multidisciplinary collaboration
- ◆ Perspectives from patient, clinician and laboratory

Friday 2nd September 2011 10:00-16:30

Controversies and Change in Immunoglobulins

A series of debates and votes on hot topics in the profession

- ◆ Cryoglobulins: should they always be typed?
- ◆ Paraproteins: free light chain measurement can replace urine measurements
- ◆ Coeliac Disease: a critical appraisal of current tests
- ◆ IgG4 is useful in helping to diagnose autoimmune disease

Monday 10th October 2011 10:00-16:30

Near Patient Testing in Microbiology

- ◆ Culture for UTI diagnosis: use of the urine dipstick
- ◆ HIV testing: experiences of POCT in the clinic and community
- ◆ Validation, monitoring, quality and training: the role of the pathology laboratory
- ◆ RSV testing: benefits for infection control and bed management
- ◆ MRSA and Near Patient Testing
- ◆ Procalcitonin testing and antimicrobial prescribing

**Registration and details of future meetings:
www.acb.org.uk/site/meetings.asp**

ACB Venture Publications Committee

The ACB Venture Publications Committee is looking for suggestions for new book titles to complement the Laboratory Medicine series. We aim to produce one book a year that is relevant to every day laboratory practice. Most of our publications have been predominantly in the field of Biochemistry, although the latest book, Primary Care and Laboratory Medicine, also covers other Pathology disciplines. We hope to expand the series to include more topics related to

Microbiology to reflect the changing membership of the ACB.

We would very much welcome suggestions from members, especially in the field of microbiology. If you have any bright ideas or would be interested to know more about the work of the committee, please contact Dr Marta Lapsley, ACB Venture Publications Chair by email on marta.lapsley@esth.nhs.uk or telephone 01372 735257. ■



Deacon's Challenge

No 121 - Answer

A patient in your local lipid clinic had a serum total cholesterol concentration of 7.2 mmol/L. He was treated with a statin; and 3 months later his serum cholesterol concentration is 6.0 mmol/L. Given that the controls for your cholesterol assay run standard deviations of 0.041, 0.062 and 0.094 mmol/L at 2.7, 4.3 and 6.7 mmol/L respectively, and that the intra-individual biological variation of serum cholesterol concentration is quoted as 5.4%, determine whether this represents a significant change in his serum cholesterol.

FRCPATH, Autumn 2010

Assume the difference between the two measurements ($x_1 - x_2$) is normally distributed with unknown mean and combined standard deviation for both measurements ($s_{1,2}$). If there was no real difference between the two measurements then the mean difference would be zero i.e. we need to test the null hypothesis by calculating z:

$$z = \frac{x_1 - x_2}{s_{1,2}}$$

$$x_1 = \text{initial cholesterol concentration} = 7.2 \text{ mmol/L}$$

$$x_2 = \text{final cholesterol concentration} = 6.0 \text{ mmol/L}$$

$$s_{1,2} = \text{standard deviation for the difference between both measurements } (x_1 - x_2).$$

The standard deviation for each measurement will be made up of two components: the total analytical and intra-individual biological standard deviations.

We are given the analytical standard deviations ($s_{\text{Analytical}}$) at three concentrations but not at the patient's concentrations. Therefore the best compromise is to adopt the $s_{\text{Analytical}}$ value given at 6.7 mmol/L (= 0.094 mmol/L) - which happens to be the mean of the patient's two values and use this value at both concentrations. Since the patient results were obtained in two separate analytical runs it is necessary to assume that it is the *total* $s_{\text{Analytical}}$ that is given and not the *within run* or *between run* value.

The intra-individual biological CV is given without stating at which concentration range it applies. Assuming that it applies to both patient concentrations then the corresponding biological standard deviations ($s_{\text{Biological}}$) need to be calculated at both concentrations:

$$s = \frac{\text{CV(\%)} \times \text{Concentration}}{100}$$

$$\text{At 7.2 mmol/L, } s_{\text{Biological}} = \frac{5.4 \times 7.2}{100} = 0.389 \text{ mmol/L}$$

$$\text{At 6.0 mmol/L, } s_{\text{Biological}} = \frac{5.4 \times 6.0}{100} = 0.324 \text{ mmol/L}$$

The total standard deviation (s_{Total}) is then calculated at both concentrations:

$$s_{\text{Total}} = \sqrt{(s_{\text{Biological}}^2 + s_{\text{Biological}}^2)}$$

$$\text{At } 7.2 \text{ mmol/L, } s_{\text{Total}} = \sqrt{(0.389^2 + 0.094^2)} = \sqrt{(0.1513 + 0.0088)} = \sqrt{0.1601} = 0.400 \text{ mmol/L}$$

$$\text{At } 6.0 \text{ mmol/L, } s_{\text{Total}} = \sqrt{(0.324^2 + 0.094^2)} = \sqrt{(0.1050 + 0.0088)} = \sqrt{0.1138} = 0.337 \text{ mmol/L}$$

