Issue 4

pathology@viapath

INSIDE THIS ISSUE

Message from the Editor

Welcome to the fourth edition of "pathology@viapath" and thank you for your positive feedback on previous editions. It is good to know that the work we have focused on has been interesting and informative but if you have missed any previous publications, don't worry, they've been posted on Viapath's website at www.viapath.co.uk/newsletters

I have noticed that there is a common trend towards themed months. January is no exception, so I was not surprised to learn that some of my colleagues participated in dry January. In this edition, some of the benefits they will have reaped from this are explored.

This issue also discusses some important medical advances. I find it fascinating that some of the most important were discovered by accident. One such example is the treatment of jaundiced babies. The story so fascinated the BBC that they have re-enacted the events with Viapath's help. This is quite different to the history of dissection. Since very early times, dissection has changed little, so is now in need of serious review in order to improve techniques. In this issue, the discovery of a new species of *Candida* which is posing a new threat to seriously ill patients is also highlighted and if you have had kidney stones and wondered what they look like, then turn to the illustrations.

Viapath is involved with many aspects of pathology, so if there are any topics that you would like covered in future editions of pathology@viapath, please get in touch!

The Benefits Of Dry January

The problems of alcohol misuse.

Did you know? 50% of murders are committed by people whilst under the influence of alcohol

More than 90% of the population in the United Kingdom consumes alcohol with an estimated 75,000 individuals being alcohol dependent. It is estimated that potentially up to 20% of hospital admissions are related to alcohol excess. Drink-related deaths and alcoholic liver disease rates have more than doubled in the past 20 years. A high proportion of accidents both inside and outside the home are associated with subjects with high blood alcohol concentrations. Approximately 50% of murders are committed by people whilst under the influence of alcohol.

Detection of alcohol misuse

Detection of harmful alcohol intake relies on a combination of self-report questionnaires (CAGE – Cut down, Annoyed, Guilty, Eye-opener and AUDIT – Alcohol Use Disorders Identification Test) and biochemical markers. Most individuals with alcohol disorders tend to under-report when using the CAGE and AUDIT questionnaires. Measurement of ethanol itself in blood or urine detects consumption of alcohol in the previous 12-36 hours but cannot give any information about chronic intake. Urine ethyl glucuronide testing widens the time window to 48-72 hours and is used at Viapath's laboratory at King's College Hospital (KCH) as part of the monitoring of patients on the liver transplant waiting list who have a history of alcohol misuse. Other markers such as gamma-glutamyl transpeptidase (GGT) and Mean Cell Volume (MCV) are increased in chronic alcohol misuse but have poor specificity. GGT is raised in individuals with any form of liver disease and in people who are overweight or have diabetes mellitus – an increasing proportion of the population. Carbohydrate deficient transferrin (CDT) is the term given to forms of transferrin with less carbohydrate side-chains (zero or two) compared with normal individuals (three, four or five). CDT results from the direct effects of alcohol on the enzymes involved in the creation or destruction of the carbohydrate side-chains on the transferrin

molecule rather than alcohol's effect on organs such as the liver. CDT reflects alcohol consumption in the previous one to two weeks rather than the one to two days for ethanol measurements; similar in a way to glycated haemoglobin versus blood glucose in diabetes. Viapath's CDT service was described in the third edition of the Newsletter. Please click here to read the article

The Driver & Vehicle Licensing Agency (DVLA) and alcohol

During the 1990s it became obvious that there was an increasing problem with drink driving and in particular with individuals who were either significantly over the legal limit of alcohol for driving or were serial offenders (High-risk offenders – HROs). HROs are individuals who were more than twice the drink-drive limit for blood or breath alcohol or had been disqualified more than once for driving under the influence of alcohol. To regain their licence at the end of a driving ban HROs have to undergo a medical examination and blood test to exclude alcohol and drug problems.

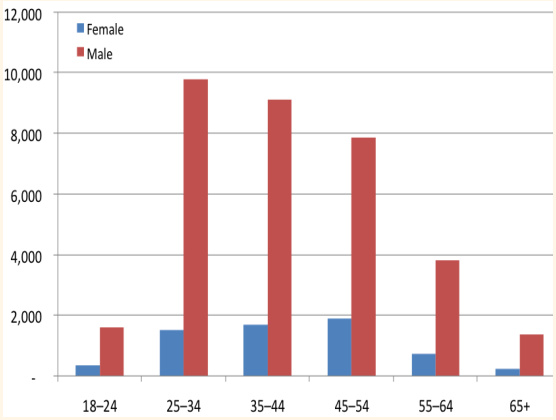

Fig 1: Age and gender distribution of HROs 2015/16

In an average year approximately 25,000 HROs seek the return of their driving licence. In 2008 the Department of Transport (DoT) began to realise that the biochemical markers GGT & MCV, in use for the assessment of HROs seeking the return of their driving licences, were often abnormal in individuals who were abstinent from alcohol. The DoT commissioned a study at KCH and South London & Maudsley Hospital (SLaM) with Professors Sherwood (KCH) and Wolff (Institute of Psychiatry) that showed that CDT had greater specificity than GGT or MCV in HROs (DoT Road Safety Reports 103/104 published January 2010 and available on the DoT website). This was particularly the case in subjects who were overweight, had diabetes or chronic illnesses such as arthritis or rheumatism. CDT was adopted in 2012 as the sole biochemical marker in such cases within England, Wales and Scotland (Northern Ireland is not included). Viapath has carried out CDT testing for the DVLA since 2013 testing more than 90,000 individuals using capillary electrophoresis. The typical HRO is male between 25 and 55 years of age (Fig 1: Age and gender distribution of HROs 2015/16.)

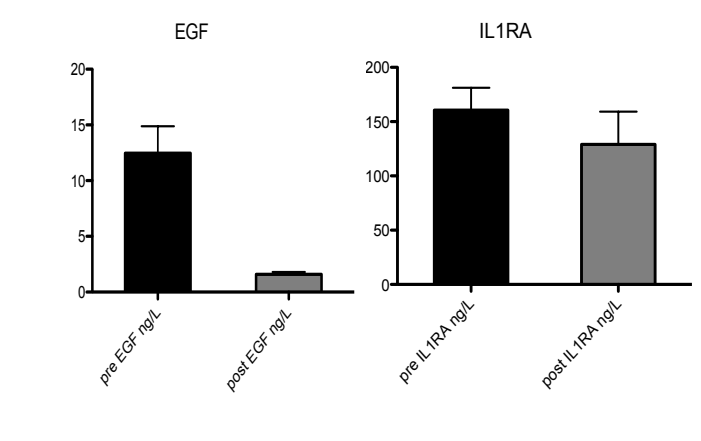

Fig 2: Inflammatory cytokines in the Dry January Study

The Dry January Study

In January 2015, Viapath supported the participation of KCH and University College London (UCL) in a study which was part of the 'Dry January' national campaign. This was aimed at assessing the benefits of abstinence for one month on general wellbeing in 94 subjects consuming excess alcohol and in the possible mechanisms of the physiological harm due to alcohol excess. CDT was used as in indicator of adherence. Basic parameters including physical examination, weight, blood pressure, routine biochemistry and haematology tests and liver stiffness (by transient elastography) were measured at the beginning and end of the study period. The most striking features of the results were reductions in weight, blood pressure, insulin resistance (assessed by the Homeostasis Model Assessment score), liver stiffness and pro-inflammatory cytokines and chemokines (epidermal growth factor [EGF], vascular endothelial growth factor [VEGF] and the interleukins [IL-2, IL-6, IL-8]. These reductions were independent of changes in lifestyle factors – no association was found between reduction in these biological variables and changes in diet, exercise or smoking. At 6-8 month follow-up, a significant reduction in alcohol consumption was noted from baseline using the AUDIT score. This study suggests that even short-term periods of abstinence have significant benefits to health.

