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Ulster Med J 2018;**87(1):**1-2

Editorial

A Helicopter Emergency Medical Service for Northern Ireland.

John Purvis, Honorary Editor

2018 sees the launch of the Northern Ireland Trauma Network. This represents the culmination of intensive work over the last few years by many individuals and organisations. An audit of Trauma care in Northern Ireland published in 2016 (based on data collected in 2014) revealed that the overall mortality from major trauma was about 25%. The commonest cause of major trauma was a road traffic collision (RTC) followed by a fall from a height.[1]

98% of major trauma patients received some level of prehospital emergency care usually from Northern Ireland Ambulance Service (NIAS) paramedics with 11% of patients receiving input from British Association of Immediate Care Schemes (BASICS) doctors.[1]

38% of patients had a low Glasgow Coma Scale (<9) and potentially, may have benefited from an advanced airway prior to arrival in the Emergency Department (ED). The statistic for patients requiring advanced airway management after arrival in ED was essentially the same at 39%!

40% of patients admitted to an ED outside the Belfast Trust then required a secondary transfer to the specialist teams in the Royal Victoria Hospital, Belfast.[1]

One major component of the new network is a helicopter emergency medical service (HEMS). The tragic motorcycling death of popular HEMS campaigner, Dr John Hinds, resulted in increased public and political support for a HEMS service in the province – the HEMS4NI campaign collected over 84,000 signatures and Government agreed to add to start-up funding raised by the Northern Ireland HEMS charity partner - Air Ambulance Northern Ireland.[2]

An operating base has been developed at the Maze Long Kesh complex near Lisburn and a three-year contract signed for supply of helicopter and pilots with a commercial provider, Babcock Mission Critical Services. A reserve craft is hangered at St Angelo airfield near Enniskillen. NIAS supply paramedic staff and medical equipment. Doctors specialising in Anaesthetics, Intensive Care and Emergency Medicine have been seconded from all hospital trusts in the province.[2]

I recently had an opportunity to visit the Maze Long Kesh Base and interview Dr Darren Monaghan, Clinical Lead for NI HEMS.

On entering the base, the first thing one sees is a map of Northern Ireland with isochrons – circles showing the flying time from the base to any particular location – all of Northern Ireland can be covered in just over 30 minutes. Beside the map, sits an air desk paramedic who listens to NIAS radio traffic and can pre-emptively activate the helicopter if calls such as major RTC, falls from a height or declared major incident are overheard. Otherwise, the team respond to requests from emergency services on the ground. The helicopter operates from approximately 7 AM to 7 PM reflecting variation in daylight hours and difficulty landing a helicopter in unprepared and unlit sites. The pilot requires considerable expertise to choose suitable landing sites as close as possible to the scene (figure 1).

Outside daylight hours, a rapid response vehicle with NIAS code Delta 7 is operated by the doctor/paramedic team.

Altogether, 2 pilots, 6 paramedics and 14 doctors contribute to the rota.

At the moment, patients brought back to Belfast are unloaded at Musgrave Park Hospital and then transferred by ambulance to RVH. This can take up to 25 minutes if Belfast traffic is unfavourable and has to be factored in when determining if a HEMS response is best close to Belfast. It is hoped that the situation will improve significantly whenever the helipad opens on top of the new Critical Care block in RVH in Spring 2018.

The equipment and skills brought by the team to the patient include; sophisticated pain relief, rapid sequence induction anaesthesia and advanced airway techniques (including video laryngoscopy and portable ventilation) which can be particularly important for head injuries, focused ultrasound for identifying chest and abdominal trauma and then the ability to perform on scene interventions based on the results. Tranexamic acid can be used for haemorrhage control.

The latest NICE guidance recommends that RSI and intubation should be performed within 45 minutes of the initial call to the emergency services, preferably on scene, which certainly can be greatly facilitated by a HEMS response.[3]

As well as rapid interventions, it is hoped that the diagnostic skills of the team can choose the appropriate hospital for the patient avoiding time-consuming secondary transfers.

The EC 135 helicopter seats pilot and paramedic upfront and to the rear, the Dr alongside the casualty. The paramedic's

seat however can swivel around to face the patient's head. Interestingly, the pilot requires confirmation of navigation points and flight safety checks so the paramedics have enjoyed learning some aviation skills!