Finally the combined standard deviation (for the difference $x_1 - x_2$) is calculated:

$$s_{1,2} = \sqrt{(s_{7.2 \text{ mmol/L}}^2 + s_{6.0 \text{ mmol/L}}^2)}$$

$$s_{1,2} = \sqrt{(0.400^2 + 0.337^2)} = \sqrt{(0.1600 + 0.1136)} = \sqrt{0.2736} = 0.523 \text{ mmol/L}$$

The z-score is calculated by substituting values for x_1 , x_2 and $s_{1,2}$:

$$z = \frac{7.2 - 6.0}{0.523} = 2.3 \text{ (2 sig figs)}$$

This z-score is greater than 1.96 (the value corresponding to $P=0.05$) so the two results are significantly different.

Alternative approach:

Since $s_{\text{Biological}}$ is very similar at both concentrations then they could be treated as being approximately equal. If $s_{\text{Biological}}$ is calculated at the mean concentration of 6.7 mmol/L (which is also the concentration at which $s_{\text{Analytical}}$ was determined):

$$s_{\text{Biological}} = \frac{5.4 \times 6.7}{100} = 0.362 \text{ mmol/L}$$

$$\text{and } s_{\text{Total}} = \sqrt{(0.362^2 + 0.094^2)} = \sqrt{(0.1310 + 0.0088)} = \sqrt{0.1398} = 0.374 \text{ mmol/L}$$

For the special case where $s_1 = s_2$, for two results to differ significantly at the 5% level, their difference has to exceed $2.8s$. In this case $2.8s = 2.8 \times 0.374 = 1.05 \text{ mmol}$. This is less than the observed difference of 1.2 mmol/L so that the results are significantly different. ■

Question 122

You need to make up a phosphate buffer with a pH of 7.4 and a total phosphate concentration of 50 mmol/L. Calculate the amounts of sodium dihydrogen phosphate and disodium monohydrogen phosphate that need to be weighed into 1 litre of water, given that the pKa is 6.82 (atomic weights: Na 23, P 31).

FRCPath, Autumn 2010

Pensions Review – Lord Hutton’s Final Report

Emma Lewis, FCS Executive Member and
Marten Davies, Member of NHS Pensions Governance Group

Introduction

Lord Hutton published the final report of his review of public sector pensions on 10th March 2011. See www.hm-treasury.gov.uk/indreview_johnhutton_pensions.htm. This 217 page document follows on from the interim report published in October 2010. The considerable media attention at the time indicated the anxiety-making headlines for all public sector staff however it is important to be clear about its wider content and its true status. The review only gives recommendations. It is not policy. However the current Government has now accepted it as a basis for further consultation with public sector workers and their unions. It covers a wide variety of public sector pension schemes with a range of benefits, contributions and financial bases. The Government has declared that it would seek to introduce changes during the lifetime of this parliament, i.e. before 2015.

The review carried forward principles of fairness to both workers and taxpayers, aiming to ensure adequate levels of pension during retirement, as well as schemes being transparent, simple and financially sustainable.

Currently the NHS Pension Scheme is in two parts, the 1995 part and the 2008 part. A description of the features of these are given in the booklet “Scheme Guide” downloadable from http://www.nhsbsa.nhs.uk/Documents/Pensions/SD_Guide_-_V6_03.2011.pdf. Note that it is important to consult the current version of this document.

The detailed regulations of the scheme are in the form of Statutory Instruments which, for convenience have been informally consolidated. These can be downloaded from <http://www.nhsbsa.nhs.uk/Pensions/2963.aspx>

Reform of the NHS Pension Scheme in line with Lord Hutton’s recommendations would be as amendment to these Statutory Instruments.

Hutton’s Recommendations

There are twenty-seven recommendations in all. The main ones are:

1. That the final salary scheme moves to a defined benefit career average revalued earnings scheme (CARE). See note 1.
2. Accrued pension rights would be preserved and a link to the final salary scheme maintained for these payments already made.
3. The retirement age would increase in line with the future increases in the state pension age i.e. increase to 65 and then increase this in line with the state pension age.
4. Employers should aim to maximise participation with automatic enrolment from October 2011. There is an opt-out mechanism - see note 2.
5. Members should move to the new scheme as soon as practicable.
6. During the accrual phase benefits will be uprated in line with average earnings. After retirement they should be indexed in line with prices to maintain their purchasing power.
7. Contribution rates will be set by the Government but tiered contribution rates are recommended. Employer’s contributions would be capped.
8. Members should have greater choice over when to take their pension which would then be adjusted accordingly. Flexible retirement should be encouraged and abatement will be abolished.