Professor Roy Sherwood
Scientific Director, Viapath at King's College Hospital
Professor of Clinical Biochemistry at King's College London

References:

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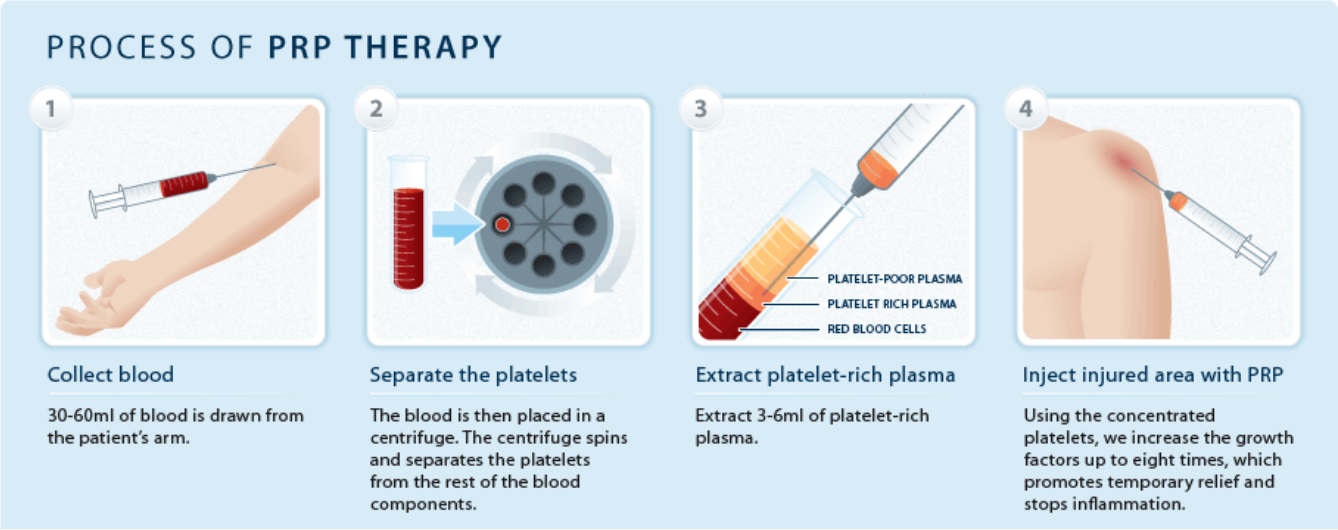
Platelet Research Project Impacts Clinical Practice Of Top Cosmetic Dentist To Directly Improve Patient Care.

Platelets are circulating, anucleate cytoplasmic fragments of their parent cells, the megakaryocytes, which are confined to the blood cell manufacturing compartments inside bones. Each megakaryocyte produces between 2000 – 3000 platelets which are then released into the bloodstream. Whilst platelets tend to be considered as having their primary role in haemostasis, the process of blood clotting, they are intricately involved in the initiation of wound healing. Indeed, haemostasis can be considered as the first stage of blood vessel healing. Despite being mere cell fragments, platelets have complex, specialised structure and physiology in order fulfil their dual role.

A number of specialised structures are present in platelet cytoplasm, the most abundant of which are the α-granules. These granules contain an array of molecules essential to both haemostasis and wound healing. Platelets activated by the clotting process release α-granule contents into the immediate vicinity of the wound and the clot to concentrate vital molecules for haemostasis and wound healing. Some of the molecules are termed growth factors as they promote healing processes, and others, such as fibronectin directly take part in tissue repair.

How can we harness the wound healing properties of platelets in the clinical setting?

It is possible to concentrate platelets from patient blood samples by removing the red and white blood cells, leaving behind the platelets suspended in the fluid that transports the cells along blood vessels, the plasma. This is termed platelet-rich plasma (PRP) and recent years have seen an increase in the use of applying the patient's own PRP to wounds to promote soft and hard tissue regeneration and speed up healing. Using the patient's own cells means rejection is not a problem, it is cheaper and safer than artificial growth factors, and matches natural healing mechanisms. Patient's PRP has been used in treatment of chronic skin and soft tissue ulcers and many surgical and dental settings. The PRP can be activated to ensure growth factor release.



How can Viapath help?

Platelets have a short lifespan of 8-10 days in the body and are viable for only 5 days when stored for transfusion purposes. There are few data on PRP stability when stored for promoting tissue repair and patients often have blood taken daily to generate fresh PRP. The Haemostasis & Thrombosis Laboratories at St. Thomas' Hospital were recently approached by one of the UK's pioneers in use of PRP in dentistry, Dr Mitra Najafi of Stardent, to investigate platelet and growth factor stability in stored PRP to ascertain whether she could reduce the frequency of bleeding her patients.

What did we do?

Dr Gary Moore, Consultant Scientist for Haemostasis & Thrombosis, designed a study that stored (his own) PRP under a variety of conditions. The platelets were tested daily for platelet numbers and structural integrity, functional responses to activation, and the amount of growth factor released during activation. The functional testing involved activating the PRP with collagen because that is what Dr Najafi employs in her clinical practice.

The expertise of numerous colleagues was needed to complete the project, with Robert Archer and Kerri Brown testing platelet integrity and function, and James Maloney, Kasia Mayger and Elaine Bromidge working on a new assay to measure the released growth factor.

The testing was done over an eight day period and showed that although platelets deteriorate over time, as was

anticipated, they retain significant growth factor availability for up to 5 days when stored in a particular type of container at room temperature, and intermittently mixed to reduce spontaneous aggregation (platelets sticking to each other).

PRP is used in a non-surgical anti-ageing procedure called the Vampire Facelift.

Clinical outcomes

A detailed report was submitted to Dr Najafi who was then able to alter her clinical practice and reduce frequency of bleeding and PRP generation based on objective evidence. As well as dentistry, Dr Najafi uses PRP in a non-surgical anti-ageing procedure called the Vampire Facelift because it first involves taking the blood from the patient and removing the red and white cells before undertaking multiple injections (vampire bites!) of the PRP into the skin of the face to promote tissue repair and rejuvenation. It is also more palatably referred to as the Natural Facelift as the platelet-derived growth factors regenerate tissue by recruiting the patient's own stem cells.