Clinical governance and audit are key features of the service, prehospital anaesthesia in particular, requires close governance. One of the anaesthetic doctors acts as Clinical Lead for this aspect of the service. Results are audited by a Clinical Advisory Group which will form part of the overall Trauma Network. By the date of my visit, the team had been tasked on 150 missions and treated 98 patients with 12 requiring prehospital anaesthesia. The group hopes to publish an audit of its first 100 patients soon. In between missions, there is time for extensive teaching and training and each speciality (pilot/paramedic/medic) has much to learn from the others.

Darren hopes to see the service grow over time and perhaps extend into medical emergencies in remote locations in the province. Response times would also be favourable for some adjacent parts of the Republic of Ireland but there are technical and legal difficulties for doctors working outside their own jurisdiction. There may also be the possibility in the future of St Angelo becoming an active base.

It is just the beginning…

Fig 1. Front gardens adjacent to major roads can make good landing sites.

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LIST OF REFEREES FOR 2017

We pass on our sincere thanks to all our referees for 2017

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Ulster Med J 2018;**87(1):**3-10

Grand Rounds

'When *Right* could be so Wrong'. Laterality Errors in Healthcare

Gerard J Gormley[1], Martin Dempster[2] Richard Corry[3], Carl Brennan[1, 4]

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'I'm afraid I've got some bad news for you.'
He looked questionably at me.
'And what's that, Mr Marsh?'
'I'm terribly sorry but I've gone and operated on the wrong side,' I said.
He looked at me in silence…[1]

INTRODUCTION

Distinguishing *right* from *left* can be challenging. During basic clinical training, we grappled with distinguishing *superior* from *inferior*, *proximal* from *distal*, *medial* from *lateral* but did you ever consider that some individuals may have had difficulty in telling *right* from *left*? We make right / left (RL) decisions on an everyday basis. Whether providing someone with travel directions or taking a car journey - laterality decisions are unavoidable. For many, discriminating right from left is an automatic process; an unconscious competency. However for a significant proportion of our population, distinguishing right from left is a complex task that requires conscious thought and effort.[2] Regardless of our ability to discriminate right from left, all of us at some stage can get it wrong – *to err is human*.[3]

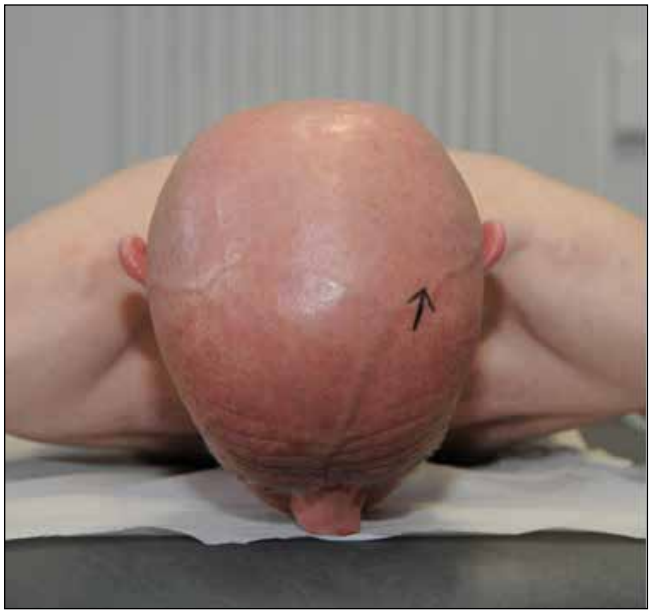

Fig 1. Which side is the arrow on?

In many situations RL errors may lead to only minor consequences - such as providing the wrong travel direction. However in industries such as healthcare and aviation - RL errors can lead to significant harm.[4-6] Interestingly it has been proposed that a laterality misjudgment may have been a contributory factor in the sinking of the Titanic *"He turned the ship right instead of left and, even though he was almost immediately told to correct it, it was too late and the side of the starboard bow was ripped out by the iceberg"*.[7]

In this article, we will review some of the science behind RL discrimination and how this applies to healthcare. We will also consider some measures to prevent such laterality errors occurring.

SPATIAL AWARENESS AND RIGHT LEFT DISCRIMINATION

The neuropsychological process underlying RL discrimination is complex.[8] Despite an increasing evidence base - much remains unknown. We will provide a brief overview of some of the neuropsychological processing.