There are recommendations to change the way the schemes are administered and run. Whilst not suggesting that all the public sector schemes should become a single scheme, it does recommend that the discrepancies should be reduced by a move towards a common

framework for scheme design, with each scheme having a pensions board to ensure effective governance. They should issue regular benefit statements and the government should establish a framework for independent oversight of the governance, administration and data transparency of the schemes.

The report also recommends new primary legislation to adopt a common legal framework across the schemes to provide greater transparency. The report further recommends looking at streamlining administration of the pension schemes.

Of note the report does not recommend non-public sector workers having access to public sector pension schemes. See note 3.

On 1st April the Pension Scheme issued a notice indicating that scheme members will not be disadvantaged by any changes in diminishing pension accrued before any change comes into force. Hence there is no need to take any immediate action. This can be seen at: www.nhsbsa.nhs.uk/3363.aspx.

TUPE

Members who are subject to pathology service consolidations, particularly where this may involve a transfer to a non-NHS employer are covered by the very complex TUPE regulations. The April 2011 Pension Scheme Employer's Newsletter reminds that the Department of Health issued guidance in 2006 (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063847) however the current Government is seeking to revise the TUPE regulations to reduce the burden of pensions protection on potential private sector providers.

Next Steps

Now the Government has accepted the report as a basis for consultation, further papers should be issued in the autumn. Whilst the report states that members should move to new scheme as soon as practicable, it is hoped that the new schemes and legislation would be in place by the end of this parliament i.e. by 2015.

Notes

1. CARE: Benefits are not linked to final

salary but to a proportion of pensionable earnings during the member's career, updated in line with earnings. Existing members will be moved to the new CARE scheme for future service ie after 2015. This scheme is already in place for GPs.

2. Automatic enrolment: It will be possible to opt out of automatic enrolment but notice should be given within one month of this starting. The first month's deductions will be refunded. There will be a new low-cost pension scheme for those who wish to opt out; this is NEST- National Employment Savings Trust.

The idea is that everyone should have a second pension in addition to the State Pension. This would reduce the need for state benefits in retirement.

Those that opt out of the CARE and NEST pension schemes would be automatically enrolled again after three years. They can opt out again, giving notice within one month. And so on every three years until you lose the will to live!

3. Whilst widening the access to our pension scheme was suggested in the interim Hutton report, on reflection, it was decided that the risk of an influx of large numbers of new members was too high a risk for government to take on. On the other hand, government itself may doubt that Hutton took account of the current environment; it wants willing (external) provider competition. The current TUPE and Fair Deal pension protection was seen as a disincentive to the private sector.
4. Some of us oldies have already returned our Pensions Choice exercise documents. The Hutton recommendations may now have an impact on our earlier decision. Some may have chosen to remain in the 1995 scheme with normal retirement age (NRA) at 60 but may now need to work longer (CARE NRA 65 or more).

The Department of Health is considering an option for members to revisit this particular choice. There will NOT be a chance for those who opted for the 2008 scheme but now wish to change their mind. ■

Difficult Financial Path to Tread

Ruth Lapworth, ACB Secretary

Report from ACB Council Meeting, 24th March 2011

At this time of year the audited accounts and financial statements of the Association for the previous year are presented by the Finance Director for review by Council before they are presented at the Annual General Meeting. The Association's income is derived from members' subscriptions, publications and national meetings. It is becoming increasingly difficult to run national meetings in the current format and generate a profit. It is recognised that the cost of meetings can be prohibitive especially when study leave is being squeezed as part of the efficiency savings required by NHS Trusts. Alternative venues and meeting formats are therefore being considered for the future as meetings cannot run at a loss without having a major impact on our long term financial viability.

Charitable Funds Underused

The fact that many members do not submit applications to access the charitable funds available to support specific functions was also discussed. The remit of each of the individual funds is described in the ACB Members' Handbook.

The future of the healthcare science workforce and the proposed new training and career pathway under Modernising Scientific Careers was the second major item for discussion. There is still uncertainty around the calibre of the candidates emerging from the Scientist Training Programme (STP) recruitment process and the readiness of the Higher Education Institutes (HEIs) to provide the required MSc programmes due to start this autumn. A huge amount of time and effort has been spent by the Education Committee,



Terry Dyer, ACB Treasurer, explains the accounts at this year's AGM in Harrogate

Regional Tutors and others to meet the exacting timetable for recruitment. Once the dust has settled, it is hoped that issues raised by those involved in the process will be reviewed and addressed for next year.