Scientific achievements

The Diagnostic Haemostasis & Thrombosis Laboratory team were able to combine Viapath's core professional values of innovation, collaboration and expertise to design and deliver a project of sufficient rigour to inform clinical practice of a service user. The study was considered sufficiently useful to the wider scientific and clinical communities to warrant submission to an international, peer reviewed journal and was published in October 2016 with the following citation:

Moore GW, Maloney JC, Archer RA, Brown KL, Mayger K, Bromidge ES, Najafi MF. Platelet rich plasma for tissue regeneration can be stored at room temperature for at least five days. *British Journal of Biomedical Science* 2016 Oct8: 1-7. [Epub ahead of print].

For more information on the study, details about the department's platelet diagnostics or to receive a copy of the paper, please contact:

Dr Gary Moore

Consultant Biomedical Scientist, Diagnostic Haemostasis and Thrombosis Laboratories, St. Thomas' Hospital
Telephone: 020 7188 0814
Email: gary.moore@viapath.co.uk

Other publications relating to platelets:

Posters:

Gurney DA, Moore GW, Rangarajan S. Platelet glycoproteins: predictors or progression markers in cardiovascular disease? International Society on Haemostasis & Thrombosis 2007, Geneva.

Mitchell MJ, McCormick Á, Maloney JC, Moore GW, Austin SK. A reduced response to TRAP-6 in platelet aggregometry studies is not usually due to a PAR-1 receptor defect. International Society on Haemostasis & Thrombosis 2015, Toronto

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Platelet Aggregometry Testing: A Potential Move Towards Semi-Automation

What are platelets & why are they important?

Platelets (also occasionally called thrombocytes) are tiny disc shaped components within the blood that assist in clot formation following damage to the inner lining (endothelium) of the blood vessels. The term platelet arose in the early 20th century following the observation that the structure was 'plate like'. Although commonly termed a blood cell, mature platelets are not strictly cells as they contain no genetic material and are fragments of a parent cell.

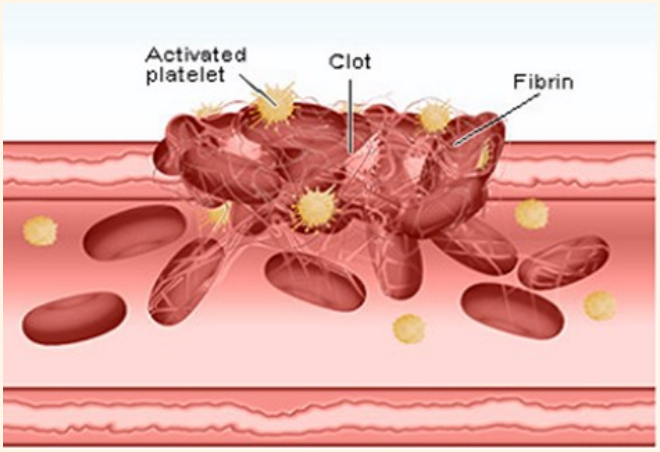


Fig 1: Wound healing

Human platelets play a central role in primary haemostasis (the prevention of bleeding). Damage to the endothelial cells of the blood vessel invokes the release of potent stimulators of platelet activation. Activation of platelets results in a structural change from discoid to a larger shape of much greater surface area containing many cytoplasmic protrusions. The activated platelets adhere and aggregate forming a haemostatic plug that occludes the site of injury preventing further blood loss.

In addition to haemostasis, platelets play a role in inflammation and in the promotion of atherosclerosis and wound healing.

The different functions of platelets can be detected by a wide range of tests. Diagnosis of inherited or acquired platelet dysfunctions is required to identify patients at risk of bleeding.

What platelet tests are currently available?

Within Viapath's Diagnostic Haemostasis and Thrombosis Laboratory, the tests of platelet function available include the platelet function assay (PFA) using the PFA-100; light transmission platelet aggregometry (LTRA) using the PAP8 -E aggregometer, measurement of ATP release from platelet dense granules by lumiaggregometry using the Chrono-log analyser, quantitation of platelet nucleotides by luminescence and assessment of surface platelet glycoprotein expression by flow cytometry. The tests are used for the diagnosis of haemostatic disorders and managing patients with platelet and haemostatic defects.

What is platelet aggregometry?

Central to the diagnosis of platelet disorders is measurement of aggregation by light transmission aggregometry (LTRA) in response to specific platelet agonists. The agonists activate platelets via different mechanisms so that we can tell which area of function is compromised. LTRA allows for the diagnosis of specific receptor/pathway dysfunction by adding single agonists to platelet rich plasma in vitro and observing the aggregation in real time. Platelet aggregation in response to adenosine-diphosphate (ADP), arachidonic acid (AA), thrombin receptor activator peptide (TRAP), collagen, thromboxane analogue (U46619) and epinephrine (EPI) is routinely measured.

The platelet aggregometer works on the basic principle of light transmission. Platelet poor plasma (PPP) is prepared in parallel to platelet rich plasma (PRP) from each patient undergoing testing. Light transmission is set at 100% using PPP. PRP is set at 0% light transmission. As platelets aggregate in response to the agonist added, the light transmission of the sample increases. The nature and extent of aggregation is analysed and interpreted to record the presence of a specific platelet defect.

- Platelet rich plasma is produced using gentle centrifugation
- Sub-samples of platelet rich plasma are stirred in a cuvette between a light source and a photocell
- Agonist addition induces platelet shape change and aggregation
- Aggregation is viewed as an increase in light transmission

Current assay setup for LTRA within Diagnostic Haemostasis at Viapath

- LTRA is currently performed manually using the PAP8-E aggregometer.

- Platelets must be tested within 4 hours of collection as they are still 'alive'.
- The maximum capacity on a given day is 3 patients and 1 control. Currently the assay is performed once a week.
- One member of staff is required for a full day to run LTRA. As the process is manual it is not possible to set up anything else simultaneously.
- The member of staff must be highly trained, only a limited number of staff can carry out the procedure.
- Experienced scientific and medical staff are required to interpret the complex result patterns.

Why is a semi-automated method required?

A semi-automated method would be expected to increase sample throughput and allow more members of the laboratory team to perform the procedure.

Outline of the study to compare manual versus semi-automated method of LTRA:

Viapath's Diagnostic Haemostasis Laboratory is currently evaluating a semi-automated method of platelet aggregometry and comparing it with the current manual method. The methods are employed in parallel to assess consistency of results.

The evaluation aims to determine if the implementation of the Sysmex CS2400i platelet aggregometry method would increase the output of platelet testing, increase reliability and free up staff time. A further aim is to assess if staff find the method more user friendly.

Fig 1: PAP8-E (Manual)

Fig 2: Sysmex CS2400i (Semi-automated)

Overview of the semi-automated method versus the manual method:

- The semi-automated method runs one sample at a time versus 3 patients and one control simultaneously via the manual method.
- Manual testing means patient phlebotomy must be co-ordinated; the semi-automated method should provide more flexibility and allow samples to be run consecutively.
- Agonists must be prepared manually for both methods. Once on board the analyser, agonists are added to the PRP automatically minimising operator input. Agonists are added manually to every tube of PRP using the current method.
- The semi-automated method does take extra time to perform a full panel of agonists compared to the manual method however the operator is free to perform other tasks during this time.
- Aggregation profiles cannot be viewed in real time using the semi-automated method and must be assessed after the run has finished. Decisions regarding repeat runs must be made at this time.

