Submissions

Suitable contributions for The Clinical Biochemist Newsletter are welcomed by the Editor. The deadline for submissions for the December 2019 issue is 27 October, 2019.

Also see the Aacb web site: www.aacb.asn.au

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The Clinical Biochemist Newsletter is published quarterly. Subscription is included in membership dues (domestic and foreign).

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Other AACB Publications

The following AACB publications can be obtained from the Aacb Office:

The Clinical Biochemist - Reviews:
Edited by Amanda Hooper e-mail: Amanda.Hooper@health.wa.gov.au

The Clinical Biochemist - Monographs
Published by the Australasian Association of Clinical Biochemists Inc.
Editorial

Feature

Executive Summary

Book Review

Bad Blood

A Practical Guide to Global Point-of-Care Testing

Branch News

NSW/ACT

Victoria

Omni science

Case 1 - Floating Gel – Dr Geetha Rathnayake and Robert McFarlane

Case 2 - Point of Care Testing – Dr Susan Matthews and Prof Mark Shehard

Case 3 - Immune Checkpoint Inhibitors – Dr Thushari Vithange, Dr Nelson Siu Kei Lam, Dr Ken Lee Wan, A/Prof Zhong Xian Lu and A/Prof James CG Doery

Case 4 - TFT Conundrum – Dr Ken Lee Wan, Dr Thushari Vithanage, A/Prof Zhong Xian Lu and A/Prof James CG Doery

Journal Club

Diagnostic Improvement for Diabetes Insipidus?

Diagnosis and management of anabolic androgenic steroid use

New Members

Forthcoming Meetings
Randox is a leading manufacturer of third-party biochemistry reagents offering 111 assays including a wide range of unique and superior performance assays such as Lp(a), Enzymatic Fructosamine and 5th Generation Bile Acids.

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Welcome to the September issue. Spring and the Annual Scientific Meeting is upon us. The theme of the conference this year is “Clinical Biochemistry: Optimising Value In Healthcare” with what looks like an exciting program. There will also be a satellite meeting on Point-of-Care Testing and a Quality Control workshop. The weekend prior to the conference is the time that the Membership and Fellowship candidates sit the viva exams – we wish good luck to all of them.

This month we have branch reports from our NSW/ACT (from branch chair Dorothy Kouzios) and Victorian (branch chair Valena Braniff) branches, filling us in on the latest events in our two most populous states. We also have two book reviews from myself and Ian Farrance. I look at Professor Mark Shepherds textbook on Point-of-Care-Testing and Ian reviews “Bad Blood”, the infamous story of the now discredited in vitro diagnostic company, Theranos.

South Australia and Victoria have provided us with a number of interesting Omnisciences as well as two Journal Club articles. In the latter, Susan Matthews from SA/NT looks at a “Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus” whilst Alan McNeil from Victoria reviews the “Diagnosis and management of anabolic androgenic steroid use”.

We also have an executive summary from our President Peter Ward and CEO Kevin Carpenter. I would also like to point out that this month we have entered the new NPAAC Supervisory environment. The AACB is keen to provide a further response and Peter and Kevin would be happy to hear your thoughts.

I hope you enjoy this month’s reading and look forward to seeing you at the conference.
Executive Summary

Lots of activity in the AACB in the last few months with more to come before the year’s end. Firstly, I would like to acknowledge the passing, just before Easter, of Professor Howard Morris, the President of the IFCC and a dear friend and colleague to many in the AACB.

A very successful and well attended 7th Harmonisation Workshop was held at the beginning of May. There was a strong endocrine basis to this year’s workshop with one of the highlights being the move towards harmonisation of Endocrine Dynamic Testing. There appears to be a delay by some laboratories in the implementation of some of the agreed harmonised reference intervals and as an industry this needs to be resolved.

The AACB Council met in April for a strategic planning weekend where the results of the members’ survey formed the basis of the development of a plan for the next three years. Rather than engaging a consultant to facilitate the process, our multitalented CEO, Kevin Carpenter, led us through the steps of building the Strategic Plan.

Some of the key initiatives in the Plan require a change to the AACB Constitution – Motions for the proposed revisions will be presented to the 2019 AGM at the Annual Scientific Meeting in Adelaide. The proposed changes include amendment of the name of the AACB to include laboratory medicine (AUSTRALASIAN ASSOCIATION FOR CLINICAL BIOCHEMISTRY AND LABORATORY MEDICINE) and the inclusion of a President Elect and a Past President on the Executive to provide mentorship and continuity in line with other similar professional bodies.

If the changes are supported at the AGM, they will be put to a vote of the entire membership and a majority of two thirds or more of the members are needed to support the motions to amend the constitution. The AACB Council believes that these changes will improve the viability of the Association and we seek your support for these changes to be accepted.

The AACB has recently adopted GoToWebinar allowing the branches to webcast scientific meetings for regional members. Branches are starting to utilise this facility and most recently a webinar entitled Biotin, Infamy, Innocence and Risk, presented by Dr Christina Trambas, was broadcast to members.

Remember to register online for branch presentations and other events and on the night to use the QR code to record your attendance online. This allows the easy linking of your attendance with your CPD record.
The 2019 Roman Lecturer, Professor Leslie Burnett, is coming towards the end of his lecture schedule and from all reports the presentation entitled “Genomics: Hype, Reality and Potential” has been very well received.

Expansion of the Special Interest Group concept to include discussion forums through the website continues!! The forums fall under the heading of the AACB Pulse. Currently six Pulse forums, including a general forum, have been created. Members are encouraged to use the facility to communicate within the groups.

Finally, but very importantly, the project for the National Certification Scheme for Medical Laboratory Workforce is now complete. The project was led by AIMS and the AACB with the assistance of Human Capital Alliance (HCA) and funded by the Australian Government Department of Health through the Quality Use of Pathology Program. The final report has been submitted to the Department of Health and an Implementation Plan developed by HCA was delivered to the Project Steering Group in April of this year.

The implementation is now the responsibility of the professional bodies and one of the first steps will be to register, with ASIC, a new company limited by guarantee: The Australian Council for Certification of Medical Laboratory Scientific Workforce Limited (ACCMLSW). The Constitution of the new company is currently being finalised prior to an interim board being formed with directors in place until the 2020 Inaugural Annual General Meeting. This is an important early phase in the plan to build credibility of the Medical Laboratory Workforce through competency assessment.

Lab Tests OnlineAU is the gateway for all Australians to access the information they need about pathology tests to help Australians take control of their health and make the right decisions about their care.

We draw on some of Australia’s most respected experts for our information. More than 100 practising pathologists and senior scientists share their experience and knowledge and work with us on a voluntary basis. We are independent and not aligned with any commercial interests.

There is a growing public appetite for health information. Our audience is increasing rapidly each year.

Our audience is skewed female and younger.

70% of our visitors are aged 44 or younger.
Bad Blood

Bad Blood, the compelling true story which describes the impressive rise and eventual fall of Theranos and its flamboyant CEO and founder Elizabeth Holmes. A contemporary lesson on how analytical chemistry cannot be manipulated to suit an individual’s personal aspirations. It is not your usual Clinical Chemistry textbook, but a ‘textbook’ account of some powerful investigative journalism by author John Carreyrou. Bad Blood – secrets and lies in a Silicon Valley startup, Financial Times and McKinsey business book of the year award winner for 2018, written by John Carreyrou, paperback edition by Picador 2019. In addition, Eric Topol has reviewed an earlier edition of Bad Blood and his description includes an excellent overview of the whole Theranos saga.