Spatial awareness considers an individual's ability to maintain body orientation in relation to their surrounding environment[9] – whether *front* or *back*, *up* or *down*, or *left* or *right*. *Egocentric* orientation considers direction in relation to one's own body (e.g. either your right or left hand) and *extra-egocentric* orientation applies to direction in your setting (e.g. the left or right hand of the patient sitting in front of you).[10] Research would suggest that, despite being a fundamental task, not everyone has the same spatial orientation capabilities.[10] In terms of directions of spatial orientation, an individual will find more challenge in distinguishing *right* from *left* than *above* from *below* or *front* from *behind*.[11]

Our ability to differentiate left from right in ourselves *(i.e.*

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in an egocentric context) begins in early childhood.[12] By the age of 11 years, 50% of children can correctly differentiate left from right in others (i.e. in an extra-egocentric context). When distinguishing right from left, many higher cerebral functions are recruited including language (both receptive and expressive), memory, visuospatial processing and integration of sensory information such as visual stimulus.[11] In addition, *mental-rotation* is often required in distinguishing right from left (i.e. when two individuals are facing each other - their *right* side is directly opposite your *left* side). This *mental-rotation* function is thought to originate from the brain's fronto-parietal region.[11]

Many have theorised why some individuals are more prone to confusing right from left. One theory relates to the association between cerebral hemispherical asymmetry and increased RL discrimination ability: a greater degree of cerebral hemispherical asymmetry has been linked to an improved ability in RL discrimination.[12] Schizophrenia has also been linked with cerebral hemispherical asymmetry and researchers have studied individuals with schizophrenia (and dyslexia) with the aim to identify specific genes that may be involved in handedness.[13] Although a number of such genes were identified, it is felt likely that such a complex process is polygenic.[13]

Gender has also been investigated as a factor associated with RL discrimination ability. Though the evidence is not conclusive, males would appear to show a greater RL discrimination capability compared to females.[11] Such a finding could be explained by the fact that males tend to exhibit a greater degree of cerebral hemispherical asymmetry and visuospatial function.[11]

There is no systematic evidence to indicate that handedness is associated with RL discrimination ability. Whilst some studies have reported that being right-handed is associated with greater RL discrimination ability, other studies have reported no difference.[2,14]

WRONG SIDED ERRORS IN HEALTHCARE

Unfortunately, wrong-sided errors occur in healthcare. Laterality misjudgments represent some of the most catastrophic errors in medicine.[4,15] If a body part has a bilateral representation there is an inherent risk of performing surgery or procedure on the incorrect side of the body. Very few surgical specialties escape the potential risk of wrong-sided events occurring.[4] Efforts by many organisations such as the National Patient Safety Agency and The Joint Commission have reduced such 'never events' – but they continue to occur.[16,17] Last year, there were 179 wrong-site surgeries reported to Strategic Health Authorities in England and many of these involved RL disparity errors.[18]

Surgical specialties, of course, are not the only clinical specialty where RL errors can occur. Other reported events include eye injections, nerve blocks, radiotherapy and thoracentesis.[4,18,19]

Fig 2. Can you spot the error?

Using a root-cause analytical approach, Millar *et al* quantified and explored wrong-sided thoracentesis.[19] They concluded that such errors are frequently multifactorial in origin with human error as a common factor.

They reported that the majority of events occurred on the patient's *right-side* (i.e. where the thoracenteses should have occurred on the patient's *left-side*). We theorise that right-handed individuals (i.e. the commonest form of handedness – c.90% of the population) tend to prefer performance to their right-side or their 'fluent side'. When making a RL decision in clinical practice (which is often subject to time pressures and interruptions) clinicians may therefore display laterality by subconsciously favouring their dominant side (e.g. their right-side) regardless of the actual side of the pleural effusion (e.g. the left-side).

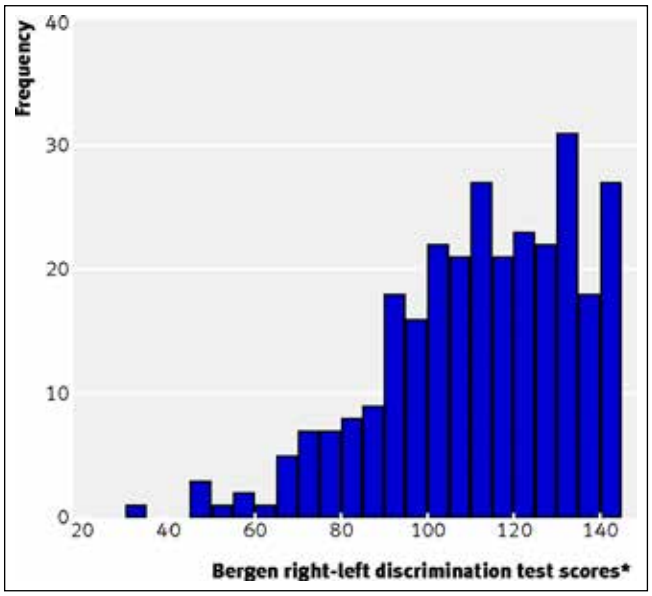
Another common source of non-operative RL errors concerns requests for radiological investigations. The next time you are speaking to a radiographer, be sure to ask them how many times they have received requests to image the wrong side of a patient's body!