Expected outcomes of the evaluation

- To establish agreement between the current and new testing platform.
- To test how long the reagents remain stable on board the analyser.
- To check the lowest PRP count that will produce aggregation.
- To test how long PRP is viable for testing.
- To establish the maximum throughput of samples in a working day.
- To increase efficiency and throughput of platelet testing and provide more flexibililty to the clinicians and patients.
- The study is being conducted in collaboration with laboratories at St Barts and the London NHS Trust and Bristol University Hospitals Trust with a view to publishing the results and validating the method for use by the wider diagnostic community.

For more information about the automation of platelet aggregometry, please contact:

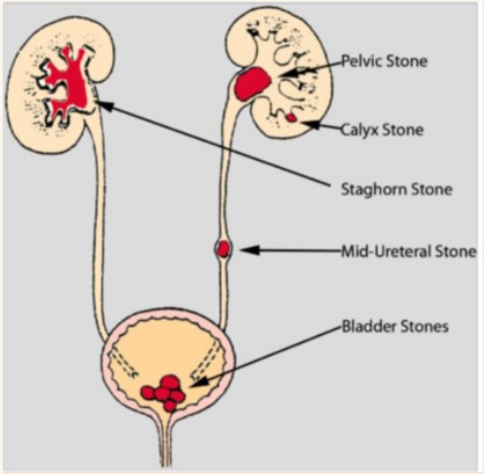
Dr. Áine McCormick: aine.mccormick@viapath.co.uk

The Stone Service

Facts and figures

Nephrolithiasis (stone formation in the kidneys) is a recurrent condition with significant morbidity. While symptomatic episodes require appropriate treatment, prophylactic work up to prevent recurrence is of great importance.

- Kidney stones are found in as many as 1 in 10 people
- Kidney stones most often affect people aged 30-60
- Stones are more common in men than women



What causes stones?

The function of the kidneys is to remove waste products from the blood. If the concentration of waste products is significantly increased, the waste products can crystallise in the kidneys and eventually form hard stones. Stones can form anywhere along the urinary tract.

Kidney stones can be caused by a variety of things, including dehydration, diet, medications or infections. Rare genetic conditions that predispose to stone formation include primary hyperoxaluria and cystinuria amongst others.

Recurrence of kidney stones is very common but can be easily prevented with appropriate investigation and management. Lifestyle and dietary advice can help to reduce the risk of recurrence.

Treatment

Treatment may consist of surveillance, breaking up the stones using shock waves (lithotripsy) or surgery with ureteroscopes where the stones are broken up with a laser. These do not involve any surgical cuts to the skin. For larger stones, a telescope can be placed into the kidney remove the stone. This is known as percutaneous nephro-lithotomy or PCNL. Open surgery is very rarely needed. Further information about the treatment of stones, can be found on Guy's and St Thomas' NHS Foundation Trust website:

http://www.guysandstthomas.nhs.uk/our-services/urology/specialties/stone-unit/patients.aspx

Why analyse stones?

Determination of the chemical composition of stones aids investigation of the pathophysiology of stone formation, and will help to decide treatment modality and prevent recurrence.

Composition	Frequency (%)	Causes, Mechanisms and Prevention
Calcium Oxalate or Calcium Phosphate	70-80	• Hypercalciuria • Low urine volume • Hyperoxaluria • Hypocitraturia • Hypomagnesuria • Low urinary pH
Uric acid (can be combination with Ca Ox)	10-15	• Low urine pH • Carbonic metabolic acidosis • Hyperuricosuria • Low urine volume
Magnesium ammonium phosphate (struvite)	10-15	• Urine Infection
Cystine	<1	• Cystinuria
Drug-induced stones	<1	• Loop diuretics • Chronic anhydrase inhibitors • Abused laxatives • Anti-retroviral therapy • High dose sulfadiazine • Mediations containing ephedrine • Ciprofloxacin • Magnesium trisilicate

How do we analyse stones?

At Viapath, stones are analysed using fourier-transformed infrared (FT-IR) spectroscopy, which is a specific, rapid and versatile method. Infra-red radiation causes atomic vibrations and consequently energy absorption, which results in different absorption bands for different chemical compositions. Scans are then interpreted using in house calibration models and spectral libraries.

Images of kidney stones passed or removed from patient

Image	Composition
	100% Uric Acid
	40% Calcium Oxalate, 60% Calcium Phosphate Removed by Pyelithotomy
	70% Calcium Oxalate, 30% Calcium Phosphate
	100% Calcium Phosphate in the Form of Brushite

How can we help?

The Stone Unit based at Guy's Hospital is one of the largest in the country. It has state of the art treatment options including a dedicated operating theatre for patients with stones. Viapath offers a stone analysis service in Reference Chemistry which is complemented by metabolic investigations in the Inherited Metabolic Disease Laboratory (urine amino acids for cystine, ornithine, arginine and lysine) and genetic/molecular investigations in the Purine Research Laboratory (APRT/HPRT mutations) within Biochemical Sciences. The Genetics Laboratory based at Guy's Hospital offers cystinuria genetics.

Stone samples in plain universal containers can be sent to Viapath's Reference Chemistry Laboratory at St. Thomas' Hospital. A detailed analysis report is provided and turnaround times are 7 working days. The laboratory can also be contacted for further clinical advice and guidance on the emails below.

Contact Details

Reference Chemistry Laboratory at St Thomas'

4th floor, North Wing, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH

Email: Zehra.Arkir@viapath.co.uk or Gillian.Richards@viapath.co.uk

References

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NHS Choices, 2016. Kidney Stones. Click here [Accessed 18/01/17]

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The Birth Of Phototherapy

From The Chance Discovery In The 1950s That Sunlight Exposure Treats Jaundiced Newborns To The Successful Use Of Phototherapy Treatment Today

Jaundice, also known as icterus, is a term used to describe a yellowish tinge to the skin and sclerae (the white part of the eye) that is caused by an excess of bilirubin in the blood (hyperbilirubinaemia).

Up to 80% of normal newborn babies become clinically jaundiced sometime during the first week of life. For the majority of cases, there will be no pathological effects, but these babies do need to be monitored because bilirubin is potentially toxic to the central nervous system.

The use of phototherapy is an established and widely used treatment for newborn babies with ***severe*** jaundice; but how does it work?

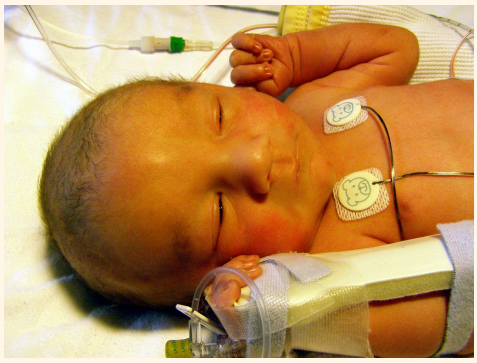

Fig 1: Baby with jaundice

Biochemistry of jaundice

Bilirubin is a normal breakdown product of red blood cells (it is derived from haem). Free bilirubin is toxic and must be transformed (conjugated) by the liver so it can be removed from the body.