So, you are not familiar with the Theranos story? In summary: Theranos, through its CEO Elizabeth Homes, promised to provide point-of-care testing for 100+ tests from a few finger-stick drops of blood. The Theranos device(s) were claimed to operate with better analytical performance and at less cost than routine diagnostic laboratory procedures. Multiple tests would be available (general chemistry and haematology, plus numerous immunoassay and infectious disease procedures) which could be combined to provide a ‘complete health profile’. Elizabeth Holmes founded Theranos when she was 19 years old and both she and Theranos soon became respected Silicon Valley identities. She gave numerous and very popular TED talks and appeared on the covers of Forbes and Fortune magazines. [Type Theranos and/or Elizabeth Holmes into Google and there will be a deluge of information – the date sequence of items will be critical however, as the adventure unfolds from about 2003 through to the current well publicised court proceedings.]
By 2013, Theranos was valued at nearly US $10 billion and had even negotiated partnership arrangements with Walgreens (the second largest pharmacy-store chain in America) and Safeway supermarkets (in America) to have their blood testing procedures/devices in stores around the country. The problem? Their technology never really worked. It never came close to working as advertised. Elizabeth Holmes was so good at selling her vision that everything progressed well until real patients were using Theranos ‘tests’ to make personal health decisions. The public and the regulators were unaware of the Theranos deception until John Carreyrou broke the story as a reporter at the Wall Street Journal. Because his investigations were so integral to the company’s demise and final liquidation in 2018, Bad Blood offers a most remarkable and insightful overview. Among the numerous private investors who lost many ‘millions’, an interesting Australian connection to the story is that of Rupert Murdoch, the largest single investor. Murdoch lost US $121 million on the deal but used this loss to offset taxable income from other investments.3

Due to the exceptionally secretive nature of the Theranos ethos as clearly outlined by John Carreyrou, little seems to be available in the peer-reviewed scientific literature regarding the Theranos technology or its technical ‘developments’. In contrast to this however, the names of Theranos and Elizabeth Holmes appear on many patents taken out in order to secure their ‘revolutionary’ technology. For example; ‘Theranos’, entered into the quick search criteria for the United States patent and trademark office provides 155 individual entries.4 This relatively large number is not unusual for a company engaged in product development, as each new or apparently novel component or process may have a separate patent. Similar information may also be obtained if a ‘Google patent search’ is used.5 However, having a patent does not in any way guarantee that the item described actually works!

Even though not featured in Bad Blood, articles relating to Theranos which do appear in the earlier peer-reviewed literature generally seem to discuss the philosophy of patient empowerment to initiate their own laboratory testing and result interpretation. In many aspects, this direct to patient concept has many features in common with what has been described elsewhere as P4 medicine (predictive, personalised, preventative and participatory).6,9 In particular, Michael Page has reviewed and commented on a 2015 article by Eleftherios Diamandis which discusses aspects of ‘customer-driven healthcare’ and the Theranos philosophy in an earlier edition of this newsletter.6,10 In fact, the 2015 article by Diamandis is particularly relevant to the current discussion. It was published towards the end of halcyon days of Theranos, before the significant issues of fraud and technology failure were publically known. The title of the article Theranos phenomenon: promises and fallacies, provides a clear indication of its contents which also includes an appropriately sceptical overview of the Theranos technology. To quote: “The quality of the results are not known since the Theranos system has not been independently evaluated, nor do any published results exist to compare with conventional technologies”.11 In 2016 however, what appears to be the first independent evaluation of the Theranos approach was published in the Journal of Clinical Investigation.12 This evaluation compared 22 common laboratory tests obtained by finger-stick (Theranos) with traditional venepuncture testing by two of the major US private laboratories (Quest and LabCorp).13 The results showed significant discrepancies between the Theranos results and both of the regular laboratory services. A current commentary on Theranos by Fiala and Diamandis (now that many of the issues are publically known) provides a critical summary of the Theranos fiasco and the relative silence by medical and scientific professionals regarding the technical and scientific aspects of Theranos devices and Theranos testing procedures.13 To quote: “Despite the extensive work of investigative journalist Carreyrou on Theranos business troubles, scientists remained silent observers for over 10 years. The 8 Theranos-related papers indexed in PubMed from our group, along with their accompanying editorials and a few papers from others, provide the only parallel scientific perspective to the remarkable story described in this new book.”14

And finally, two additional articles which relate to the Theranos technology:

The specialised finger-stick blood collection tube patented by Theranos and originally approved by the FAD has been unapproved. “The importance of BCT [blood collection tube] classification has been demonstrated by the FDA report on Theranos, a high-profile Silicon Valley clinical laboratory that was using its patented capillary tube “Nanotainer” as a Class I rather than a Class II medical device for more than two years”.15

In a review of Bad Blood, surely the final word (or at least nearly the final word) should go to John Carreyrou and Theranos. “In the days after my first journal article, Holmes definitely asserted that she would publish clinical data from her blood-testing system to disprove my reporting.” ... “Two years and three months later, she finally delivered that pledge: in January 2018, Theranos published a paper about the miniLab in the peer-reviewed scientific journal Bioengineering and Translational Medicine.”16 This article provides a reasonably detailed report describing the analysers various components and inner workings: “We describe a simple-to-use miniaturized clinical laboratory system designed to test a diverse range of clinical analytes in distributed laboratory or near-patient settings.” ... “The miniLab can detect analytes in blood using multiple methods, including molecular diagnostics, immunoassays, clinical chemistry and haematology.”16 However, the method comparison...
and assay performance data are only provided for a Zika virus molecular diagnostics assay, an anti-herpes simplex virus type-2 IgG immunoassay, a lipid panel and a lymphocyte subset panel; but all using venous blood sampling and not finger-stick. All method comparisons seemed to have been done in an appropriate and reasonably rigorous manner. And another surprising Australian connection? Of the 50 references cited by Theranos, 3 were from the Clinical Biochemist Reviews.

Bad Blood, which extends the investigations of John Carreyrou and articles which were originally reported in the Wall Street Journal, is more akin to an adventure novel than a serious investigation into the failures of laboratory medicine. An excellent read for all, but particularly for clinical biochemists.

References:
2. Technology, Entertainment, Design (TED) talks. Type ‘TED Elizabeth Holmes’ into Google or see https://www.youtube.com/watch?v=ho8geEtCYjw (accessed July 2019).
A Practical Guide to Global Point-of-Care Testing

David Hughes
BSc, FAACB

David is a scientist working in Clinical Chemistry with 20 years experience. He is a Fellow of the AACB and the Education Officer for the NSW/ACT branch. His interests are Harmonisation, Endocrinology and everything clinical chemistry.

Although Point-of-Care Testing (POCT) has been around for a considerable time it is only recently that it has begun to be seen as a singular discipline rather than a disparate collection of testing across many professions and disciplines. This textbook produced by CSIRO Publishing is an attempt to provide an integrative approach appropriate for this new paradigm. The editor and primary contributor, Professor Mark Shephard, has extensive experience in the management of POCT networks, teaching, and both professional and government working parties in the field. As befits an Australian publication it draws largely on well-respected local contributors and sources along with some international ones.

The textbook is divided into three sections. The first is focussed on the management of POCT services. The second and largest section describes the clinical use and methodologies of POCT whilst the last section is a review of the various clinical settings that POCT may be used in.

Prof. Shephard begins the book with an introduction that first defines POCT and then examines the drivers and benefits of near patient testing. He also contributes to the beginning chapter of the management section where he discusses the establishment and management of a POCT service. He describes regulatory structures with particular reference to Australia - although he also lists the international organisations that have drawn up guidelines on POCT. A useful list of the various Clinical and Laboratory Standards Institute (CLSI) guidelines relating to POCT is also included. The rest of the first section provides guidance on the selection and evaluation of the POCT devices themselves, training and competency of the staff using them, quality management and accreditation. The final chapter of this section is on assessing the effectiveness of POCT.

