Clinical Biochemistry News

ACBI

ACB

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Newsletter of the Association of Clinical Biochemists in Ireland
and the Association for Clinical Biochemistry and Laboratory Medicine (Republic of Ireland Region)

Ditchley House, Little Island. Built in the early 19th Century. Home to Robert Delacour Beamish, High Sheriff of Cork in 1842 and member of the Cork brewing family. Griffith's Valuation in the mid-nineteenth century valued the house at £34. Ditchley House is now part of the Radisson Blu hotel complex in Little Island, venue for ACBI 2016 .

Contents

Little Island, Cork

LITTLE ISLAND, a parish and island, in the barony of BARRYMORE, county of CORK, and province of MUNSTER, 4 miles (E.) from Cork; containing 1103 inhabitants. It is situated on the estuary of the Lee, and is separated by a branch of that river from the parish of Caherlog, with which it communicates by a handsome causeway of hewn stone and a metal spring bridge, constructed in 1833 at the expence of Silver C. Oliver, Esq. It comprises 1627 statute acres, chiefly under tillage and in a high state of cultivation; there is no waste land or bog. About 20 acres have been lately reclaimed from the slab of the river by the Rev. R. Bury, and brought into cultivation..... ***A Topographical Dictionary of Ireland, 1837.***

Little Island was connected to the mainland by a crossing in the 18th century and subsequently by the Island Bridge. Many buildings in Cork were built from limestone mined in the Little Island area. The limestone regions are also rich in fossil deposits. Local archaeological sites of interest include St. Lappin's Church, built in the gothic revival style using local stone and the Wallingstown graveyard with 16th century church ruins on the grounds. The Little Island railway station was opened in 1859 and serves Cork city, Cobh and Midleton.

Nowadays the region is home to over 700 businesses employing thousands of people, including major companies such as Pfizer, Eli Lilly, BASF, Janssen, Leo Pharma and Pepsico.

Wallingstown Church and Graveyard

Google Maps aerial view of Little Island

Members' Publications

The benefits of utilising geo-mapping for visualising the vitamin D status of Dublin city and the surrounding urban districts.
Laird E, Shannon T, Crowley VE, *Healy M*.
Ir J Med Sci. 2016 Oct 21. [Epub ahead of print]

A 1-year prospective study of the effect of infliximab on bone metabolism in inflammatory bowel disease patients.
Veerappan SG, *Healy M*, Walsh B, O'Morain CA, Daly JS, Ryan BM.
Eur J Gastroenterol Hepatol. 2016 Nov;28(11):1335-44.

Oral spray wintertime vitamin D_3 supplementation has no impact on inflammation in Gaelic footballers.
Todd JJ, McSorley EM, Pourshahidi LK, Madigan SM, Crowe W, *Laird EJ*, *Healy M*, McNeilly A, Magee PJ.
Scand J Med Sci Sports. 2016 Oct 5. doi: 10.1111/sms.12785. [Epub ahead of print]

Vitamin D3 supplementation in healthy adults: a comparison between capsule and oral spray solution as a method of delivery in a wintertime, randomised, open-label, cross-over study.
Todd JJ, McSorley EM, Pourshahidi LK, Madigan SM, *Laird E, Healy M*, Magee PJ.
Br J Nutr. 2016 Oct;116(8):1402-1408.

Vitamin D Status and Supplementation Practices in Elite Irish Athletes: An Update from 2010/2011.
Todd J, Madigan S, Pourshahidi K, McSorley E, Laird E, Healy M, Magee P.
Nutrients. 2016 Aug 9;8(8), 485;doi: 10.3390/nu8080485.

Vitamin D_3 supplementation using an oral spray solution resolves deficiency but has no effect on VO_2 max in Gaelic footballers: results from a randomised, double-blind, placebo-controlled trial.
Todd JJ, McSorley EM, Pourshahidi LK, Madigan SM, *Laird E, Healy M*, Magee PJ.
Eur J Nutr. 2016 Mar 25. [Epub ahead of print]

Laboratory services: regaining and maintaining control.
Lee GR**,** *Fitzgibbon MC***,** *O'Shea P*.
Int J Health Care Qual Assur. 2016 Jun 13;29(5):507-22

In control? IQC consensus and statutory regulation.
*Lee GR***,** *Fitzgibbon MC***,** *O'Shea P*.
Int J Health Care Qual Assur. 2016 Jun 13;29(5):492-506.