The proposal for automatic registration for those members who meet the requirements of the European Communities Confederation of Clinical Chemistry and Laboratory Medicine (EC4)/European Federation of Clinical Chemistry and Laboratory Medicine (EFCC) was approved by Council and will be taken to the AGM. More information on this initiative is available in April's ACB News.

Work has now started on redesign of the ACB website. It is hoped that the new improved site will be available shortly. ■

Reaching New Horizons in Exeter

Simon Salter, Francesca Mills and Mandy Perry

ACB SWW Meeting, 30th November 2010, Royal Devon & Exeter Hospital, Exeter

The South West ACB Meeting was held in the Royal Devon and Exeter Hospital, which hosted the regional Siemen's Award. Seven speakers entered the Siemen's Award with a very high standard of presentations. In the afternoon session, there were three excellent talks on a wide variety of topics that led to stimulating discussions.

Dr Mathangi Balasubramani started off the day presenting her work on oestrogen receptor gene polymorphisms and their effect on bone density in children. Interestingly, the polymorphism in question (rs1269056) is an intronic single nucleotide polymorphism (SNP) and yet still appears to alter the expression levels of the oestrogen receptor. The objective was to link the ESR2 genotype of a child to the bone mineral density observed. This was to be done by determining the relationship between the SNP and the expression level of the gene. So, cDNA was created to make a range of concentrations from which a standard curve of gene expression could be made. This worked well for the control gene of GAPDH, but unfortunately not for ESR2 rs1269056. As such it was not possible to quantify the gene expression of this polymorphism in patients and link this data to the BMD.

It was an interesting piece of work and very well presented, but sadly research does not always go as smoothly as we hope!

Metallic Tingling

The next talk was given by Anna Barton, presenting a clinical case of zinc poisoning. The case focussed on a 50 year old man who

had a four year history of tingling sensations causing him to drop things and unsteadiness causing falls. Neurological investigations showed Romberg's sign and pseudoathetosis among other neurological symptoms.

Tests showed leucopenia and neutropenia with low vitamin B12, which was treated. Three months later the vitamin B12 was normal, but the patient showed no signs of improvement. Further tests showed low copper and caeruloplasmin with a high zinc. Questioning of the patient led to the discovery that he had ill fitting dentures which he kept in place with excessive use of denture fixative –containing 38 mg/g zinc. It was thus apparent that many of the symptoms displayed by this patient were a result of copper deficiency secondary to zinc excess. The case showed the more unusual side of clinical biochemistry and reminded us all that some cases are not as straight forward as text books like to make out, but can have quite surprising aetiologies.

Emma Crouch followed on with a talk on her development of a sensitive oestradiol assay, a subject which is becoming increasingly popular. Sensitive oestradiol has become of interest to oncologists who are treating breast cancer patients with aromatase inhibitors. Aromatase inhibitors are contraindicated in women with functioning ovaries, so were originally restricted to post-menopausal women. They are now also used in women over 40 who have chemotherapy induced ovarian failure. In these patients oestradiol must be monitored, because if ovarian function recovers during aromatase therapy then the efficacy of the treatment will be reduced.

Current immunoassay analysers are not good enough to reliably measure such low levels of oestradiol in these patients and thus, sensitive oestradiol methods are required.

Pharmacogenomic Approach to Warfarin

Fiona Davidson gave the final talk before tea, looking at defining a warfarin dose based upon pharmacogenetics. Four polymorphisms were investigated – CYP2C9 *2 and *3, VKORC1 and CYP4F2, with CYP4F2 being a controversial one as there are conflicting papers in the literature with regard to its effect upon warfarin. There exist a number of algorithms that use these genetic factors as well as other clinical and demographic factors to estimate the correct warfarin dose. This project looked at their ability to accurately predict the actual stable dose of warfarin in a defined population. It was shown that increasing numbers of variant alleles in these genes lowers the stable dose requirement of warfarin, however CYP4F2 has no impact. Three algorithms managed to accurately predict the warfarin dose in 60% of patients (to 1 mg/day) with the Gage *et al*, (2008) algorithm giving the best results. These dosing algorithms made better predictions in patients with atrial fibrillation, rather than DVT or pulmonary embolism. This interesting talk showed the great value of these dosing algorithms.