The bulk of the book is found in the second section which has chapters devoted to specific diseases (eg diabetes, coagulopathies and infectious disease) and the relevant devices that are used. These chapters are written by appropriate experts in each clinical area, most of whom have considerable experience. One very minor grievance is that in those cases where contributors are from the In-Vitro Diagnostics (IVD) industry I feel there is insufficient disclosure in the chapter itself (their employment is listed in the index of contributors). Each chapter in this section discusses the global burden, aetiology and physiology of the particular disease and then provides a technical summation of the range of devices available. Generally this includes the methodology used, specifications (e.g. sample volume, measuring range and time to result) and the required analytical goals specified by various national and international organisations. Pre-analytical sources of errors are also discussed.

The range of disciplines discussed in the second section is impressive with three chapters on diabetes and kidney disease, two on cardiovascular disease, two on haematological disorders, one on acid-base imbalances, one on drugs of abuse and finally eight chapters devoted
to infectious diseases. One chapter is devoted to highly infectious disease threats such as Ebola and provides a good overview on risk mitigation and the range of testing available in these high risk environments.

The last section considers the various clinical settings for testing, whether it be in general practice, remote and extreme settings or in tertiary care. POCT practice is discussed in such diverse settings as remote and indigenous regions (an area of which Prof Shephard has considerable experience), sports science, disaster management and pharmacy.

There is a final concluding chapter where Prof. Shephard attempts a crystal ball view (albeit an educated one!) of the near-future of POCT. Here he discusses the potential scope of POCT and the barriers that may need to be overcome to achieve it. He sees a future where there is greater connectivity and integration into the wider health system but acknowledges the need for a greater evidence base and more engagement between stakeholders. He briefly describes possible technological advances such as wireless ECG devices connected to mobile phones and wearable/implantable instruments.

Prof. Shephard and the other contributors have provided us with a comprehensive review of near patient testing that will be found to be relevant by both the novice and those experienced in POCT management alike. The layout is clear and the individual clinical chapters provide up-to-date information. The publishing date of this edition is 2016 and most of the references used are later than 2010.

A copy of the book was provided to the reviewer for the purpose of the review.

### Dates to Remember

**Point of Care Testing Satellite Meeting**
14 October 2019
Adelaide SA

**AACB 57th Annual Scientific Conference**
15 - 17 October 2019
Adelaide SA

**Quality Control Workshop**
18 October 2019
Adelaide SA

**15th APFCB Congress**
17-20 November 2017
JECC Jaipur India
My first year as the Chair of the AACB NSW/ACT branch has been an enjoyable and rewarding experience, and I would like to take this opportunity to acknowledge and thank Peter Ward (former Branch Chair) for his advice and support. Peter’s mentorship has been invaluable and has made the transition into this role seamless.

I would also like to sincerely thank all of the current committee members for their commitment and contribution this past year with the planning of the topics to be presented at monthly and regional meetings, organisation of speakers and sponsorship, including putting together and publishing of the newsletter. Their dedication and expertise in many areas, have been instrumental in driving the success of the organisational Branch activities.

NSW/ACT Branch AGM
Our AGM was held on the 23rd July at the Northern Sydney Education Centre in North Ryde. The AGM was well attended and saw all current committee members unanimously voted back into the same roles, with the exception of one resignation.

Branch Scientific Meetings
Our monthly scientific meetings have been successful overall with attendance numbers varying between 25 to 45. One of the most challenging aspects we face as a branch is promoting and encouraging lab staff to attend the monthly scientific meetings which is paramount to their professional development and ongoing education.

Our first meeting on the 19th February 2019, was the annual combined AIMS/AACB Clinical Review, titled ‘In the Heat of the Moment-The Pathology of Burns’, held at Beckman Coulter in Lane Cove. The feedback received from the 69 attendees was overwhelmingly
positive. The presenters, Dr Kar-Soon Lim (Burns Anaesthetist), Dr Justine O’Hara (Burns and Plastic Surgeon) and Dr Alessandra Bianchi (Haematologist, Transfusion Medicine), captured the attention of the audience with their very descriptive and graphic visuals. The presentations covered many areas associated with the management and treatment of burns patients, the metabolic changes (acidosis) the patient undergoes, including coagulopathy and haematological changes in severe cases with blood transfusion requirements.

An additional combined meeting with the Mass Spectrometry group was held on the 12th February 2019. Professor Stefan Grebe from the Mayo Clinic in Rochester, USA was the guest speaker. The topic was on ‘Clinical Mass Spectrometry-It’s Role and Limitations’, with 40 attendees, not only from the research and medical science field, but scientists working in disciplines such as forensics and clinical pharmacology.

The Regional Meeting in September, aptly named “It’s a Wagga thing”, is to be held in Wagga Wagga, at the Clinical School of the University of Notre Dame. Dr Janet Warner, Deputy CEO of the RCPA and Chemical Pathologist will be presenting. The topic is on Macrotroponin – How should we manage this inconvenient truth? A topic of great concern and interest for many automated core laboratories. I’m sure it will create some lively discussions.

Thank you to Dr Amanda Caswell and Anthony Flaskas, the Laboratory Manager at Wagga Wagga Base Hospital, for making the Regional meeting possible with their exceptional skills in organizing and promoting the event.

The summary table below lists all of the NSW/ACT Branch Scientific Meetings for 2019.

**NSW/ACT Branch Registrations - QR Codes**
In addition to registering attendance via the AACB website, the local Branch has been promoting the use of QR codes at the monthly meetings prior to the presentations taking place. The QR codes are produced by the Publications Officer at AACB Head Office for each meeting and emailed to the Branch Chair, who then distributes them amongst the attendees on the night.

The QR codes are scanned by using your mobile phone, which then takes the user to a ‘docs.google.com’ feedback page. The Feedback page asks the attendee to rate the event from 1 to 5 (1=poor, 5= excellent) regarding how satisfied the attendee was with the event and how relevant/helpful it was to their job. Attendees are also asked to comment about key takes from the presentations and overall feedback. Participants who meet the criteria, by registering before the event (AACB website) and scanning the QR code, receive their CPD certificate.

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<th>Date</th>
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<td>Clinical Mass Spectrometry-It’s Role and Limitations’</td>
<td>Professor Stefan Grebe</td>
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<td>19th Feb</td>
<td>AIMS/AACB Annual Clinical Review. In the Heat of the Moment-The Pathology of Burns</td>
<td>Dr Kar-Soon Lim, Dr Justine O’Hara, Dr Alessandra Bianchi</td>
<td>Beckman, Coulter</td>
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<td>March</td>
<td>NSW Health Pathology Update</td>
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<td>April</td>
<td>Industry Presentations</td>
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<td>May</td>
<td>Roman Lecture</td>
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| June  | Posters from the 2018 ASM  
• Audit of Procalcitonin retesting intervals  
• Thyroid function in growing children: The Australian Look Study  
• Bilirubin Interference on an enzymatic paracetamol assay and its removal by ultrafiltration  
• Interference with several 25 Hydroxyvitamin D immunoassays in a patient with IgM Paraproteinaemia |
|    |
| July  | Copeptin:  
• The reliable bigger brother to ADH  
• Is serum copeptin a modifiable biomarker in Autosomal Dominant Polycystic Kidney Disease. |
|    |
| August | Back to Basics – Cases  
• When all is not as it seems – A rare case of a disorder of sexual development  
• A racing creatinine: model car fuel toxicity  
• Email from a friend: Genetic Metabolic Disorder in a child |
|    |
| September | Regional Meeting – Wagga Wagga  
Macrotroponin – How should we manage this inconvenient truth. |
|    |
| October | 2019 AACB ASM Adelaide |
|    |
| November | Trivia Night & Presentations  
Making the Perfect Baby - |

Participation has slowly been increasing over the last few meetings and with continual promotion at each branch meeting it will give us an insight into the actual numbers of those who have registered, attended the scientific meeting and scanned the QR Code compared to:

• those who have registered and not attended, and  
• those who have who have not registered but have attended the meeting.  
• The August meeting was a good example of this and an interesting breakdown of numbers.  
• 22 people registered for the event beforehand  
• 13 of those scanned the QR Code  
• There was 1 duplicate attendance (someone filled the form twice)  
• 4 people scanned the QR Code but weren’t registered beforehand  
• A manual head count showed that 27 people had attended.  