High-sensitive cardiac troponin-I facilitates timely detection of subclinical anthracycline-mediated cardiac injury.
Jones M, O'Gorman P, Kelly C, Mahon N, *Fitzgibbon MC*.
Ann Clin Biochem. 2016 May 11. pii: 0004563216650464. [Epub ahead of print]

Establishment of reference intervals for aldosterone and renin in a Caucasian population using the newly developed Immunodiagnostic Systems specialty immunoassay automated system.
*O'Shea P***,** *Brady JJ*, Gallagher N, Dennedy MC, *Fitzgibbon M*.
Ann Clin Biochem. 2016 May;53(Pt 3):390-8.

Clinical utility of C-terminal telopeptide of type 1 collagen in multiple myeloma.
Ting KR**,** *Brady JJ*, Hameed A, Le G, Meiller J, Verburgh E, Bayers C, Benjamin D, Anderson KC, Richardson PG, Dowling P, Clynes M, *Fitzgibbon MC*, O'Gorman P.
Br J Haematol. 2016 Apr;173(1):82-8.

Vitamin D status and fertility outcomes during winter among couples undergoing in vitro fertilization/intracytoplasmic sperm injection.
Neville G, Martyn F, *Kilbane M*, O'Riordan M, Wingfield M, McKenna M, McAuliffe FM.
Int J Gynaecol Obstet. 2016 Nov;135(2):172-176.

Correction of vitamin D deficiency in a cohort of newborn infants using daily 200 IU vitamin D supplementation.
Onwuneme C, Diya B, Uduma O, McCarthy RA, Murphy N, *Kilbane MT*, McKenna MJ, Molloy EJ.
Ir J Med Sci. 2016 Aug;185(3):683-7.

Striking difference of periarticular bone density change in early psoriatic arthritis and rheumatoid arthritis following anti-rheumatic treatment as measured by digital X-ray radiogrammetry.
Szentpetery A, Heffernan E, Haroon M, *Kilbane M*, Gallagher P, McKenna MJ, FitzGerald O.
Rheumatology (Oxford). 2016 May;55(5):891-6.

Seasonal variations in plasma free metanephrine concentrations are not evident in the West of Ireland.
Griffin TP, Casey R, Wall D, Bell M, *O'Shea PM*.
Clin Chem Lab Med. 2016 Oct 1;54(10):e289-92.

Abnormal glucose tolerance post-gestational diabetes mellitus as defined by the International Association of Diabetes and Pregnancy Study Groups criteria.
Noctor E, Crowe C, Carmody LA, Saunders JA, Kirwan B, O'Dea A, Gillespie P, Glynn LG, McGuire BE, O'Neill C, *O'Shea PM*, Dunne FP; ATLANTIC-DIP investigators.
Eur J Endocrinol. 2016 Oct;175(4):287-97.

A cross-sectional study of the effects of β-blocker therapy on the interpretation of the aldosterone/renin ratio: can dosing regimen predict effect?
Griffin TP, Browne GA, Wall D, Dennedy MC, *O'Shea PM*.
J Hypertens. 2016 Feb;34(2):307-15.

Space Odyssey by Dr. Peadar McGing, Mater Hospital

At the back of the 46A, as I started to write this on the way home from work, there was a guy talking very loudly. I would question whether or not he was drunk, but either way I was not inclined to believe his story. Apparently he had been kidnapped by aliens, then thrown out of their space ship, and had parachuted onto the Dublin Mountains. The presence of this strange space traveller was a bit of a coincidence though as I had been about to write about a recent Surgical Case Conference I attended in our hospital. I'm sure you're wondering what the connection is (and no, I'm not casting aspersions on our esteemed surgical colleagues). I occasionally attend the surgical meeting, and what drew me in for the 07.45 start that day was the talk title - 'NEEMO: A Spaceflight Analog. Medicine on the Edge.'