Tumour Marker Use in Bristol

Roanna George from Southmead Hospital in Bristol gave a clear and interesting presentation of an audit of the use of tumour markers at Southmead Hospital. CEA and CA125 requesting were audited and adherence to national, local and laboratory guidelines was used to assess where the guidelines differ and therefore where practice could be standardised. A questionnaire was completed for the last fifty requests for each analyte. The results showed that for CEA requesting there was poor compliance with national and local guidelines for frequency of testing. In addition, no baseline CEA was measured pre-operatively contrary to the laboratory requirement. A discussion with clinical staff was suggested to ensure that timely monitoring was implemented. CA125 requesting showed poor compliance with the national guideline that stated 'recommendation of CA125 as an adjunct in distinguishing benign from malignant pelvic masses' and the laboratory guidelines for reasons for CA125 measurement. Improvements were suggested to revise the laboratory criteria for acceptable CA125 requests, to only accept requests when a pelvic

The Siemens' Award participants from left to right: Hayley Sharrod, Mathangi Balasubramani, Sumithra Subramanian, Roanna George, Fiona Davidson and Anna Barton. Emma Crouch not present for photograph



mass has been found. The conclusions of the audit were that tumour markers are still being requested inappropriately and that work with clinical colleagues is required to bring local recommendations in line with national guidelines.

Hayley Sharrod (Southampton General Hospital) presented a case of a 65 year old man who was referred to ITU after a three day history of shortness of breath. Ten days prior to this he had spent two weeks on ICU with sepsis due to an infected femoral-femoral bypass graft. The patient had been on paracetamol and flucloxacillin since admission and had a high anion gap metabolic acidosis (HAGMA) inconsistent with the degree of sepsis and all other causes ruled out. Patients on long term paracetamol therapy who develop HAGMA are found to have 5-oxoprolinuria (also seen in hereditary glutathione synthetase deficiency). There are around 25 documented cases which share three common features:

1. Concurrent condition causing glutathione depletion.
2. Resolution of acidosis following withdrawal of paracetamol.
3. No evidence of hereditary glutathione synthetase deficiency.

Paracetamol is a widely used drug that is metabolised in the liver – 55% glucuronidation, 30% sulphation 15% cytochrome P450 (forming NAPQI). In therapeutic paracetamol doses, NAPQI binds to glutathione and is excreted but in glutathione depleted patients there is less ability to detoxify NAPQI. Hayley developed a method for measurement of glutathione synthetase to show that it is inhibited by NAPQI and suggests that clinical practice in ITU should be reviewed as a result. Future work involves a larger scale study to determine the incidence of these cases.

Sumithra Subramanian from Southampton General Hospital presented a case of a five year old boy who was admitted to A&E having been found unresponsive in bed that morning. He had otitis media with a purulent discharge and was started on IV antibiotics. CSF and

blood cultures grew *Streptococcus pneumoniae* indicating pneumococcal meningitis. Immunological investigations showed that the child had low levels of all immunoglobulins which can be seen in a variety of conditions, including x-linked agammaglobulinaemia (XLA). XLA was one of the first primary immunodeficiencies to be described and is caused by a mutation in the gene coding for Bruton's tyrosine kinase (Btk) involved in B-cell development. This condition leads patients to have no B-cells in the periphery and can be diagnosed by analysis of Btk using flow cytometry. Management of these patients involves prompt treatment of infections, replacement of immunoglobulins, prophylactic antibiotics in winter, regular monitoring, chest physiotherapy if any lung damage present and bone marrow transplant.

After lunch and much deliberation, the Siemen's Award for the best talk was presented to Hayley Sharrod by Allan Thompson of Siemens. The talks were all of high quality and it was noted that all participants should be congratulated for delivering such engaging and interesting presentations.

Dr Marina Morgan is Consultant Medical Microbiologist at the Royal Devon and Exeter. She gave a vibrant and enthusiastic talk, including cases of some serious *Streptococcus* infections.

Dr Morgan spoke about Panton-Valentine Leucocidin (PVL)-associated *Staphylococcus aureus* infections. PVL is a toxic substance produced by some strains of *Staphylococcus aureus* (SA) which is associated with an increased ability to cause disease. Like other *S. aureus* strains, PVL-SA predominantly cause skin and soft tissue infections (SSTI), but can also cause invasive infections. The most serious of these is a necrotising haemorrhagic pneumonia with a high mortality, which often follows a "flu-like" illness, and may affect otherwise healthy young people in the community.

PVL-associated SA infection should be suspected if a patient has a necrotising SSTI, recurrent furunculosis or abscesses, or there is clustering of SSTIs within a household or social

group. It should also be considered in invasive infections in immunocompetent people, particularly community-acquired necrotising/haemorrhagic pneumonia in young, previously fit people. Haemophthisis should be a major alerting sign. Of particular note to biochemists, PVL infections are associated with enhanced inflammatory response (higher ESR and C-reactive protein [CRP]) and local disease (myositis/pyomyositis).