Thank you to Erin McLemon for the summarised QR Code feedback which is sent the next day.
NSW QAG (Formerly QC Sub-Committee) – Lyn Boscatto, Convenor
Meetings are held every second month at the Northern Sydney Education Centre in North Ryde, during refreshments in the dining room, before the Branch meeting. All are welcome to be part of the committee.

The NSW QAG membership comprises of members from 6 public hospitals and 2 from industry. The objectives of the QAG is to promote the development of laboratory best practice and the dissemination of information and discussion of issues which arise.

Overall, input from everyone and an increased laboratory/industry representation ensures that the activities and discussions remain relevant, and projects are not being duplicated. The continued liaison with NSW Health Pathology Clinical Streams ensures activities are not reproduced, including communication with other state QAGs.

Discussions and Studies
- Macroprolactin - Harmonisation of PEG procedure and production of QAP in association with Harmonisation Committee and ACEN
- GH and IGF harmonisation – units, RI, commutability
- Cortisol assays – contribution of standardisation to between assay bias
- Potential new QAP programs
- Assist with QAP production e.g. bone markers
- Common reference intervals

Regional Representation – Don Clausen
Our Regional Representative has been diligent in promoting the AACB to local scientists working in the clinical laboratory environment and academic arena. Don was pleased to report at our AGM, that some staff working in both professional environments had joined the AACB.

In addition, Don initiated and opened discussions with the University of New England (UNE) and Southern Cross University to promote the Chemical Pathology Course that was held at the Gold Coast this year, including the upcoming Annual Scientific Conference in Adelaide. Feedback received from regional scientists who had attended the Chemical Pathology Course this year, was that they were enthused about the depth and variety of the topics presented. They found the entire week very educational, relatable to their vocation and a great avenue for networking with other professionals.

Don mentioned in his AGM report that he had recently been invited on to the academic board of Southern Cross University to discuss improvements to the curriculum and give input into the Clinical Chemistry subject. He is also a guest presenter at UNE, giving lectures on QC within the laboratory environment.

Furthermore, Don promotes the AACB informally at the North Coast AIMS meeting in discussion with other delegates, including promotion of the Webinars to colleagues in regional areas.

NSW Study Group
Our Education Representative, David Hughes has done an exceptional job in organising the study group sessions for those who are studying towards achieving their MAACB. The topics to be discussed with cases studies are emailed to everyone beforehand.

The sessions are conducted on a monthly basis, and prospective MAACB candidates dial in with their phones and use the GoToMeeting application.

MAACB Exams: This year we originally had four candidates, out of which only two eventually sat for their exams.

Sponsorship
Lastly, the NSW/ACT AACB Branch wishes to thank all the Sponsors for their continuing support and generosity throughout the year in making the Branch meetings possible.

- Beckman Coulter
- Sciex
- Roche Diagnostics
- Radiometer
- Wish-Med
- Thermofisher Scientific
- Abbott
- Bio-Rad
- Point of care diagnostics
- Diasorin

Back to basics registrar Dr Simon Townsend Dr Myron Lee Dr Zahrul Ismadi
Abbott Table Trivia Night December 2018

Trivia Night Winners Roche Diagnsotics Table

2018 ASM Poster Top Picks Professor Julia Potter, Caroline Cross, Frank Alvaro and Dr Simon Thompson
This year has been another stable year for the Victorian Branch. The branch remains active in organising very successful monthly meetings with solid attendances throughout the year along with study and tutorial groups and an active JournalClub. Webinars were trialled at the monthly educational meetings and there is also a dedicated group of Quality minded folk contributing to VQARG. I would like to thank every member of the Victorian Branch Committee for their tireless contributions in organising such wonderful monthly educational activities. It is an exceptional effort to spend the time in the current climate of increased workloads. We said goodbye to our previous Newsletter editor Jia Liao who stepped down from the committee. I would also like to thank Dr Tina Yen who furnished us with some speaker ideas for our branch meeting presentations.

On behalf of the committee, I would like to extend my sincere gratitude to everyone that presented at our monthly meetings. Of course the meetings would not be as successful without the support of Industry by way of sponsorship. Sponsors for the past year have been Beckman Coulter, AMSL, Waters, Agilent, Shimadzu, Thermo Fisher, Biorad, Siemens, AACB and Abbott diagnostics.

For the 2018-2019 period, one of the highlights once again was the Roman Lecture. We hosted Professor Leslie Burnett who gave a most interesting dissertation on his field of interest: Genomics: Hype, Reality and Potential. Leslie spoke of the history of genomics and gave some insight of his own genome and his impressions of the future of the profession. A lovely dinner was enjoyed at University House where one feels the immense history of academia and knowledge.

The February meeting was once again an exceptional group of case presentations by Dr Joel Smith, Dr Ken Lee Wan, Dr Azni Abdul Wahab, Dr Thushari Vithanage and the Beryl Beigler Award recipient from RMIT; Ce Shi. I would like to thank these presenters for their presentations.

At the August 2018 meeting, Prof. Morris discussed how IFCC improves the quality/value laboratory medicine despite the various challenges it faces. A major challenge lies in the delivery of precise and accurate patient results with cost-effective services. Whilst strategies were made to upgrade analytical test performances, the ultimate goal of laboratory medicine is to generate reliable results that influence clinical decision making for the best outcome for the individual patient. In-line with this, some assays were standardised/harmonised enabling clinicians worldwide to adopt international practice guidelines to optimise patient care. We were lucky to have had Professor Morris visit Victoria.

Other presentations were:
- Dr Brian Beer who spoke on Forensic Biochemistry and is it of any use.
- Dr Steven Ramsay; Mass Spectrometry in the Clinic – The Ugly Duckling.
- Prof Frank Bowlin; Big Data in Laboratory Medicine.
- Dr Christina Trambas; Biotin: Infamy, innocence and risk
- Professor Hans Schneider – Calcium Regulation and PTH and new assays
- Poster Session from 2018 ASM. The Derek Rae Memorial recipient for best poster was Gary Liu representing Melbourne Pathology.
- Christmas Trivia – winning team from Melbourne Pathology

It is my privilege to be Chair of such a talented and dedicated group of members. I look forward to a fascinating 2020.
Committee for 2019-2020

Branch Chair
Valena Brannif

Secretary
Jhoanna van’t Wout

Branch council rep
Intissar Bittar

Education rep
Craig Baker

Treasurer and webinar
Gary Liu

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Ray Czajko

Committee member
Dr Kay Weng Choy

Dr Zhong Lu

Group photo at Roman Lecture at VCCC, Peter Mac.

Case presenters at Monash Medical Centre. Dr Thushari Vithanage, Dr Azni Abdul Wahab, Dr Joel Smith, Dr Ken Lee Wan, Ce Shi
Interactive Clinical Cases

Once you have read each question and tried to answer it, click on the question to check your answers.
Dr Geetha Rathnayake and Robert McFarlane
Territory Pathology, Royal Darwin Hospital, Tiwi, NT
Email: Geetha.Rathnayake@nt.gov.au

CASE HISTORY

A specimen with a request for high sensitivity troponin was loaded onto Abbott Architect i2000 analyser. The analyser came to a sudden stop without further sampling. The sampling probe came to the rest position and separator gel was seen covering the probe.