MEDICAL STUDENTS' ABILITY TO DISCRIMINATE RIGHT FROM LEFT

Very few studies have considered RL discrimination ability in healthcare professionals. In one study, a cohort of 290 medical students had their RL discrimination ability objectively measured using a psychometric test called the Bergen Right Left Discrimination Test (BRLDT).[20] Results of this study revealed that medical students displayed a range of ability in discriminating right from left. The higher the BRLDT score the better ability to discriminate right from left.

In this study, male students out-performed female students in RL discrimination but handedness did not appear to have any bearing on BRLDT test performance.

In terms of orientation, the greatest challenge for medical students seemed to involve mental rotation where they had to discriminate right from left when directly facing an individual – i.e. the commonest orientation in healthcare when a doctor



Participants' scores on the Bergen right-left discrimination test. *Scale of 0-144

Fig 3. Range of medical student's scores in the Bergen Right Left Discrimination Test[22]

faces their patient (or viewing a standardised radiograph image). Interestingly, those students considering a career in surgery, compared to a career in GP or medicine, were more likely to have a greater ability at RL discrimination.[20]

WHAT STRATEGIES CAN INDIVIDUALS USE TO ENHANCE RL DISCRIMINATING ABILITY?

When objectively measured, individuals vary in their ability to correctly discriminate right from left[11,20] so that some are more prone to making RL errors. Can individuals judge their own RL discrimination ability? Evidence would suggest that individuals *perceived* RL discriminatory ability is significantly associated with their *objective* ability in distinguishing right from left.[20] However this is by no means an infallible assessment. Many individuals with difficulty differentiating right from left use a diverse range of assistive strategies and techniques.[20] Table 1 lists some of the various discriminatory strategies and techniques. One of the commonest techniques is demonstrated in figure 4. Extending the left thumb at a right angle to the outstretched index finger forms the letter 'L' to identify the left hand and side.

TABLE 1.

Range of 'techniques' that individuals use to aid their discriminating of right from left.[20]

Discriminatory technique category	Example
Relates to a physical activity	'*Right* hand used to strum a guitar'
Relates to a unilateral body feature	'BCG scar on my *right* side'
Relates to a unilateral dress or accessory feature	'Wear my watch on my *left* side'
Use of word association	'Write with my *right* hand'

Do these techniques enhance an individual's ability to discriminate right from left? Evidence would suggest that despite using such techniques, individuals are still challenged in correctly discriminating right from left.[20] What remains unknown however is whether individuals can be trained to improve their RL discrimination ability.

Fig 4. A commonly used technique to aid the discrimination of right from left. By placing the index finger and thumb at right angles – the letter 'L' is made on the 'Left' side.

REDUCING RIGHT/LEFT ERRORS IN HEALTHCARE

Adverse events can arise in clinical practice when errors and latent conditions become aligned.[21] In a complex system such as healthcare, adverse patient events are often multi-factorial but one common recurring cause is human error.[21] We will now consider some approaches that aim to reduce wrong-side errors occurring – these incorporate individual, system and cultural strategies.

LEARNING FROM THE "HIGH-RELIABILITY" INDUSTRIES

In recent years, healthcare organisations have been increasingly looking to other (so-called "high-reliability") industries such as commercial aviation and nuclear power[22] for learning in error-prevention strategies. For several decades, such industries have shown incremental improvement in operating safety and reliability by embracing a universal truth for human operators – to err is human[3] In "high-reliability" industries, systems of working for human operators are relentlessly reviewed and redesigned to anticipate, prevent and mitigate for the *absolute certainty of human error*. Healthcare professions, in contrast, have been slow to accept this truth and have lost ground. In a world that increasingly expects error-free healthcare, we are now playing catch-up.