Cornish Roy's Cortisol Casebook

The day ended with a talk by Roy Fisher, who has worked in the South West Region for many years. His talk, "A Cornish Cortisol Casebook", detailed five very interesting adrenal cases and included specific learning points. One case presented two brothers who are compound heterozygotes for a mutation in the HSD3B2 gene, leading to a very rare form of Congenital Adrenal Hyperplasia. This diagnosis was made from a urine steroid profile. Roy highlighted that it is necessary to assess males presenting with significant hypospadias for possible 3-HSD deficiency. Compound heterozygotes need to be considered and it is important to be aware of phenotypic variability and failure of penetrance.

Another case was of bilateral macronodular hyperplasia causing coexisting Conn's and Cushing's syndromes. Although Cushing's syndrome due to macronodular adrenocortical hyperplasia has been recognised as a rare cause of ACTH-independent hypercortisolism, bilateral macronodular hyperplasia causing coexisting Conn's and Cushing's syndromes has rarely been reported in the literature.

The last case outlined a patient with a very large oestrogen secreting adrenal tumour as a rare cause for his gynaecomastia. Urine steroid profiling identified that the tumour also had excess co-secretion of cortisol, testosterone, androstendione, DHEAS and progesterone.



Allan Thompson of Siemens presenting the Siemens Award to the winner, Hayley Sharrod

Adrenal carcinomas are usually considered to produce either oestrogens or androgens or cortisol and in this case the production of all groups of steroids including progesterone is unusual. After removal of the tumour, hormone levels normalised and the gynaecomastia regressed. Roy pointed out that there are always interesting and challenging cases in and around clinical biochemistry, which often involve considerable input by the biochemist, research and contact with colleagues in other labs. His take home message was that biochemists should get involved with clinicians and offer expertise as everyone gains, particularly the patient. ■

A Stroke of Good Luck for School Students at the RCPATH

Michaela Glynn, Pre-registration Clinical Scientist, St Thomas' Hospital, London

The 8th Annual Schools Science Conference, presented by science4u.info in partnership with the Royal College of Pathologists was held at the College on 16th March 2011

I first heard of the annual Schools Science Conference last year when I was asked by a fellow pre-registration Biochemist to come along and help facilitate a session on point of care testing. I was very impressed by the enthusiasm of the students who attended, but also surprised at the initial lack of understanding about pathology. *"Do you have to cut up dead people?" "Do you have to be a qualified medical doctor?"* were just some of the questions. Needless to say, I was more than happy to help when Ruth Semple (Public Engagement Manager) and Sam Jayaram (Press & Communications Manager) at the College asked me to help design a session for this year's conference.

The conference, which is held at the Royal College of Pathology is aimed at students studying for GCSEs and endeavours to inspire them to continue studying science. The tag line for this year's conference was 'Science is the Future' and focussed on increasing awareness of progress in science and how this impacts on peoples' lives - emphasising the importance of science in everyday life.

Meet the Scientists

Don Henderson (Imperial College), founder of the event gave an inspiring introduction reminding the audience about various

scientific advances that have changed the way that we live our lives. I then gave a short address from the perspective of a scientist at the beginning of my career, explaining how pathology is at the heart of modern medicine and really is 'the science behind the cure.' I also reinforced the fact that as young students, they are the scientists of the future, and advised that they should consider the number of varied careers available in pathology.

The day involved a number of sessions, workshops and stalls including 'Meet the scientist,' and 'Be healthy! Stay healthy!' Professor Dame Nancy Rothwell presented the key lecture titled 'A stroke of bad luck – new discoveries in the treatment of brain disease.'

One of the sessions, Café Scientifique was designed by a team involving Ruth, Sam, Joe O'Meara (Association of Clinical Biochemistry), Hedley Glencross (Institute of Biomedical Science) and myself, entitled 'Personalised Medicine – It's all in the genes.' The aim of this session was to facilitate understanding about the science behind targeted treatments, to explore what the future might hold for personalised medicine and to discuss the ethical issues around the use of genetic information. It was agreed that an example which satisfies all of the above is the detection of BRCA and HER-2 and the use of Herceptin as a targeted therapy in the treatment of breast cancer.