The specimen was from a 21-year-old manual labourer from Darwin, Australia, working outside in the heat. Darwin can be warm and humid in the wet season, which is from November until April. The patient presented with acute onset muscle cramps and diaphoresis in March 2018. He otherwise was in good general health. Physical examination revealed tachycardia and profuse diaphoresis. He was in marked discomfort secondary to migratory cramping throughout his body. He had a history of two such previous admissions during the last 12 months, in May 2017 and in November 2017.

The specimen probe of the i2000 was cleaned externally. The analyser was re-started after putting it on brief pause. Results of quality control specimens run just after startup were fine.

The specimen was inspected after removal of the label. Separator gel could be seen floating on top. Plasma under the gel showed mild to moderate haemolysis. Careful aspiration and aliquoting of the plasma allowed performance of chemistry tests.

The general chemistry platform in the laboratory is the Vitros Fusion 5.1 (Ortho Clinical Diagnostics). The results of the specimen had to be suppressed due to a high haemolysis index of 227 (Reference Interval (RI) 0-50). The table below provides a selection of relevant suppressed results, in blood chemistry and in haematology. Results from two hours later are also shown. Initial results, even though not 100% reliable, gave a picture for the extent of dehydration and severity of acute kidney injury.

Creatinine was high initially. However, urea took several hours to go up to 7.8 mmol/L (RI 3.0-7.5). This pattern of urea taking several hours to go up compared to creatinine was seen in his previous two admissions.

Urine albumin and protein were elevated. Very similar elevated levels were evident in his previous admission in May 2017 but normalised the following day.
His repeat blood chemistry the following day showed marked improvement in creatinine, 92 µmol/L (RI 60-110), and urea 6.4 mmol/L (RI 3.0-7.5). The patient was discharged on the following day with advice to see the GP for other blood test results.

Table. Laboratory results at initial admission and two hours later

<table>
<thead>
<tr>
<th></th>
<th>Suppressed results at admission</th>
<th>Results 2 hours later</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma Chemistry (Heparin)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolysis index</td>
<td>227</td>
<td>&lt;15</td>
<td>0·50</td>
</tr>
<tr>
<td>Sodium</td>
<td>150</td>
<td>140</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>5·1</td>
<td>4·1</td>
<td>3·5-4·5 mmol/L</td>
</tr>
<tr>
<td>Total CO2</td>
<td>&lt;5</td>
<td>21</td>
<td>22-32 mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>6·0</td>
<td>7·1</td>
<td>3·0-7·5 mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>292</td>
<td>233</td>
<td>60-110 µmol/L</td>
</tr>
<tr>
<td>Total Protein</td>
<td>144</td>
<td>103</td>
<td>64-84 g/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>82</td>
<td>59</td>
<td>39-50 g/L</td>
</tr>
<tr>
<td><strong>Haematology (EDTA)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>207</td>
<td>-</td>
<td>135-185 g/L</td>
</tr>
<tr>
<td>Red Cell Count</td>
<td>6·92</td>
<td>-</td>
<td>4·50-6·50 x10¹²/L</td>
</tr>
<tr>
<td>Haematocrit</td>
<td>0·62</td>
<td>-</td>
<td>0·40-0·54</td>
</tr>
<tr>
<td>Platelets</td>
<td>490</td>
<td>-</td>
<td>150-450 x10⁹/L</td>
</tr>
<tr>
<td>White Cells</td>
<td>17·9</td>
<td>-</td>
<td>4·0-11·0 x10⁹/L</td>
</tr>
<tr>
<td><strong>Urine chemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>18·92</td>
<td>mmol/L</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>863</td>
<td>0·19 mg/L</td>
<td></td>
</tr>
<tr>
<td>Urine Protein</td>
<td>1131</td>
<td>&lt;150 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

**QUESTIONS**

1. What are the causes for floating of separator gel?
2. Why did the gel of this patient’s specimen float?
INTERACTIVE QUIZ

Case 2

Dr Susan Matthews and Professor Mark Shephard
International Centre for Point-of-Care Testing, Flinders University, South Australia
E-mail: susan.matthews@flinders.edu.au

CASE HISTORY

An 86 year old female presented to a remote, Central Australian Health Service (CAHS) with atrial fibrillation and was subsequently evacuated to Alice Springs. The referring clinician queried the accuracy of the point-of-care (POC) creatinine result. The POC and laboratory biochemistry results collected on 29.3.2018 (at times shown) were:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>i-STAT Result 1030</th>
<th>CAHS i-STAT Reference Interval</th>
<th>Lab Result 1657</th>
<th>Lab Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>129</td>
<td>135 – 145 mmol/L</td>
<td>130</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.6</td>
<td>3.5 – 5.0 mmol/L</td>
<td>4.6</td>
<td>3.5-5.2 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>92</td>
<td>95 – 108 mmol/L</td>
<td>91</td>
<td>95-110 mmol/L</td>
</tr>
<tr>
<td>Total CO₂⁻/HCO₃⁻</td>
<td>31*</td>
<td>23 – 32* mmol/L</td>
<td>26**</td>
<td>22-32** mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>4.5</td>
<td>2.9 – 9.4 mmol/L</td>
<td>4.8</td>
<td>3.0 – 8.0 mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>460</td>
<td>53 - 115 µmol/L</td>
<td>50</td>
<td>45 - 90 µmol/L</td>
</tr>
</tbody>
</table>

QUESTIONS

1. What possibilities could you offer to explain an elevated creatinine result?
2. What further information would you seek to explain the discrepant POC and lab creatinine results?
3. What significance is the POC (Abbott i-STAT) creatinine method in this case?

Answers on page 31
Case History

A 67-year old male presented to Emergency Department with low grade fever, dehydration and acute delirium. He had undergone six cycles of chemotherapy followed by three cycles of immunotherapy with ipilimumab and nivolumab for his metastatic cholangiocarcinoma. His biochemistry investigations were as follows:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>137</td>
<td>135-145 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.5</td>
<td>3.5-5.2 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>96</td>
<td>95-110 mmol/L</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>25</td>
<td>22-32 mmol/L</td>
</tr>
<tr>
<td>Urea</td>
<td>6.9</td>
<td>2.8-7.2 mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>92</td>
<td>60-110 µmol/L</td>
</tr>
<tr>
<td>ALP</td>
<td>74</td>
<td>30-110 U/L</td>
</tr>
<tr>
<td>GGT</td>
<td>158</td>
<td>5-50 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>63</td>
<td>5-35 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>34</td>
<td>5-40 U/L</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>20</td>
<td>0-20 µmol/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>32</td>
<td>32-47 g/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>6.5</td>
<td>3.0-7.7 mmol/L</td>
</tr>
<tr>
<td>Cortisol</td>
<td>36</td>
<td>185-625 nmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>&lt;0.01</td>
<td>0.40-4.80 mU/L</td>
</tr>
<tr>
<td>FT4</td>
<td>46.2</td>
<td>8.0-16.0 pmol/L</td>
</tr>
<tr>
<td>FT3</td>
<td>6.6</td>
<td>3.2-6.1 pmol/L</td>
</tr>
</tbody>
</table>

Thyrotoxicosis was noted as well as inappropriately low cortisol.
INTERACTIVE QUIZ

QUESTIONS

1. What are the possible causes of the very low cortisol in this patient?
2. What further tests would you consider?
3. What are the actions of ipilimumab and nivolumab and what is the likely long term outlook for the patient?