The aviation industry, following root-cause-analysis of a number of high-profile air disasters in the 1970s, began to appreciate the role of human error in airplane crashes.[23] The predominant failure was increasingly identified as dysfunction of the human teams managing the crisis rather than technical aircraft failure per se. Recurrent team failures included a breakdown in key skills such as leadership, situation

awareness, decision-making and interpersonal communication – such skills were termed *Non-Technical Skills* (NTS).[24] NTS can be defined as the 'cognitive, social and personal resource skills that complement technical skills and contribute to safe and efficient task performance'.[24] In 1981, United Airlines was the first airline to commence training for flight staff in NTS and the training was called *Cockpit Resource Management* (CRM)[25,26] – by the mid-1990s, CRM had become *Crew Resource Management* (to include cabin crew) and it was a global standard across the industry.

The healthcare industry is increasingly realising the importance of NTS, in complementing clinical and technical expertise. In 2003 psychologists, in conjunction with clinical anaesthetists, developed a taxonomy to describe the NTS relevant to safe and effective anaesthetic practice called the ANTS (Anaesthetists' Non-Technical Skills) Framework.[25] This framework was designed to help anaesthetists recognise and assess the non-technical performance of themselves and others. Training courses to coach anaesthetic NTS, often employing simulation-based education (SBE), are now delivered throughout the United Kingdom and Ireland. Similar taxonomies have subsequently been developed for surgeons (Non-Technical Skills for Surgeons – NOTSS)[27] and scrub practitioners (Scrub Practitioners' List of Intra-operative Non-Technical Skills - SPLINTS).[28]

So how might a high-reliability industry tackle the problem of RL disparity? The science of *Human Factors* would suggest a number of strategies to prevent RL errors including:[29]

- Education regarding risk awareness and meta-cognition
- Use of Standard Operating Procedure (SOP) & Checklists
- Use of technology
- Training to encourage effective team-functioning

EDUCATION ON RL DISPARITY

The first step in addressing any error is to increase awareness amongst operators of the risk of the error and potential consequences. Wrong-sided errors continue to occur and these errors can be devastating for both the patient and the *second victims*, namely the healthcare professionals involved.[30] Table 2 lists some of the factors which may potentially contribute to RL errors (adapted and modified from Pandit et al, 2017)[31]

The term *metacognition* is defined as an "awareness and understanding of one's own thought processes" and higher order thinking skills. One of the main purposes of this article is to foster metacognition and self-awareness amongst practitioners that:

- RL discrimination ability is not reliably automatic or intuitive for many individuals
- RL decisions are frequently critical
- RL decisions should be afforded appropriate conscious effort and diligence, and should be actively processed through *working memory*

Table 2.

Categorised factors that may lead to right left errors in healthcare

Operator factors	• High pressured environment • Stress and time pressure • Fatigue and/or hunger • Novice operator or procedural uncertainty • Poor handover or change of staff mid-procedure • Poor record-keeping or inappropriate use of abbreviations • Interpersonal difficulties and authority gradients
Patient factors	• Patient sedation or confusion • Language or communication difficulties • Similar patient names • Bilateral pathology
Procedural factors	• Distractions and background noise • Excessive team numbers • Checking failure • Change in patient position • 'Leading' environment layout • Side marking incorrect, erased, covered or transferred

WORKING MEMORY

The Multi-Store Theory of Memory[32] would suggest that there are three states of memory; namely *sensory*, *short-term* and *long-term* stores. The short-term memory is also referred to as the *working memory* and, in computing parlance, can be likened to an individual's processor unit or home screen. The working memory also controls an individual's conscious *awareness* and conscious thoughts.

The reality of the working memory is that it is capacity-limited and that active short-term memories are fragile and easily displaced or forgotten. Conscious thinking is also most effortful and to prevent mental overload, tends to be the least-preferred option particularly when busy. We can often function quite efficiently and effortlessly on an intuitive 'auto-pilot' setting. Although, undeniably efficient, such intuitive performance unfortunately represents a trade-off against thoroughness and accuracy (The Efficiency-Thoroughness Trade-Off).[33] Ability and reliability in RL discrimination varies between individuals and for some, RL decisions cannot be safely trusted to automatic performance. The danger in RL decisions therefore comes from situations where we fail to engage our working memory and commit such decisions to an unconscious process. In turn, anything that impacts upon the working memory will jeopardise RL discrimination and make errors more likely.

The working memory is vulnerable to many potential threats such as acute stress, time-pressure, fatigue, distractions, emotional extremes and intoxication to name a few.

DON'T DISTRACT ME!