Genetic Conundrums

The session began with an introduction to who we are and what we do as pathologists. This was followed by an interactive 'gene hunting' activity which involved some home-made chromosomes. The aim was to demonstrate how hard it is to find a gene

related to a specific disease, but that once we locate it and determine an association, we may be able to use it to predict individual patient risk. We then moved onto a case study about a lady who was under the National breast cancer screening age, but was diagnosed with a HER-2 positive tumour and treated with Herceptin. We introduced the role of the histopathologist in analysing the biopsy sample and their input into the multi-disciplinary team. The students were then asked to come up with advantages and disadvantages to storing genetic information on a large number of people; thinking about the use in scientific research, but also about who might misuse the information.

The second part of the scenario involved the patient's 22 year old daughter. We asked the students to discuss whether they thought the daughter should be screened for the BRCA genes, would they want to know if they were in her position and how would they act on the knowledge?


An impressive discussion was held by all the groups, with interesting and sometimes obscure points raised! Particular interest was in the idea of 'nature v nurture,' and the impact an 'at risk' individual can make on their relative risk of disease by avoiding certain environmental factors. Another question was raised about diabetes as an inherited disorder, which opened up discussion of Type 1 and Type 2 diabetes. Many thanks must go to my fellow London based trainee Biochemists who were recruited to help facilitate group discussions. It was a thoroughly enjoyable day, and initial feedback from both students and teachers has been very positive. I would highly recommend getting involved in public engagement activities in your area. If you happen to be within the London region, then I am also one of the Public Engagement Regional Coordinators, so please do get in touch if you have any ideas or would like to become involved at email: Michaela.Glynn@gstt.nhs.uk ■

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New Location for ACB Scotland's Bi-Annual Meeting

Following very successful meetings in Crieff Hydro Hotel in 2007 and 2009, we are moving to a new location for 2011. If you attended either meeting I'm sure you will agree that the setting in the Ochil Hills in Perthshire was idyllic and the conference facilities excellent – however, the rather remote central Scotland location made 'green' travel difficult and we sought to find an alternative.

A location that shows off the best of the Scottish countryside with excellent (and affordable!) hotel and conference facilities within easy reach of public transport was a tall order, but we believe that we have found it in Norton House Hotel, Ingliston, Edinburgh. Set in 55 acres of grounds, you can hardly believe you are only 2 miles from Edinburgh Airport, and a stone's throw from the M8 and M9 motorways. Additionally Haymarket station is only 6 miles away and there is a bus stop at the entrance to the hotel grounds. Voted AA Scottish hotel of the year in 2008-2009 and offering a 3 AA Rosette restaurant as well as excellent leisure and spa facilities, we would recommend getting your study leave forms in early!

And it's not just the location that is promising: an excellent programme has been put together with some of the top names in their respective fields contributing. As well as variety in the clinical and managerial issues covered, we are also introducing variety in the presentation of these, using workshop and debate formats as well as the traditional lectures.

Dr Bernie Croal is coordinating a workshop style session on Key Performance Indicators (KPI) in Clinical Biochemistry. There will be 2 talks on the concept of KPIs from Dr Rachael Liebmann and Dr Julian Barth followed by an interactive workshop on identifying relevant KPIs, and discussing their implementation.



A session on diabetes will include a presentation from a local paediatrician, Dr Ian Hunter, on differentiating between type 1 and type 2 diabetes, in the face of an ever-increasing incidence of childhood obesity and its complications. Dr David Preiss will look at translating trial evidence into clinical practice in the management of type 2 diabetes, and Profs Garry John and Naveed Sattar will debate the use of HbA1c in the diagnosis of diabetes.

A session on screening will update on recent changes to the antenatal and newborn screening programmes in Scotland. The antenatal perspective will focus principally on the introduction of first trimester combined ultrasound and biochemical screening and the enhanced second trimester quadruple test for Down's syndrome. An update on newborn screening will provide an insight into the introduction of screening for MCADD and Sickle Cell disorders in the region.

A session on bone metabolism will cover osteoporosis pathophysiology and management, serum bone markers and Paget's disease with presenters including Dr Alastair McLellan and Profs Stuart Ralston and Bill Fraser. There will also be case studies from

local mineral metabolism clinics.

The meeting will conclude with what promises to be an entertaining debate on the use of Point of Care Tests on the High Street, delivered by Mr Gilbert Wieringa and Dr Danielle Freedman.

The meeting will also include presentation of Members' Papers, including the John King Award, and a plenary lecture from ACB Past President, Dr Julian Barth.

And, of course, no ACB Scotland meeting would be complete without a 'shindig' - a conference dinner has been planned for the Thursday evening.

We hope that this programme will meet our aims of providing a varied, educational and stimulating meeting, mixing traditional presentations with more novel delivery styles.