Answers on page 33
CASE HISTORY

47 year old female presented with palpitations, chest discomfort, weight loss and dizzy spells. On examination, she was obese with irregular pulse and goitre. Her full blood examination, troponin studies, renal and liver profile were unremarkable and her other laboratory investigations were as follows:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>57.2</td>
<td>0.40-4.80 mU/L</td>
</tr>
<tr>
<td>FT4</td>
<td>17.4</td>
<td>8.0-16.0 pmol/L</td>
</tr>
<tr>
<td>FT3</td>
<td>7.4</td>
<td>3.2-6.1 pmol/L</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5.8</td>
<td>0.5-5.5 mmol/L</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1.1 mmol/L</td>
<td>0.2-2.0 mmol/L</td>
</tr>
</tbody>
</table>

Her thyroid function tests were sent to other laboratories to be measured on alternative platforms:

<table>
<thead>
<tr>
<th>Platform</th>
<th>TSH Reference Interval</th>
<th>FT4 Reference Interval</th>
<th>FT3 Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beckman</td>
<td>57.2 0.40-4.80 mU/L</td>
<td>17.4 8.0-16.0 pmol/L</td>
<td>7.4 3.2-6.1 pmol/L</td>
</tr>
<tr>
<td>Coulter</td>
<td>58.3 0.50-5.00 mU/L</td>
<td>21.1 9.0-25.0 pmol/L</td>
<td>7.4 3.5-6.5 pmol/L</td>
</tr>
<tr>
<td>Siemens</td>
<td>49.0 0.30-5.00 mU/L</td>
<td>17.0 9.1-19.6 pmol/L</td>
<td>5.8 2.4-5.9 pmol/L</td>
</tr>
<tr>
<td>Abbott</td>
<td>68.7 0.27-4.20 mU/L</td>
<td>21.3 12.0-22.0 pmol/L</td>
<td>6.7 3.1-6.8 pmol/L</td>
</tr>
<tr>
<td>Roche</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A TRH stimulation test was performed to distinguish between TSH-secreting adenoma and thyroid hormone resistance:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Baseline</th>
<th>+20mins</th>
<th>+60mins</th>
<th>+120mins</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>57.9</td>
<td>279</td>
<td>227</td>
<td>125</td>
<td>0.40-4.80 mU/L</td>
</tr>
<tr>
<td>FT4</td>
<td>13.1</td>
<td>14.4</td>
<td>14.4</td>
<td>15.0</td>
<td>8.0-16.0 pmol/L</td>
</tr>
<tr>
<td>Prolactin</td>
<td>327</td>
<td>3770</td>
<td>1752</td>
<td>725</td>
<td>70-570 mIU/L</td>
</tr>
</tbody>
</table>

Her thyroid antibodies and other pituitary function tests were normal.

DNA analysis revealed mutation in exon 9 G344R (glycine to arginine) which is one of many mutations associated with the diagnosis of thyroid hormone resistance.

QUESTIONS

1. What are the potential causes of elevated FT4/FT3 and TSH?

2. How would you exclude assay interference?

3. What is a Thyrotropin-Releasing Hormone (TRH) Stimulation Test and its significance?
Case 1

DISCUSSION

Question 1

Separator gel in serum or plasma–based blood collection tubes is a barrier polymer. Initially this is present at the bottom of the tube before collection of blood. This moves upwards in-between serum/ plasma and cells upon centrifugation.

Three broad variables can affect the positioning of gel. These are manufacturer variables, laboratory variables and patient variables. Specific gravity, yield stress, viscosity, density, and tube material could be considered as factors controlled by manufacturer. Further to that, the laboratory has control over centrifugation speed, temperature and acceleration/deceleration as well as storage conditions. Some patient specific conditions like low haematocrit, increased serum density, anticoagulation therapy, contrast dye media and increased plasma proteins may cause abnormal gel flotation.

Question 2

Increased plasma/ serum density is a well-known cause for floating of separator gel. This has been well described in the literature in dialysis patients when specimens are contaminated with Citra-Lock. It is also very well described with specimens contaminated with iodinated contrast media. Case reports for floating separator gel due to increased total protein is a known phenomenon. The literature describes cases with floating gel due to high total protein in relation to plasma cell dyscrasias. However the author couldn’t find a case with abnormal flotation of the gel in patients with severe dehydration in the literature.

The published case reports are related to multiple myeloma with total protein elevation above 135 g/L. This patient presented with severe dehydration, which is evident in his blood chemistry and haematology. Supressed results due to haemolysis demonstrated a total protein of 144 g/L with an albumin result of 82 g/L. After 2 hours of admission total protein was 103 g/L (64-84) and Albumin 59 g/L (39-50) after IV rehydration. In this specimen globulin was 44 g/L (23-39) with a sum of immunoglobulin (IgG + IgA+ IgM) level of 17 g/L. In one published case with a total protein of 145 g/L, the monoclonal IgG level was 108 g/L and other cases had total proteins of 139 and 142 g/L with monoclonal-proteins IgG-κ of 89 g/L and IgA-κ of 92 g/L, respectively.

Protein elevation with severe dehydration might have caused the plasma density to increase. Follow up testing demonstrated normal serum protein and albumin. However, unlike the last two admissions his serum creatinine did not improve completely. After one and a half months his serum creatinine remained at 109 µmol/L with a eGFR of 83 mL/min/1.73m².
References


Question 1

Each day, ~1-2% percent of muscle creatine is converted to creatinine, to produce energy (ATP). Since the amount of creatinine produced per person is relatively constant and nearly all creatinine is removed by glomerular filtration, serum creatinine is a good indicator of renal function.

 Likely causes of an elevated serum creatinine include:
  • Increased production (e.g. associated with an increased muscle mass, muscle trauma)
  • Decreased excretion (e.g. reduced glomerular filtration rate, urine obstruction)
  • Methodological (e.g. interference).

Question 2

Clinically discrepant patient results should be reviewed immediately for pre-analytical (e.g. positive patient identification, collection date), analytical (e.g. method) and post-analytical (e.g. reference intervals) error/s. Past history, clinical presentation and/or treatment of the patient must also be investigated.

The patient’s creatinine (50 µmol/L), measured by the lab, was normal (45-90 µmol/L). In contrast, the patient’s POC creatinine (460 µmol/L), collected ~6 hours earlier, was significantly elevated (53-115 µmol/L) and ~9 fold higher than the lab result. The lab and POC urea results were normal (4.8 mmol/L, RR 3.0-8.0 and 4.5 mmol/L, RR 2.9-9.4, respectively), suggestive of normal renal function. POC creatinine results previously reported for this patient fluctuated significantly (337 µmol/L and 85 µmol/L) within less than 2 days, with no reported dialysis. It was noted the patient received intermittent treatment with 500mg of Droxia® (hydroxyurea) for essential thrombocythaemia. A subsequent Medchart audit of remote, primary care listed 17 patients as being prescribed hydroxyurea for treatment of throat cancer, sickle cell anaemia or essential thrombocythaemia.
Question 3

The Abbott i-STAT uses an enzymatic creatinine method with amperometric detection of oxidised hydrogen peroxide (Trinder reaction product). The manufacturer's product insert for i-STAT creatinine lists hydroxyurea (0.92 mmol/L) as “increasing i-STAT creatinine results” and recommends “use (of) another (creatinine) method”. The lab creatinine, measured using a Jaffe (alkaline picrate) method, was not affected by the drug. Abbott i-STAT operators are alerted to interference by hydroxyurea (and propofol, thiopental sodium) by a warning label near the device cartridge port (shown below).