Clinical tasks often occur in busy and challenging working environments.[34] From the ambient noise of telephones and monitors, to verbal interruptions and competing demands, such tasks are often nested in complex environmental dynamics. Distractions place an additional burden on working memory and jeopardise conscious RL discrimination. Evidence supports the theory that interruptions and distractions impact on an individual's ability to discriminate right from left.[34] In a situation where an individual's attention is divided between performing a task (such as discriminating right from left) and facing a distraction it is not surprising that the task may suffer.

Educational and organisational frameworks in healthcare need to recognise the importance of human factors in our challenging working environments. When making critical clinical decisions, such as marking a limb or performing a unilateral procedure, minimising interruptions and distractions is desirable. In response to a number of distraction-related air disasters, the Federal Aviation Authority enacted "The Sterile Cockpit" rule in 1981 – this rule dictates that flight crews must refrain from all 'non-essential conversation', to minimise unnecessary distractions, during all critical phases of flight (such as during turbulence or when plane altitude < 10,000 feet).[35] A similar "silent theatre" procedure has been adopted in some operating theatres to minimise distractions during the critical phases of a surgical operation. Those individuals who are prone to confusing right from left are likely to benefit from similar initiatives.

Design of our clinical environments can also have an impact on human factors. In terms of socio-materialism (i.e. how material objects interact with our socio-function and dynamics) there is increasing use of physical spaces known as 'distraction free zones / quiet areas'.[36] Such areas signal to others that an individual is making an important decision (for example prescribing in a neonatal Intensive Care Unit). Such *socio-material* interventions may provide a safe sanctuary for those challenged in making RL decisions.

HUMAN SUGGESTIBILITY

Practitioners favour laterality procedures that play to their dominant side. The majority of individuals are right-handed so this would suggest that an RL error is more likely to occur in procedures that favour a left-handed approach. Such an unconscious drift may also be encouraged by other factors that play to human suggestibility. Examples of this would be where the practitioner anchors to an incorrect handover of laterality or where the procedural environment is set-up in such a way that subconsciously guides the unwary professional to the incorrect side. In the latter, such misleading cues can be very subtle where the practitioner is drawn, for example, to the side which is nearest, most spacious, uncovered, undraped or better illuminated, or when the room appears set-up to allude to a particular side. An example of this would be where the furniture, such as a procedure trolley or ultrasound machine, can seemingly act as an obstacle to one side and a misleading signpost to the other.

USE OF STANDARD OPERATING PROCEDURE (SOP) & CHECKLISTS

Another safety strategy employed to great effect by high-reliability industries is the formal Standard Operating Procedure, often used in conjunction with checklists. Assuming good design, an SOP is inherently safe by eliminating variation and confusion, and promoting predictability and consistency of performance.

In an attempt to prevent wrong-site procedures in healthcare, a number of SOPs have been recommended or mandated within the NHS. Some examples for the operating theatre include the Surgical Safety Checklist,[37] 'Stop before you block' initiative for unilateral nerve blocks[38] and skin-marking policies prior to surgery. Given that RL errors are not restricted to operating theatres, SOPs are also increasingly available for unilateral non-surgical procedures and are already commonplace in procedures such as thoracentesis[39] and eye injections.[40]

Formal SOPs prevent and trap RL errors by a number of means:

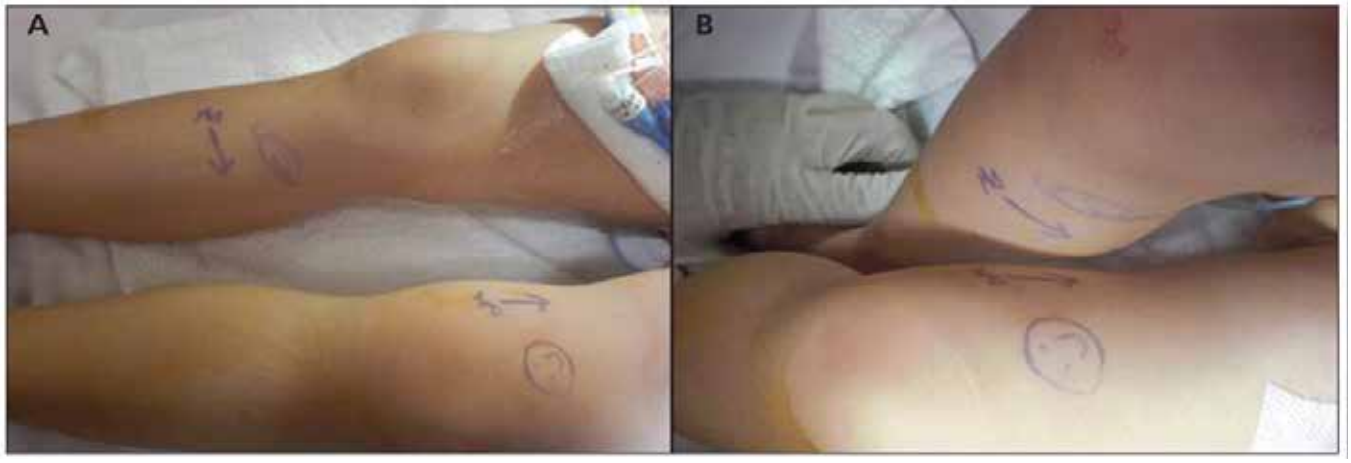


Fig 5. A cautionary case where a child's leg was marked 'No' for surgery but the ink transferred to the other leg when the legs touched each other. Dominique MA Knight and John H Wedge *CMAJ* 2010:**182**:E799. Used by kind permission of the Canadian Medical Association.

- Command a 'time-out' or 'pausing-practice' prior to the procedure to force engagement of conscious thought in relation to correct side and site
- Seek to promote a distraction-free environment
- Recruit the team to 'cross-check' RL decision and reach collaborative consensus
- Create an opportunity for challenge from patient or other staff

The World Health Organisation launched a Surgical Safety Checklist as part of a "Safe Surgery Saves Lives" Initiative in 2008.[37] The intention of the checklist is to promote team-functioning and prevent surgical 'never events' such as wrong-site surgery and retained foreign objects. At three points in any operation, the theatre team are obliged to stop and reevaluate against critical errors – the focus of two of these checks is to confirm that the imminent operation is progressing to the correct site and side. Whilst this worldwide initiative has saved countless lives globally, 'never events' such as wrong-site surgery unfortunately continue to occur.[4,18] More research is needed to understand why errors still occur despite the use of safety checklists, particularly regarding the socio-cultural nuances of checklist practices.[41]

USE OF TECHNOLOGY

Technology and other innovations are increasingly employed to provide additional layers of protection and safety in healthcare. One such example in relation to wrong-sided errors is the recommendation that thoracenteses should be performed under direct ultrasound guidance[39] – the clinician must thereby objectively confirm the correct side by direct visualisation of the underlying pathology (e.g. a pleural effusion) at the time of the procedure. In human factors parlance, the ultrasound technology in this example acts as a *constraint* - a constraint can be defined as "the state of being checked, restricted, or compelled to avoid or perform some action".[29]

Laterality errors, though relatively infrequent, can also occur with radiological imaging and the reporting of such images[42]. The risk of potential patient harm from such errors can be significant. In recent years, computer software has been developed to flag-up image reports where there appears to be a RL conflict.[42]

TRAINING TO ENCOURAGE EFFECTIVE TEAM-FUNCTIONING

In January 2000, a 70 year-old gentleman named Graham Reeves, underwent a left nephrectomy at the Prince Philip Hospital in Llanelli, Wales.[43,44] It was only upon completion of the operation that the theatre team, with one exception, realised that Mr Reeves had undergone wrong-site surgery and that the 'good' left kidney had been accidentally removed in error. Mr Reeves, despite a subsequent salvage operation and treatment with haemo-dialysis, died five weeks later. The one exception in the theatre team that day was a medical student – she had realised the error from a review of the imaging but had been unable to successfully challenge the surgical team as to their impending blunder. Mr Reeves was a victim of an RL error because of an administrational error which had caused the wrong side of operation to be listed on the operating schedule – he also fell foul of an authority gradient.[3,44]

Authority gradients represent power-differentials whereby an individual's actual or perceived status will rank them within a power-hierarchy or 'pecking order'. Problems occur where authority gradients are steep because the power gap becomes a block to communication and challenge for lower-status individuals. Within the operating theatre, for example, surgeons tend to occupy top-status. In the case of Mr Reeves, the authority gradients on that day were simply too insurmountable for the young medical student and the consequences were disastrous.[45] Perhaps, through education, training to empower students and staff may be a worthy endeavor?