NEEMO is an acronym for NASA Extreme Environment Mission Operations, a programme which tests out equipment, procedures, and people, in simulated spacecraft conditions underwater. The speaker was 'one of our own', Dr Marc O'Gríofa, a UCD graduate and former intern at the Mater. The 'spaceflight analog' of the title is the Aquarius undersea research laboratory which is situated about 20 meters below the sea surface off the coast of Florida.

Dr O'Gríofa, who also has a PhD in Bioengineering, has been involved with space programmes since 2006, and during the past summer was one of six 'aquanauts' carrying out research in the Aquarius laboratory. And what research! Not mere POCT glucose or the likes. No, Marc described how they carried out DNA sequencing in their undersea lab using a mini-PCR instrument and a mini-DNA sequencer.

A very interesting medical research project he described was CASPER, not Casper the Friendly Ghost whose films my daughters loved when they were very young. No, this CASPER is a high-tech vest with a full name of Cardiac Adapted Sleep Parameters Electrocardiogram Recorder. CASPER was developed by Dr O'Gríofa in collaboration with Irish biomedical engineer Dr Derek O'Keefe. It's easy for us to forget that astronauts orbiting the earth experience sunrise and sunset every 90 minutes, not very compatible with our usual circadian rhythm. Marc used the electrocardiogram to determine if an individual had a good or bad sleep, a key measure as NASA has identified sleep disruption as one of the major issues to be addressed for long term space exploration.

Photo courtesy NASA [downloaded from https://blogs.nasa.gov/analogsfieldtesting/2016/07/27/neemo02/] Pictured at the end of Mission Day 1 are the NEEMO 21 aquanauts, clockwise from top: Matthias Maurer (ESA), Marc O Griofa (Teloregen/VEGA/AirDocs), NASA astronaut Megan McArthur, NASA astronaut Reid Wiseman, Dawn Kernagis (Institute for Human & Machine Cognition), and Noel Du Toit (Naval Postgraduate School). Inside the Aquarius habitat are Florida International University Habitat Technicians Hank Stark (left) and Sean Moore (right). What do the bottom of a blue ocean and the surface of a Red Planet have in common? Both are extreme environments.

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Moving from one aspect of circadian rhythm to one more familiar to us working in land-based clinical chemistry labs, namely cortisol. Aquarius reproduces conditions of living in a spaceship or in the International Space Station. As part of their studies Dr O'Gríofa described how they are doing detailed studies on telomere length and the effects thereon of simulated space travel. The NASA website gives a nice summary of the aims of this study. 'Telomeres are "caps" on the ends of chromosomes that protect them from fraying, much like the end of a shoelace, and an enzyme, called telomerase, maintains their length. Telomeres shorten over time, and the rate at which this occurs can be increased by stress, leading to accelerated aging, cardiovascular disease, cancer, and an impaired immune system. The Telomeres investigation collects crew member blood samples to determine how telomeres and telomerase are affected by space travel.' Marc described to us how they are particularly interested in how space travel-induced hypercortisolism may affect telomere length.

Ever since at age five I got my first Eagle Annual with its colour pictures of giant space rockets I have been interested in space travel. I've seen space craft in museums, visited the Kennedy Space Centre, and had my photo taken with an astronaut. However, it was a surprise to find myself listening to a talk in my own hospital about research on molecules I work with every day but which are part of the plan to send human beings to Mars. Life is strange, but fascinating.

Karen Heverin, Trainee Clinical Biochemist, Mater Hospital, describes her trip to this year's ACB Focus meeting

My first trip to FOCUS was a resounding success, acquiring lots of new information, meeting other trainees, and gaining a sceptical outlook on our laboratory testing - all part of being a Clinical Biochemist I am told! If you haven't been before it is certainly worth the trip to the UK. The very best in this business were brought together to impart their expertise on the FOCUS audience in the idyllic setting of the University of Warwick.