References


**DISCUSSION**

**Question 1**

A random or even AM cortisol is of limited value in assessing adrenal function but anything under 100 nmol/L requires follow up.

Primary adrenal failure - autoimmune, infiltration by tumours, tuberculosis or adrenoleukodystrophy - is typically accompanied by mineralocorticoid deficiency with low sodium, high potassium and elevated ACTH. In this case, the electrolytes were normal.

Secondary adrenal failure - acute or chronic exposure to dexamethasone or other exogenous glucocorticoid; oral, inhaled, topical or injected into joints or tissues - leads to predominantly glucocorticoid deficiency. Pituitary insufficiency may also occur due to hypothalamic or pituitary tumours, infarction (Sheehan’s syndrome), irradiation or hypophysitis.

**Question 2**

A Synacthen test was performed.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Baseline</th>
<th>+60 minutes</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>2</td>
<td></td>
<td>&lt;10 pmol/L</td>
</tr>
<tr>
<td>Cortisol (Baseline)</td>
<td>15</td>
<td>153</td>
<td>185-625 (Baseline) nmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;530 (+60 minutes) nmol/L</td>
</tr>
</tbody>
</table>

The very low baseline cortisol and poor response to Synacthen (<530 nmol/L) with inappropriately low ACTH indicates secondary adrenal failure.

Other anterior pituitary hormones, anti-thyroid antibodies and parathyroid function should also be checked.
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Reference Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH</td>
<td>7.4</td>
<td>2.2-16.0 IU/L</td>
</tr>
<tr>
<td>LH</td>
<td>3.9</td>
<td>2.0-11.0 IU/L</td>
</tr>
<tr>
<td>Prolactin</td>
<td>284</td>
<td>60-280 mIU/L</td>
</tr>
<tr>
<td>IGF-1</td>
<td>4.5</td>
<td>9.0-26.2 nmol/L</td>
</tr>
<tr>
<td>Testosterone (LCMS)</td>
<td>2.2</td>
<td>10.0-25.0 nmol/L</td>
</tr>
<tr>
<td>Adjusted calcium</td>
<td>2.95</td>
<td>2.10-2.60 mmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>1.19</td>
<td>0.75-1.50 mmol/L</td>
</tr>
<tr>
<td>PTH</td>
<td>0.3</td>
<td>1.5-7.0 pmol/L</td>
</tr>
<tr>
<td>Anti-TG</td>
<td>&lt;0.1</td>
<td>0-4.0 IU/mL</td>
</tr>
<tr>
<td>Anti-TPO</td>
<td>&lt;0.1</td>
<td>0-9 IU/mL</td>
</tr>
<tr>
<td>TSH Receptor Ab</td>
<td>0.5</td>
<td>0-1.8 IU/L</td>
</tr>
</tbody>
</table>

Low IGF-1 suggests growth hormone secretion is impaired while, the low testosterone without elevation of LH indicates secondary gonadal failure. Hypercalcemia may be seen in adrenal failure with corresponding suppression of PTH.

### Question 3

Immune-checkpoint inhibitors (ICI) target T-cell membrane proteins - acting as moderators of the immune response (CTLA-4 and PD-1), thereby increasing the innate capacity of the immune system to target foreign proteins, including malignant cells. While checkpoint inhibitors stimulate the activity and proliferation of T lymphocytes, which then target the tumour cells, normal tissues (e.g. pituitary, thyroid and other endocrine tissues) may also be attacked. The thyrotoxicosis seen here is likely to evolve into hypothyroidism subsequently.

![Figure 1 Central and Peripheral Role of Immune Checkpoints](image)
In the absence of ICIs (shown in red, Figure 1), the B7 protein on antigen presenting cells binds to CTLA-4 on T cells to inhibit the unregulated activation of T cells against host antigens or tumour cells. In addition, PD-L1 on the tumour cell binds to PD-1 on T cells to block T cell cytotoxic action against tumour cells. 3

In the presence of ICIs (shown in green, Figure 1), anti-CTLA-4 inhibitor (e.g. Ipilimumab) binds to CTLA-4, enabling unrestricted activation of T-cells. Similarly, binding of anti-PD-1 inhibitors (e.g. Nivolumab) to PD-1 allows uninhibited activation of T-cells, with consequent attack on tumour cells. 3

Current literature indicates Ipilimumab is the immune-checkpoint inhibitor most frequently associated with hypophysitis while Nivolumab is the inhibitor most frequently associated with thyroid disorders.1,2,3

References


INTERACTIVE QUIZ

Case 4

DISCUSSION

Question 1

There are multiple causes of elevated TSH and thyroid hormones: assay interference (macro-TSH, heterophile antibodies, rheumatoid factor, biotin and anti-Streptavidin antibodies); thyroxine replacement therapy (including poor compliance); drugs (e.g. amiodarone, heparin); TSH-secreting pituitary adenoma; and thyroid hormone resistance.

Question 2

Loh et al. has proposed an algorithm to investigate assay interference which includes:

- Perform serial dilution
- Measurement on alternative platform
- Heterophile blocking reagent/ tube studies
- Measure rheumatoid factors
- Incubation of patient serum with a presumably interference-free hypothyroid sample/ polyethylene glycol (PEG) precipitation
- Gel filtration chromatography

The consistent results across four analytical platforms were interpreted as essentially excluding assay interferences. The patient was not on thyroid medications, amiodarone or heparin.

Question 3

TRH is a hypothalamic tripeptide hormone stimulating the production and release of TSH by the anterior pituitary gland. TRH stimulation test is to assess whether the elevated T4 & T3 with normal or elevated TSH is due to thyroid hormone resistance or from a TSH secreting pituitary adenoma (TSH-oma) or to confirm congenital central hypothyroidism in infants. An increase in α-subunit or macroadenoma on MRI (80%) may also be seen in TSH-oma.

A normal response in an adult is indicated by the increase of TSH of 5-30 mU/L at 20 minutes. Increased prolactin may also occur following TRH and confirms biological response to TRH.

A delayed response with the TSH concentration lower at 20 than 60 minutes may be seen in hypothalamic dysfunction.
An absent response in TSH is consistent with TSH-oma. Response may be reduced by glucocorticoids, L-dopa, bromocriptine and fluoxetine whilst response may be enhanced by metoclopramide, oestrogens, theophylline and sertraline. 

References


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Diagnostic Improvement for Diabetes Insipidus?


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Previously employed as Principal Scientist (Biochemistry) at The Royal Children’s Hospital, Melbourne, Sue recently relocated to South Australia to a balanced academic role at Flinders University. Her current research focus is point-of-care testing for acute, chronic and infectious diseases in rural and remote primary health services in Australia.