A normal healthy full-term baby may be jaundiced from days 2-8, and for premature babies, jaundice may be present from days 2-14. This 'physiological' jaundice is extremely common and often does not require treatment; however if bilirubin concentrations are very high then treatment may be necessary. 'Physiological jaundice' results in an unconjugated hyperbilirubinaemia and is usually caused by liver immaturity, or may sometimes be seen in babies who are exclusively breast fed.

Any jaundice appearing at <1 day of age or persisting after 14 days is likely to be pathological. Pathological hyperbilirubinaemia may be caused by a number of conditions, such as haemolytic disorders, congenital hypothyroidism and some inherited metabolic diseases.

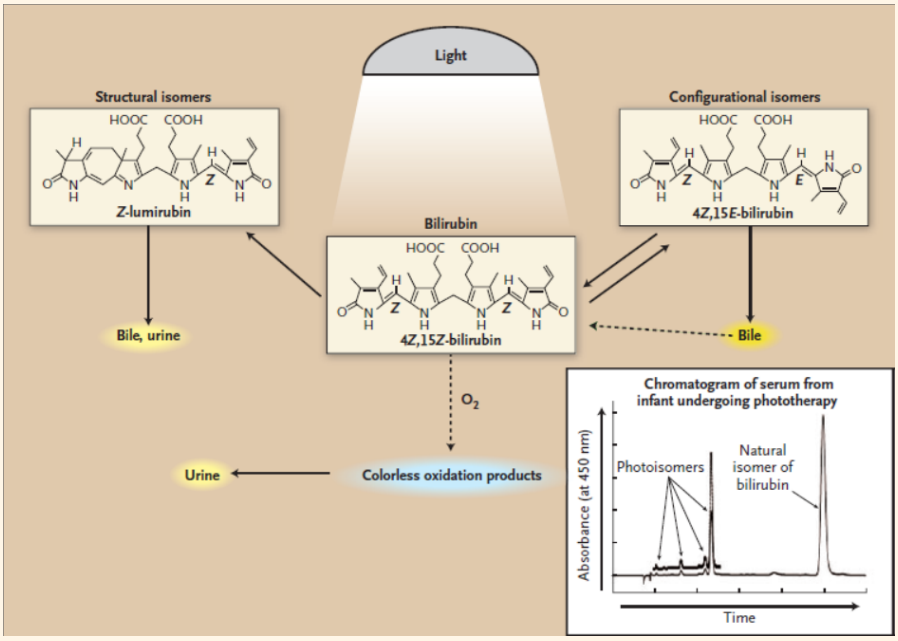

Fig 2: The mechanism of phototherapy

What is phototherapy?

Phototherapy uses blue light to change the shape and structure of bilirubin to forms that can be excreted. It is a common misconception that UV light is used for phototherapy, but it is not: Blue light, at a wavelength of 460-490 nm, is directed onto the baby's skin where it is absorbed to convert bilirubin to photoisomers and oxidation products for excretion. There are several forms of phototherapy available and depending on the severity, this may be a glowing blanket that parents can wrap around their baby at home, or a crib with multiple lights used in the hospital.

History of phototherapy

The effect of light on jaundice in newborns was first discovered in the 1950s at Rochford General Hospital, Essex, with a little bit of science and a lot of luck!

Sister J Ward was in charge of the Premature Baby Unit at the hospital and believed in the benefits of fresh air and warm sunshine over the confines of a stuffy incubator. She would take babies outside on warm summer days, bringing them in quickly before the consultants were doing their ward round. During one of these rounds, a Dr Dobbs noticed a triangular patch of skin on one of the jaundiced babies which was much more yellow than the surrounding skin. Dr Dobbs asked about this, to which Sister Ward replied she thought it might be an effect of the sun. Upon further interrogation, she confessed that she'd been taking the babies outside, and it was actually that the baby was

less yellow than before: the triangular patch was where the sheet had covered the baby. This observation was not followed up; the baby got better and was discharged home.

Fig 3: Baby receiving phototherapy

On a sunny day a few weeks later, blood was sent to the laboratory for another jaundiced baby. The serum was analysed for bilirubin and the result reported was much lower than expected, and did not fit with previous analyses. The biochemist in the laboratory, Mr Perryman, apologised to Dr Dobbs saying that the sample had unfortunately been left on the windowsill and forgotten about. Mr Perryman had re-measured the bilirubin and it was even lower than before. Mr Perryman also noticed the serum sample was no longer the yellow colour associated with jaundice, but had gone green.

The penny dropped… Light seemed to affect bilirubin… Further work was undertaken and it was soon established that blue light seemed to affect bilirubin concentrations; the light only affected *unconjugated* bilirubin and the green colour was due to the presence of biliverdin, a conversion product of bilirubin thought to be harmless to brain cells. Back in the Premature Baby Unit, jaundiced babies were cautiously allowed outside for exposure to sunlight, and their jaundice disappeared faster than if they were left inside the ward.

Recreating the history

The Blood Sciences Laboratory at Viapath was recently approached by the BBC and asked if it would be possible to recreate Mr Perryman's discovery. Serum from jaundiced babies was collected and taped to the window in direct sunlight. After only 24 hours in the sun, the bright yellow jaundiced serum had turned green, indicating the conversion of bilirubin to biliverdin. Bilirubin concentrations were also measured over the following days and it was shown that there was a significant decrease in the bilirubin concentration even at day 1.

Our work is scheduled to be broadcast on the BBC One Show in March 2017.

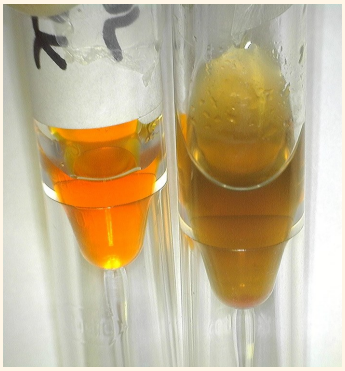

Fig 4: Serum sample 24 hours after contact with direct sunlight

Viapath's Services

In the Blood Sciences Laboratory at Viapath, we offer total bilirubin and conjugated bilirubin measurements to aid in the diagnosis of jaundice for children and adults.

Please contact the Blood Sciences Laboratory at St. Thomas' for further information on bilirubin analysis on 0207 188 9247 or by email:

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Development Of A Novel, Rapid Assay For Detection Of Heparin-Binding Defect Antithrombin Deficiencies: The Heparin-Antithrombin Binding (HAB) Ratio

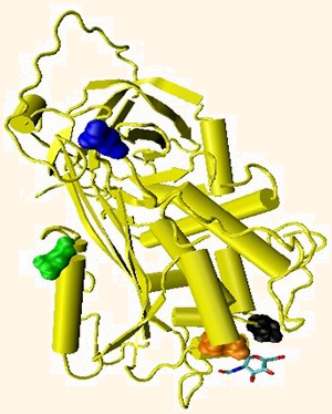

Fig 1: Antithrombin

Clinical relevance

Antithrombin (AT) is a natural anticoagulant, a substance that regulates blood clotting. AT deficiency is a blood disorder that may be inherited or acquired. The deficiency can be caused by reduced production of a normally functioning protein (Type I), a quantitative deficiency or a qualitative deficiency (Type II) where there are normal amounts of AT but it is not fully functional. Type II deficiencies affect either the reactive site (RS), which binds to the molecules that AT 'switches off', or the heparin-binding site, which permits molecules such as the therapeutic anticoagulant drug heparin to increase the ability of AT to regulate clotting.