My favourite aspect of the Trainees day was the Duty Biochemist scenarios coordinated by Dr Karen Smith, and not just because it happened to be the last session of an intense training day! I loved the interactive nature of this session, each of the trainees were given numbers to vote for what answer they would have chosen for the scenario in question. Not only was it great when you choose the right answers, but I liked how Dr Smith went through the wrong answers explaining why exactly they were incorrect in each case. Scenarios included examples of contamination and how you would pick them out, for example the use of Calcium or Alkaline Phosphatase to rule out EDTA contamination. The interference of assays also featured; most interesting were the fT4 interference cases. I have had experience of heterophilic antibody interference in the measurement of TSH before but found the fT4 cases trickier to spot. Dr Smith explained that anti-ruthenium antibodies in a patient's sample can interfere with the Elecsys assay. High dose biotin used in some Multiple Sclerosis treatments also poses a problem for TFT analysis. Knowing the limits of your assay are key, sending samples out for confirmation with a two-step assay is a good idea if you have a one-step assay. In general, interferences in TFTs are as a result of analytical factors, drugs, familial dysalbuminaemic hyperthyroxinaemia (increased total T4 concentration but normal thyroid function) or the presence of heterophilic antibodies. She encouraged us to recheck suspicious results, particularly if the change is substantial in a short period of time, if the fT4 and TSH relationship appears inappropriate or if the results don't match the clinical picture.

I also enjoyed the session delivered by Elizabeth Davison, a Consultant Clinical Scientist in Viapath. She went through some data interpretation examples in FRCPath style, providing us with some tips and tricks she learnt to save time in this gruelling exam. I particularly enjoyed her take on IQC issues. She provided us with Levey Jennings plots and welcomed all feedback from the trainees in the discussion of what had happened with this analyte and what we would look for in troubleshooting the issue. This was very practical teaching for the day to day running of the laboratory and has definitely shaped how I now look at IQC issues in the context of our own laboratory.

Last but not least the Irish trainee contingent featured in the ACB News July issue, (or at least the backs of our heads) so all in all a very engaging trip!

Empower IVD Global Workshop, Ghent, Dec 9th 2015
Powerful stuff!
Dr. Graham Lee, Consultant Clinical Biochemist, Mater University/Mullingar Regional Hospitals

Ghent Workshop

On 9th December 2015, I attended a workshop in Ghent, on behalf of the ACBI, to obtain an update regarding the latest developments and future aspirations of the 'Empower' IVD project. The meeting was organised by Dietmar Stöckl, Linda Thienpont and Kenneth Goossens, who assisted preparations on behalf of the Empower team. This is a project whose intention is to deliver a "bottom up cooperation between laboratories and manufacturers to pursue a common objective of assessing and improving test comparability and stability". The project group itself is however independent to both stakeholders, existing almost analogous to an EQA/PT scheme/ service. The project comprises four main components: (i) master comparisons with fresh-frozen single-donation serum samples (thereby alleviating commutability associated with pooled samples; (ii) monitoring of patient percentiles (iii) IQC, both across laboratories and manufacturers; and (iv) education about analytical quality in the medical laboratory (e.g. analytical performance specifications) etc.

Master Comparisons Survey

Over the last couple of years we have seen several published reports emerging from this project including that of the 2014 master comparisons survey, whereby 125 laboratories (21 countries, mostly Europe) forming 8 peer groups (manufacturers) participated in analysing (in singlet) common clinical chemistry analytes (namely those appearing in our U+E, LFT, Bone and Lipid profiles). In this project, values were assigned by reference methods, where available, otherwise the All Laboratory Trimmed Mean was used for comparisons. In short, this work highlights good analytical performance, in terms of Imprecision and Total Error (Combined Imprecision + Bias) and comparability amongst many of the analytes analysed (Cholesterol, Glucose, Total Protein, Phosphate and Uric acid) but not for others, where significant calibration differences were apparent e.g. albumin and enzymes whose target values were assigned by IFCC reference methods.