Fenske et al. (2018) reports a reliable diagnostic test for diagnosis of diabetes insipidus (DI) as an alternative to the historical indirect water deprivation test.¹

In DI, impaired salt and water homeostasis results from either: a) a deficient secretion of hypothalamic-pituitary arginine vasopressin (AVP), known as central DI, or b) a failure of the kidney to respond to AVP, known as nephrogenic DI. The inability to concentrate urine leads to excess fluid loss and increased water intake (hypotonic polyuria) by the patient to prevent dehydration. Treatment includes administration of an AVP analogue.²

Whilst the clinical presentation of primary polydipsia (excess fluid intake in the absence of physiological stimuli to drink) may mimic DI, the underlying mechanism (commonly psychiatric disorders or medications) and the treatment required (e.g. fluid restriction) is different.²

Despite having low diagnostic accuracy and requiring prolonged medical supervision, the water deprivation test remains the standard reference method differential diagnosis of the polydipsia-polyuria syndrome (PPS), which measures maximum urine osmolality during prolonged oral fluid restriction and the renal response to administered synthetic vasopressin (desmopressin) remains the standard reference method.³

Brief Overview
Fenske et al. compared the diagnostic accuracy of the indirect water deprivation test with an alternative method, the direct detection of a precursor-derived surrogate of AVP, plasma copeptin.¹

In this study, 156 patients with confirmed hypotonic polyuria were recruited from 11 tertiary medical centres and tested on separate days using a) 17-hour fluid restricted indirect water deprivation test with the collection of multiple plasma and urine samples and desmopressin administration and b) a 3 hour, 3% hypertonic saline infusion test, with plasma copeptin measured when the plasma sodium level had increased to at least 150 mmol per litre post infusion. Final diagnosis of 144 patients was reported as 57% primary polydipsia (n=82), 41% central DI (n=59) and 2% nephrogenic DI (n=3). Of the 59 patients diagnosed as central DI, 61% were considered compete (n=36) and 39% partial (n=23).¹
The paper concludes the hypertonic saline-simulated copeptin measurement is diagnostically superior to the indirect water deprivation test in distinguishing central DI from primary polydipsia.¹

**Salient Points of Interest**

The overall diagnostic accuracy of DI was significantly (p<0.001) higher for the hypertonic saline infusion test with a copeptin cutoff of > 4.9 pmol/L (96.5%) than the indirect water deprivation test (76.6%).¹

The diagnostic accuracy of the hypertonic saline infusion test (95.2%) was also superior (p<0.001) to the indirect water deprivation test (73.3%) when patients with partial central DI were compared to those with primary polydipsia.¹

Whilst a predetermined hypertonic saline infused copeptin cut-off of 4.9 pmol/L was 93.2% sensitive and 100% specific in differentiating primary polydipsia and central DI, a copeptin level of 6.5 pmol/L retrospectively offered better diagnostic accuracy (97.9% sensitivity and 100% specificity).¹

When compared for convenience and comfort, patients rated the median overall burden of the water deprivation test (6) higher than the hypertonic saline infusion test (3) using a visual-analogue scale.¹

Sixteen adverse events were reported by the study, with a higher proportion attributed to the hypertonic saline infusion test (n=9) compared to the water deprivation test (n=7).¹

**Reviewer’s Comments**

The study validated pre-determined cut-off for hypertonic saline infused copeptin of 4.9 pmol/L and provided evidence for this test in accurately identifying subtypes of DI using a prospective, international, multicentre study in 144 patients.¹

Of significance, the authors acknowledge a potential overestimation of the diagnostic performance of the water deprivation test associated with an “incorporation bias” due to the simultaneous evaluation of the accuracy of the indirect water deprivation test and the use of those results in reaching a final diagnostic decision.¹

Although the convenience and comfort of the test was ranked highly by patients, the higher rate of adverse effects with the hypertonic saline infusion test, particularly in female patients, cannot be overlooked. Whilst the study authors acknowledge that intensive plasma sodium monitoring was required to balance increasing plasma sodium within hyperosmotic ranges, while preventing marked increases, critical reviewers limit the utility of this test utility due to the possible induction of congestive heart failure in high-risk patients by the saline infusion required to stimulate copeptin.¹⁴⁻⁵

With the limitations the study considered, the use of copeptin measurement after hypertonic saline infusion may eventually replace the water-deprivation test to precisely define the cause of polyuria.⁴

**References**


Diagnosis and management of anabolic androgenic steroid use


This mini-review looks at the non-medical use of anabolic steroids to increase muscle mass and enhance athletic performance. The field is traced back to Charles Edouard Brown in the 1870s who reported increased energy and vigour after injecting himself with extracts of animal testes that probably contained trace amounts of hormone.

The extent of use today is not known, although some estimate that 1-5% of men in the general population may have used these drugs at least once in their life. More sustained use is more common in athletes and bodybuilders including those with “bigorexia”, an obsession with having pathologically large muscles. Men outnumber women 50:1.

There are different ways that people can increase circulating anabolic steroid concentrations apart from taking testosterone itself. This includes injecting hCG which has LH activity, increasing LH secretion with Clomiphene or aromatase inhibitors, taking testosterone precursors or synthetic anabolic steroids. These drugs are often used in high doses and different combinations to minimise side effects. One example is men taking hCG along with anabolic steroids to reduce testicular atrophy.

All of these drugs are associated with numerous side effects including testicular atrophy, breast development, infertility, behavioural and mood changes, suppressed HDL, liver damage (alkylated testosterone derivatives only) and erythrocytosis. Reduced fertility can be a problem in men who have used anabolic steroids in the past. If the duration of use was less than 12 months, it is likely there will be spontaneous recovery over 3-6 months. If the use was more prolonged, treatment with Clomiphene or hCG might be needed to restore testicular function.

Detection of anabolic agents is difficult. One method that is currently popular is the “biological passport” where a group of steroids and other hormones is measured at baseline, and repeatedly through an athlete’s career. This approach avoids some of the problems associated with the wide inter-individual variation of these compounds but has several limitations. One is that the assumption that the baseline sample is drug-free - this may be wrong. And there are the usual problems with specimen and data security. Another problem is that some more sophisticated drugs may not perturb the hormones that are measured.

Outside the athletic arena, the simple tests that might be helpful if anabolic steroid use is suspected are HDL, SHBG, testosterone, LH and FSH. HDL and SHBG may be suppressed. All agents tend to increase testosterone, except for testosterone analogues. LH and FSH are suppressed by anabolic steroids and HCG but are increased by aromatase inhibitors and clomiphene.
# NEW MEMBERS

## Associate
- Mr Jonathan Bush NSW/ACT
- Mr Hitendra Modi NSW/ACT
- Mrs Marsha De Bono NSW/ACT
- Ms Lisa Kerr NSW/ACT
- Ms Monika McShane NSW/ACT
- Mrs Teresa Hewlett NSW/ACT
- Ms Jade Walsh NSW/ACT
- Ms Moira Rooney NSW/ACT
- Mrs Sahar Etesam QLD
- A/Prof Christian Cobbold QLD
- Mr Chi Wai Leung QLD
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- Dr Roslyn Malley QLD
- Mr Daniel Masters QLD
- Mr Edwin Sharma QLD
- Mr Roshen Wijayagunarate QLD
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- Miss Jasmina Nguyen QLD
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- Miss Rachelle Liwayan QLD
- Mr Annadurai Ramachandran QLD
- Ms Marie Van Drimmelen New Zealand
- Mr Jeffrey Chan Hong Kong
- Dr Cheuk Lun Lee Hong Kong
- Dr Wan Norlina Wan Azman Malaysia
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## Student Affiliate
- Mrs Shahad Albannay VIC
- Mr Lei He NSW/ACT
- Mr Alexander Wurr NSW/ACT
- Miss Maya Esperanza Jennings-Martinez VIC
- Miss Alicea De Santis VIC
- Miss Alicea De Santis VIC
- Mr Vinu Parakkal VIC
- Miss Yohannah Smolders WA
- Mr Zeyad Ibrahim WA
- Mr Jake Ashton WA
- Ms Annabella Yee WA
- Dr Thivanka Manawadu New Zealand
- Mr Perez David Spain
AUSTRALASIA

AACB 57th Annual Scientific Conference
15 – 17 October 2019
Adelaide, SA
Website: https://www.aacb.asn.au/professionaldevelopment/annual-scientific-conference

Australian Society for Medical Research National Scientific Conference
20 – 21 November 2019
Fremantle, WA
Website: https://asmr.org.au/asmr-nsc/

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Website: http://africamedlab2019.org

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Dubai, United Arab Emirates
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Website: https://www.aacc.org/meetings-and-events/conferences/poct-boot-camp

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