Patients with inherited AT deficiency have an increased risk of developing a deep vein thrombosis or pulmonary embolism. In patients with acquired AT deficiency the risk of developing blood clots is not always increased and is the consequence of some other disorder, usually involving the liver, kidneys or treatment of certain types of blood disorders e.g. leukaemia. In these patients the disorder may be reversible with treatment.

Patients heterozygous for type II heparin-binding-defect (HBD) mutations have a much lower prevalence of thrombotic events compared to those heterozygous for types I, II RS and II PE (pleiotropic effect, which can affect both binding sites). Nonetheless, their identification is relevant in patients who do experience clinical events, where co-inheritance with another thrombophilia occurs or where standard doses of heparin do not achieve therapeutic APTT values due to loss of its accelerating effect. APTT is a test that monitors heparin therapy. Numerous commercial assays with similar analytical properties and design are available for measuring AT activity. Such assays readily identify quantitative deficiencies and most dysfunctional variants that cause Type II RS, but prolonged incubation with heparin in the assay design can overestimate the AT level in the presence of Type II HBD, especially in heterozygotes.

Assessment of the new methodology

Viapath's Haemostasis & Thrombosis Department has developed a novel modification of readily available AT assays that quantifies heparin-binding capacity of AT by deriving a ratio of AT activities generated from short and prolonged incubation times with heparin. A reduced Heparin-AT binding (HAB) ratio should be realized in most patients with AT deficiency due to HBD but not in those with Type I deficiency, Type II RS or individuals with no AT defects. Plasmas from genetically proven HBD patients and normal donors were assayed for AT activity by Factor Xa-inhibition and thrombin-inhibition at varying incubation times to optimise assay conditions for generation of the HAB ratio. Fourteen patients with hereditary AT deficiency, including five with HBDs, were analysed using the FXa-inhibition and nine patients with hereditary AT deficiency, including three with HBDs, were analysed using the thrombin-inhibition assay.

Results of the evaluation

The FXa-inhibition assay in two genetically confirmed HBD patients with prolonged heparin incubations clearly produced HAB ratios of 0.67 and 0.24 respectively (reference range 0.90 – 1.01). However, three plasmas containing mutations with markedly reduced or absent heparin affinity gave normal results. Nine AT deficient plasmas were tested with the thrombin-inhibition assay and all generated reduced HAB ratios whilst two normal donors did not. The three available HBD plasmas generated lower values than non-HBD plasmas. The mildly reduced HAB ratios in non-HBD deficiencies may have been due to heparin cofactor II reacting with bovine thrombin during extended incubation.

Click here to view the results

Conclusions: HAB ratio from FXa-inhibition assays distinguishes some but not all HBD from non-HBD ATs, and thrombin-inhibition assays may be diagnostically applicable with sub-type specific cut-offs.

Practicalities

This assay is performed at Viapath's Diagnostic Haemostasis and Thrombosis Laboratory: 4th Floor North Wing St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH.

The turnaround time is: 7-12 days.

For more information about the detection of heparin-binding defect antithrombin deficiencies, please contact:

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For more information about detection of heparin-binding defect antithrombin deficiencies, please refer to the recent article or contact Dr Moore for a copy:

Moore GW, de Jager N, Cutler JA. Development of a novel, rapid assay for detection of heparin-binding defect antithrombin deficiencies: the heparin- antithrombin binding (HAB) ratio. *Thrombosis Research* 2015;135:161-166

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Fundraising For The Evelina London Children's Hospital

Evelina London Children's Healthcare is part of Guy's and St Thomas' NHS Foundation Trust and is one of only two specialist children's hospitals in London.

The hospital's neonatal unit cares for around 900 babies a year, and has some of the best survival rates in the UK. The hospital has cared for over 55,000 young patients in the last year, providing around one in five of the UK's kidney transplants in children. It is the UK's leading hospital for paediatric heart services, and also specialises in kidney transplants, dialysis and neurology. Its mission is to provide world-leading treatment and care for each child and every family. Because Evelina London is on the same site as St Thomas' Hospital, which is for adult care, there is a seamless transition in treatment for children with on-going illness.

Based in a stunning purpose-built building at St Thomas', the hospital includes:

- 141 inpatient beds, including 20 intensive care beds
- 52-cot neonatal unit
- 5 operating theatres, plus 1 cardiac theatre in East Wing, St Thomas'
- a full children's imaging service with MRI scanner, x-ray and ultrasound
- a kidney dialysis unit
- an outpatients department and a medical day care unit
- a hospital school

Fig 1: A Hospital that doesn't feel like a hospital

With themed floors, a conservatory, rooms with views, sunlight and fresh air, the Evelina London Children's Hospital was designed around the needs of children and their families.

It's a seven-storey glass-fronted building, featuring a four-storey conservatory and dramatic views of Lambeth Palace and Archbishop's Park. Inpatients are on the upper levels of the building, so children staying in hospital enjoy the best views. They also overlook the conservatory, the social heart of the building, housing a gallery and performance space and the hospital school.

Pathology services for the Evelina London Children's Hospital are provided by Viapath and two of Viapath's laboratories, the Inherited Metabolic Disease laboratory and the Newborn Screening laboratory, work particularly closely with the Evelina. The Evelina provides the regional Inherited Metabolic Disease (IMD) service for south Thames covering south London, Kent, Sussex, Surrey and beyond, with outreach clinics as far as Plymouth, Cambridge and Norwich. More than 300 new patients are seen each year, with over 200 admissions to the ward. Evelina is one of the main IMD centres in the UK offering treatment to patients with all types of IMD, including procedures for diagnosis and acute and long-term management. Together with the Paediatric Metabolic Consultants, Clinical Nurse Specialists and Metabolic Dieticians the

laboratory staff are a key part of the Metabolic Multi Disciplinary Team.

Fig 2: Rachel having her CPET

Rachel Carling, Viapath's Consultant Metabolic Biochemist and Director of Newborn Screening, has been working hard to fundraise for the Evelina London Children's Hospital and has already raised over £3600

Rachel's next challenge is to run the London Marathon.

Rachel's Story

#RunRachelRun: My campaign to raise money for Evelina London Children's Hospital

On April 23rd 2017 I will be running the London Marathon. A subtle but definite emphasis should be placed on 'running' because my goal is to do exactly that: keep running. As with any challenge my approach is to tackle this head on and with just a few weeks to go until the big day, I have thrown myself into both fundraising and training. It is fair to say that one is considerably harder than the other and there is probably no need to mention that heart sink feeling I got when I realised the distances on my training plan were in miles not kilometres...