"Percentiler" Tool

With the Master Comparison scheme reported to be currently "on hold", December's meeting focused on the "Percentiler" and "Flagger" project tools (Free to participants!). Using the Percentiler, the stability of "analytical" performance over time can be assessed. To avail of this tool, laboratories initially use their LIS or middleware to extract patient data (excluding demographics) across 20 analytes (many of those included in the Master Comparisons scheme), from which a daily median value is calculated for each analyte. To help ensure that such median data is not confounded by other sources of variation (biological, acute illness etc.), and thereby reflects only analytical variation, data is only collated from "Out-patient" sources. I later understood that this source primarily equates to data from GP sources. For the same reason as above, a further preference is to omit data from weekends and holidays i.e. lower throughputs. Once collated, the only pre-requisite is for the data to be organised (listed) into a simple table (excel or text file) of rows, each corresponding to a specific analyte, and comprising 10 columns: a lab's ID (defined by the lab), date of analysis, patient source (e.g. stratified as GP etc.), analyser code (i.e. can register all analysers within a laboratory or network), test code, median result, test units, number of results (to calculate the median) and the % flagged hypo and hyper e.g. MMUH; 09/12/2015; c16000Arch1; GP; Na, mmol/L, 140.9; 100; 5; 2. Where middleware/LIS can support automatic generation of such data, user time is obviously spared. However for many laboratories this is unlikely to be the case and sufficient IT knowledge (and time) to extract such data from the local LIS is needed. This is likely a factor that could hinder laboratory participation in this project…MedLIS project to the rescue? However, if this data can be collated as described it is then sent daily (or weekly/ monthly especially where IT constraints preclude daily collation) by email to the project's consultan-

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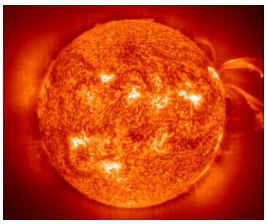
cy partners (STT consulting) who use their software to collate data from all participating labs, imputing it into a central database (MySQL). Subsequently, participating laboratories can individually log into the online Percentiler tool (https://www.thepercentiler.be/) where they can select either one or all analysers laboratory (or network) and thereby view an analyte's rolling/moving median; the latter can be based on n=5, 8 or 16 consecutive sets of median data submitted by the laboratory. For high throughput laboratories, moving medians from low numbers of submitted medians are considered most ideal for detecting analytical stabilities and *vice versa* for lower throughput laboratories and variable patient populations. For any of the 20 analytes, a laboratory can view a plot of the rolling median over a selected time period e.g. 3 months. When an analyte is analysed by a laboratory using one or more analysers, plots can be overlayed to facilitate comparison. Data can be compared simultaneously to the laboratory's long term median data e.g. 1 year as well as an analyte's target (reference) value e.g. based on the Nordic Reference Interval Project. Using the latter target values, and bias limits (%) based on desirable biological specifications or state-of-the art performance, absolute bias limits (analyte units) are derived which are applied to the laboratory's long term laboratory median and used to help evaluate the significance of any observed bias. An analyte's bias (%), which can be expressed relative to the relevant peer group (manufacturer and analyser model) or to all groups, is also obtained. The variability of the submitted median data for each analyte provides an estimate of imprecision (expressed as the robust CV, %) for the laboratory, peer group or all groups.

"Flagger" Tool

In summary, the Percentiler function appears to be a very powerful tool for monitoring test performance in terms of detecting bias shifts and drifts pertaining to an individual analyser, laboratory or manufacturer e.g. reflecting reagent or calibrator lot change– a useful and powerful tool for troubleshooting within a laboratory, network and beyond! The "Flagger" function adds further complementary information to the Percentiler, by highlighting the potential clinical impact of any such analytical performance changes. From the same laboratory data used for calculating analyte medians, the percentage of such data results above and below the laboratory's reference range (RR) [or clinical decision thresholds] is also submitted, as described above. Subsequently, laboratories can access online software (https://theflagger.be) where they can view the % of results flagging below ("Hypo") or above ("Hyper") the RRs, for any selected time period. If flagger limits were based on laboratory reference ranges, we should theoretically see 2.5% Hypos and 2.5% Hypers. However rather than using such limits, analyte-specific limits have been chosen which relate to the analyte's observed long term flagging rate. During the meeting case examples were given where patient medians where shown to increase with concomitant decreases in the hypo-flagging rates and *vice versa.* Again it was possible to demonstrate such changes at the level of a laboratory's individual analyser, whereby inter-analyser differences (and similarities) could also readily be seen. However it was further demonstrated that even when inter-analyser bias is apparent it is possible for only the % Hyper rate for each analyser to differ i.e. without affecting the % Hypo rate. It was explained that such an observation can relate to calibration differences between analysers whereby results remain comparable only at low concentrations. It was further demonstrated that even where "small" bias shifts are observed e.g. ~0.03 mmol/L -ve shift for calcium, this may translate clinically into a 33% relative increase in % Hypos i.e. 3% to 4%; authors have also reported a ~3-fold increase in % Hypers due to a +ve bias of 0.06 mmol/L! It is noteworthy that the Empower team continues to support sample exchange experiments between laboratories when significant biases are suspected!