So get the 27th and 28th October 2011 in your diary, keep an eye out for budget flights

(if required!) and look forward to an excellent meeting in a wonderful setting. Spouse rates will be available, so why not surprise your other half with a weekend break in Edinburgh?

Special rates will be available for retired members so come along and catch up with old colleagues and pass on your wisdom to the next generation, either participating in the scientific meeting or simply joining us for the evening's festivities.

Look out for the full programme and registration information online and in the next issue of the ACB News. Further details are available from ACB Scotland Meetings' Secretary Sarah Jarvis (sarah.jarvis@nhs.net). ■



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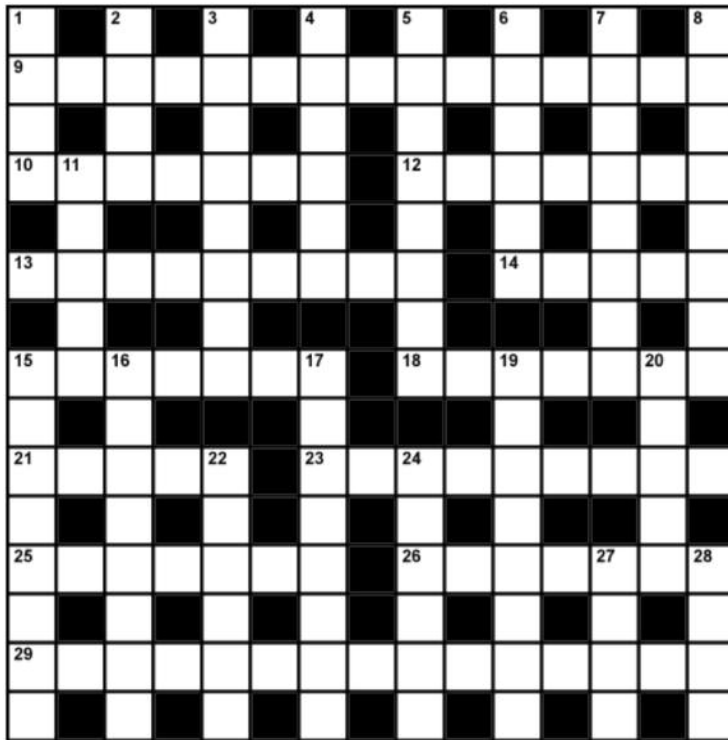
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ACB News Crossword

Set by Rugosa

Keep sane at coffee time with the ACB News Crossword. Always relating to the science and practice of Clinical Chemistry, you will never cease to be astounded by the convoluted mind of the ACB News Crossword compiler.

Prizes for your department: The first five correct solutions to appear on the ACB News fax machine (Fax: 0121-507-5290) will receive a copy of the new educational Calcium Cases CD-ROM by Aubrey Blumsohn, Christina Gray, Neil McConnell, John O'Connor, Anne Pollock & Roy Sherwood and which retails at over £50. Please state clearly the name and address of the Department that is entering the competition. Remember that ACB News appears first as a PDF on www.ACB.org.uk around the 7th of each month.



- 6 Develop relative risk-free handgun (6)
- 7 Height of unrestrained latitude (8)
- 8 Branch of maths game theory used (not Heyting Arithmetic) (8)
- 11 Love bare shape (5)
- 15 Distressed groan, in bad pain, no initial response - test for acidosis (5,3)
- 16 Promotion, on balance, is acceptable (8)
- 17 Set about matter in solution (8)
- 19 Describe unhappy researcher given no credit (8)
- 20 Control foregoing foreigner (5)
- 22 Their victory ruined boom (6)
- 24 Rational distribution (6)
- 27 Colour of fractured bone? (4)
- 28 Carry course calculator (4)

Across

- 9 Revive duplicate use for diagnostic test performance (10,5)
- 10 "Night and Day" - opponents baffled not having old disc (7)
- 12 Copper dealt with claim for metal (7)
- 13 Performance curve returned regarding deceased associate (9)
- 14 Pure end product could explode (5)
- 15 Plug appropriate road diversion (7)
- 18 Rush railway operation (7)
- 21 Desist out of disinterest, become inactive (5)
- 23 Mock unusual tiny chest (9)

- 25 Youth centre rental free, no charge (7)
- 26 Ruler holds a constituent for reaction (7)
- 29 Conveyance using energy that airports can't vet correctly (6,9)

Down

- 1 Short drive in Nash-Healey's Pininfarina (4)
- 2 Tenor sounds bigheaded (4)
- 3 Wrong matter is reviewed (8)
- 4 Sort of best, posh, first class, ideal place (6)
- 5 People moved from danger observe top lookout turn up (8)

Last month's solution



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