#RunRachelRun is my campaign to raise money for the Evelina London Children's Hospital. As a Consultant Metabolic Biochemist and Director of Newborn Screening, I have worked closely with the Paediatric Metabolic Team at Evelina London for the last 8 years so this charity is close to my heart.

Like any good scientist, I do like a nice experiment so to kick start my training plan I registered myself as a subject in the Barts Heart Centre Training Induced Spongy Heart Muscle Study. I have had an ECG, ECHO, cardio pulmonary exercise test (CPET) and MRI of my heart & knees. These tests will be repeated after 17 weeks of training and then again, 3 months after 'detraining'. Initially I received a clean bill of health and I am now keen to see whether my knees will survive and my CPET data will improve ('41' and 150% being the baseline numbers).

In addition to the training, I have also been scheming up fundraising initiatives. These include street collections at Christmas Fair's, two Boot Camps, a non uniform day & cake sale at my daughter's school and of course the great Viapath Christmas Raffle, Jumper Day and Biochemical Sciences Bake Off. The support from everyone at Viapath has been brilliant and I am touched and very grateful, in particular to Kieran Voong who charmed a brass band into donating their Christmas Eve collection to the #RunRachelRun campaign.

Fig 3: Fundraising at St Thomas'

Running is just like learning to annotate an organic acid chromatogram

The actual running business takes up a surprising amount of time. When I am not out training, I am reading about nutrition and shewees, complaining about interval training, debating the pros and cons of protein shakes and sports gels, contemplating whether adding Epsom salts to my bath water really is a good idea, buying new running kit and studying my Garmin run data. The latter clearly being the thing I look forward to most after my weekly long run; time, distance, pace, splits, calories, heart rate, cadence, elevation and GPS route. You name it, I look at it. Having only ever completed a half marathon prior to this, provided all goes to plan I realised that between now and 23rd April I should be clocking up a PB for distance run on a weekly basis. This gives me a small smile each time. So far I am up to 16 miles so I just need to add another 10.2 miles. I am convinced it is just like learning to annotate an organic acid chromatogram. At first it seems completely impossible, and a single chromatogram takes you a whole day to interpret. Over time you gradually build up to a batch a day and before you know it, you find that you love organic acids so much that you collect car registration number plates that feature their three letter abbreviations.

To read more about Rachel's fundraising efforts or make a donation, *click here*

The History Of Histological Dissection: Landmarks And Pointers Of The Past, Present And Future

The story of histological dissection transcends the past centuries and has been linked to the history of medicine itself. Here, Dr Guy Orchard, from Viapath's St. John's Dermatopathology Laboratory, investigates how this quite artistic, scientific discipline has evolved and progressed over this time period.

(A longer version of this article first appeared in The Biomedical Scientist, August 2016)

A glance at the history books tells us a great deal. Let's begin with the word "dissection" derived from the Latin "dissecare" meaning "to cut to pieces". This is quite a blunt description of what we now understand by modern dissection however it reflects the key premise of the act to dissect.

Dissection was used primarily to explore and evaluate anatomy and later improve understanding of physiology. Early reports suggest that human dissection was carried out by Greek physicians in the early part of the 3rd century BC. The Romans also had a significant role to play in the development of medicine. The most widely recognised practitioner of the time being Galan (129 CE) who lectured, wrote and exhibited extensively on anatomy and the value of dissection as a learning tool.

'Science is simply common sense at its best.'

Thomas Huxley

Despite strong resistance to the practice of human dissection, the Greeks were keen to establish a hub of medical knowledge and the government of the time supported its practice. However histological dissection became a taboo subject around the globe. This was as a result of religious beliefs merged with fear and trepidation about what might happen to the preservation of the human soul if dissection was performed on corpses. This resistance continued in the UK until 1832 when the first Human Anatomy Act was passed. Up to then it was an outlawed practice and medical professionals of the time would go to great lengths to acquire the cadavers required to study human anatomy. This spawned the era of the "body snatchers". The passing of the Act paved the way for the modern-day study of anatomy and physiology and gave a license to doctors, teachers of anatomy and bona fide medical students to dissect donated bodies.

What then have been the significant advances in terms of the practice and equipment used for medical practice and more specifically histological dissection? Again the Romans made significant strides forward in this area, with the development of a wide range of surgical instruments. The most widely known example is the scalpel. Made mainly from bronze or steel, arguably this is the most valuable dissection instrument for incisional and deep or long cutting of tissue and the almost identical form is retained in scalpels used today. Other examples include bone drills, bone forceps, male catheters, vaginal specula, spatulas and the surgical saw.

Advances in cellular pathology

Modern day dissection surprisingly has not progressed significantly over time. Our understanding of anatomy and physiology has progressed but our methods of assessing or evaluating macroscopic dissection procedures has relied mainly on surgical instruments used in the operating theatre, rather than improving on dissection instrumentation at the cut up bench. The discipline of cellular pathology has advanced tremendously and we have seen some very impressive improvements in the developing technologies. Some examples include the introduction of enclosed tissue processing equipment, sophisticated paraffin embedding machines, improved microtomes for precision in section cutting. Most significantly we have seen the rise of automation with the introduction of a plethora of staining machines for routine haematoxylin and eosin (H&E) staining, special staining and immunocytochemical (ICC) staining procedures and also have automated coverslipping machines. The growing developments in molecular technology and equipment also looks set to be an area of great expansion in the future.

We have, perhaps, spent a great deal of time perfecting and improving on new technologies without necessarily working out the parameters that ensure that the tissue we assess is optimal for the procedures we need to investigate. A classic case in point is the massive explosion of publications on the use of ICC in cellular pathology during the 1980s and 90s. There was great interest in developing automated platforms and also improving sensitivity for the detection of ever-smaller antigenic epitopes. However as we attempted to identify an ever-increasing panel of antibodies to work on paraffin sections recognition dawned that optimising tissue fixation and processing was more important to the final results than was originally believed. At this point we took tissue fixation and processing more seriously and also introduced the antigen retrieval procedures with which we are familiar today. But the first procedure undertaken on tissue in the cellular pathology laboratory is dissection.

Initial tissue dissection

Information in the scientific literature on the importance of initial dissection and how accuracy and precision are achieved is hardly discussed. To an enthusiastic observer it

appears a gaping omission! We have traditionally viewed histological dissection as quite a labour intensive, fundamentally basic, yet highly skilled (in terms of those who perform it) practice. Yet we have not studied the variables of practice that contribute to inaccuracy and lack of precision. The devices used traditionally to measure tissue at the cut up bench have included the weighing scales and the metric ruler. There is very little consideration given to the need to ensure perpendicular sectioning of tissue and to ensure optimal tissue thickness. Thus the appearance of tissue slices that have been measured by eye and by the metric rule can quite often be inaccurate and not perpendicular to the cutting face. This affects processing and embedding procedures, impacts on microtomy procedures and also can affect ICC procedures and molecular investigations.