Become Empowered!

Overall this meeting clearly showed the enormous power of the percentiler and flagger functions as complementary tools to Internal Quality Control, within a laboratory's overall Total Quality Control programme. As part of the IFCC C-STFT (Standardisation of Thyroid Function Tests) project, both tools will be used to monitor the pre- and post-standardization status of FT4/TSH assays and the impact of analytical quality or instability of both assays on medical decision making (or flagging rate). The potential of this project to improve the stability and comparability of IVD measurements is also clearly recognised however financial support, mainly from manufacturers, is considered essential to its future.



BREAKING NEWS! DUBLINERS DEPRIVED OF VITAMIN D

A recent publication I was involved in resulted in a bit of a reaction (first ref on page 3 of this Newsletter). In the paper we took a year's GP referrals from the St. James's Hospital catchment area, located patients' addresses to Dublin's postal codes, and mapped the mean deficient, insufficient and 'normal' vitamin D concentrations onto these postal areas. We could then get a visual on the spread of vitamin D concentrations in the postal districts sampled across the city. What emerged was that Dublin 8, Dublin 20 and the Lucan area had significantly more deficiency than the other postal regions. We speculated on possible reasons for this including the ethnic diversity of these areas and level of affluence as determined by the All Island Deprivation Index (*http://airomaps.nuim.ie/id/DepIndex/*).

Other significant findings concluded that women overall had better vitamin D concentrations than men (possibly due to the already recognised fact that men, for a variety of reasons, take a less proactive role in their health issues—see *www.health.harvard.edu/newsletter_article/mars-vs-venus-the-gender-gap-in-health* for a comprehensive discussion of this. We also found that younger men had significantly lower vitamin Ds than their older counterparts (>50 yrs).

The Press took notice of these findings and it was news for a day. It was interesting to see the different approaches various outlets took in reporting the study and the specific results they concentrated on. Some articles had readers comments. For some jaundiced views of our efforts see the comments after the Journal.ie piece (*www.thejournal.ie/vitamin-d-3058206-Nov2016/*).

Upcoming Meetings

14th UK & Ireland Neuroendocrine Tumour Society (UKI NET) National Conference, London, Dec 5th 2016.
www.ukinets.org/events/uki-nets-14th-national-conference/

4th International Conference on Nutrition & Growth, Amsterdam, March 2-4 2017.
http://2017.nutrition-growth.kenes.com/

World Congress on Osteoporosis, Osteoarthritis & Musculoskeletal Diseases, Florence, March 23-26 2017.
www.wco-iof-esceo.org/

2017 Society for Endocrinology Clinical Update, Birmingham, March 20-22 2017.
www.endocrinology.org/meetings/2017/cu2017/

MSACL (MS in the Clinical Laboratory), Salzburg, September 11-14 2017.
www.msacl.org

PSA in the News

The ACBI recently held an excellent one-day Scientific Meeting which included in the programme the latest on prostate cancer detection and treatment.

Early screening for prostate cancer using PSA has long been an area of contention with some saying it leads to overintervention with associated secondary risks.

Recently American actor Ben Stiller announced that he had been diagnosed with prostate cancer and that having his PSA measured had "saved his life". This re-opened the debate on the efficacy of using PSA as a screening tool for prostate cancer and, as usual, divided opinion among professionals. A report by Medscape summarises the story (www.medscape.com/viewarticle/869983 - free registration needed).

An October 2016 commentary in the Journal of Clinical Oncology outlines problems with the design of trials examining this issue and comes down in favour of targeted screening using PSA (http:ascopubs.org/doi/pdf/10.1200/JCO.2016.67.8938)