True cutting

Whilst at my local delicatessen, I watched the assistant lift a large ham from the display counter, place it on a bacon slicer and cut several slices from the joint. He was unsure about how thin he could cut the slices but a glance at the display in front of me told me what I needed to know. Later I read about the bacon slicer and also about the guillotine, used during the French revolution as an instrument of death. What was evident was how successful these devices had been, the reason being they were perfectly constructed for their purpose. I started drawing some constructions and to ponder on how something that was not dissimilar to a guillotine or bacon slicer could be used for histological dissection, the biggest issue being how to ensure precision and accuracy. The best option appeared to be adapting the devices on which we already rely (i.e. the microtome) and adjust them for this purpose. With this in mind, I approached a commercial company (Cellpath) and discussed designs and formats. The literature in this area is not extensive and covers a wide spectrum of different approaches to tackling the needs of histological investigation. Some of the key factors that can affect accuracy and precision for histological dissection need to be appreciated and include:

- flat uniformity perpendicular to the specimen cutting face
- appropriate immobilisation of the tissue specimen during grossing
- good visualisation of the cutting tissue face
- sharp knives with associated grossing equipment fit for purpose
- grossing knife action

Designs were constructed that attempted to take into account these factors. What ensued were considerations of not just final designs but also the materials to be used in construction of these devices. Trials of two devices, TruSlice and TruSlice Digital, were performed. TruSlice relies on the insertion of reinforced plastic inserts with defined recessed depths of 2, 3, 4, 6 mm. The TruSlice Digital relies on the use of an attached micrometer. Both used a guillotine like construction with a knife plate configuration that ensured a perpendicular action of the blade. Preliminary trials were extremely positive with good recordings of accuracy and precision.

Fig 1: TruSLice digital device

Following these encouraging results, I requested that we embark on a 5 site trial to determine if these initial findings were mirrored elsewhere and also to see how feedback could improve the devices.

The use of a micrometer (TruSlice Digital) to set tissue slice thickness is innovative and its use of a micrometer reminds us about how traditionally we have defined measurement and accuracy in the microtomy of histological sections from paraffin blocks. Clearly in developing these devices we have not reinvented the wheel but applied the concepts of well-trusted methodology to a different area of histological assessment.

There is a need, however, to compare and contrast the most promising devices in this area of investigation, simply to determine which will provide the best overall options for routine histological dissection. This is something that has not been performed to date. Owing to the complexity of, and variation in, tissue types dealt with in the modern histopathology laboratory, a single device that suits every need and eventuality with regard to dissection is perhaps an idealistic goal but that is not an excuse for not trying! As Thomas Huxley said: "Science is simply common sense at its best."

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Candida Auris: A Newly Discovered, Multi-drug Resistant Pathogen

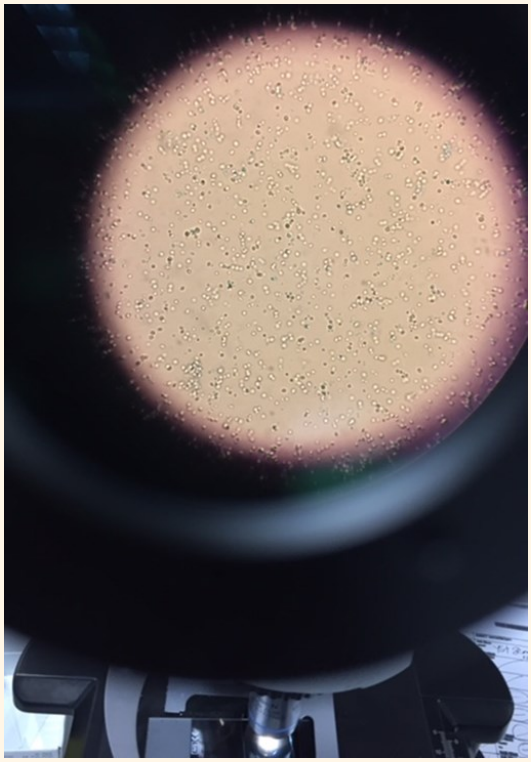

Fig 1: *Candida auris* seen through the lens (x40) of a microscope, courtesy of Dr. S. Braham

Why does *Candida auris* pose a threat?

Candida auris (*C. auris*) is an emerging multi-drug resistant fungal pathogen first isolated in Japan in 2009[1] but retrospective studies show it dates back to 1996[2] in South Korea. Since then, *C. auris* has caused outbreaks worldwide for instance in India, Brazil, Korea and some countries in South America. It was first described in Europe in October 2016, when it was discovered in a London Cardiothoracic Hospital. Gene sequencing shows that there are differences in the DNA fingerprint of the fungus from different continents.

Although "auris" translates as "ear", the fungus can also cause colonisation of other areas for example the skin, nose, urinary catheters, vascular access lines and wounds. Infection of wounds and vascular access lines increase the risk of bloodstream infection, which are common. There is a high mortality rate of 50-60%, associated with the fungal pathogen.

C. auris has a very high outbreak potential and appears to be difficult to eradicate from the environment. Hence, a strict level of infection control precautions are required including isolation of infected patients. Screening of contacts is advised to detect early colonisation.

Candida auris causes outbreaks in hospitals, especially in high risk populations where the immune system is weakened, like patients in intensive care or undergoing renal and neurosurgery.

Guidance for managing patients can be found on the Public Health England's website.

Under the microscope, *Candida auris* is indistinguishable from most other Candida species and currently available diagnostic panels are unable to identify *C. auris*, instead they misidentify the organism as for example, *Candida haemulonii*, *Saccharomyces cerevisiae* or *Candida famata*[3]. Typing methods are also unable to differentiate strains at a local level. These errors can lead to a delay in recognising the infection or an outbreak, which has an healthcare outcome and cost implications. Special diagnostic methods are needed to overcome the limitations of the existing methods.

How can the spread of infection be prevented?

Prevention of hospital infections is a priority for hospitals, but this has resource implications for overstretched NHS Trusts. To prevent the spread of *C. auris*, we need to screen patients who are in close proximity to infected patients, use special isolation rooms and expensive disposable equipment. Viapath's plan is to support the existing stringent measures for infection control with the development of a rapid and accurate method of detection of *C. auris* for use in screening. This aims to reduce the number of patients requiring isolation and help target resources towards true infections and elsewhere where they are needed. Reducing the spread of infection and potentially the length of patient stay in hospital is projected to have a financial benefit as well[4].

For further information on the scientific or clinical aspects of *Candida auris* please contact:

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Or for information on the testing procedures for *Candida auris*, please contact:

Fearghal Tucker: fearghal.tucker@nhs.net

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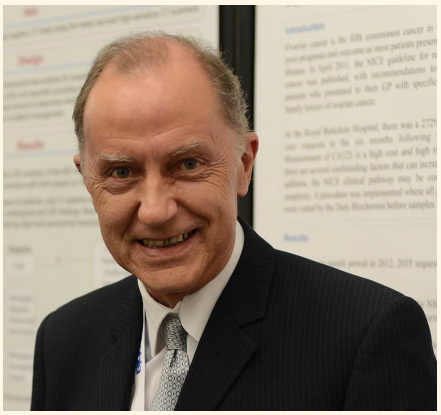
Some of Viapath's experts who have contributed to this edition

Viapath's St John's Histology Team

Dr. Áine McCormick

Dr Gary Moore



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