By the late 1970s, the aviation industry was increasingly aware that authority gradients were 'costing' the industry several planes each year. They realised that the solutions for success in an aviation crisis were much more likely to come from the team rather than from the top-dog captain whose brain was failing from mental overload. The prevailing culture, at that time, of a steep flight-deck hierarchy was killing off the team. The answer for regulators was to demand flatter authority gradients amongst flight-staff whereby, for instance, formal challenge of a senior was to be both permitted and expected. Such a change in culture, along with other improvements in flight team performance, was the principal focus of CRM training.[26]

It is a reality that *competent individuals* do not necessarily make *competent teams*. In healthcare, one of the increasingly used resources for coaching team-skills and covering the principles of CRM is Simulation-Based Education (SBE). In SBE, a healthcare team can be safely exposed to a crisis scenario and their subsequent crisis-behaviours and team performance unpicked and critiqued during the formal debrief. Interprofessional-based education, to mimic real-life healthcare teams, is desirable for achieving both fidelity and collaborative competency. More training to improve team dynamics and performance, akin to CRM, can only help to prevent and capture errors such as RL disparity and wrong-site procedures.

CONCLUSION

In recent times significant inroads have been made in reducing wrong-sided errors – however we should continue to strive and make such *never-events* truly *never* events. Reducing laterality errors requires a deeper understanding of human behaviors and their complex interplay with working environments, teams, systems and organisations. According to Greek mythology, Ariadne helped Theseus navigate Minotaur's labyrinth by providing him with a ball of thread

to guide his way out. Using this metaphor, applying human factors knowledge (such as difficulty in RL discrimination) into the milieu of clinical practice, could act as the *thread* to help guide health professionals in minimising patient harm through error. To err is human and it is no longer *right* to be *left* in the wrong.

CONTRIBUTORS STATEMENT

GG and CB contributed to the conception of this paper. All authors contributed to the drafting, critical revision and final approval of the final manuscript for publication. GJG is the guarantor.

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Medicine Outside the Comfort Zone

Far away from the NHS – Hernia Surgery in Nigeria and Kenya

Cristina Croitoru, Aleksander Stanek

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DESTINATION –KENYA

By Cristina Croitoru

Situated on the equator, Kenya has been described as "the cradle of humanity". At 580,367 km2, the Republic of Kenya has a population of 46 million. The official languages are English and Kiswahili but numerous indigenous languages are also used. The most widely practiced religion is Christianity, followed by Islam.[1] A considerable portion of Kenya comprises wildlife habitats such as the Masai Mara.[2]

Kenya is ranked as a lower middle-income country by World Bank criteria. Agriculture remains the backbone of the economy, making up 35.6% of the overall GDP [3]. As of 2011, there were 65,000 qualified nurses, 8,600 clinical officers and 7,000 doctors. In 2013, there were 0.2 physicians and 1.4 hospital beds per every thousand patients [4]. Despite major achievements in the health sector, Kenya faces many challenges. According to statistics from 2012, life expectancy averages 61 years, while infant mortality rate is high at approximately 44 deaths per 1,000 children. WHO estimated that in 2011 only 44% of births were attended by a skilled health professional.[5]

HERNIA INTERNATIONAL

Approximately 1-in-4 men will suffer from a groin hernia. In sub-Saharan Africa, there are an estimated 6.3 million untreated cases. In rural areas more men suffer from hernias than from HIV. Surgeons have found an anatomical susceptibility to hernia in Africa, characterised by a weakness of the inguinal wall[6,7]. Neglected hernias cause mortality from strangulation and physical incapacity and contribute to socio - economic problems as men from the most productive age group are often affected[7].

In 2006, Professor Andrew Kingsnorth from the Derriford Hospital, Plymouth and Mr Chris Oppong founded Operation Hernia. The organisation began work in Ghana before expanding to Africa and other regions. Operation Hernia has popularised the use of mosquito net meshes to replace synthetic mesh used in developed countries. This technique was not widely known outside of India until Kingsnorth adopted the technique following a visit to India in 2006. The method has since been widely used across Africa[9]. Last year, Operation Hernia covered Ghana only, with Hernia International covering all other countries on a global scale.

In 2016, Hernia International established itself as the UK's premier hernia charity by operating on over 2000 patients - 24 international teams (consisting of over 150 volunteers) from 19 countries worldwide have operated in 15 different locations across the globe. Volunteers from Northern Ireland included Mr Terry Irwin from Belfast City Hospital who has lead several missions in the past, and Mr Aleksander Stanek from South West Acute Hospital, Enniskillen who led the 2015 and 2016 missions to Gatundu, Kenya and has additional experience working in Nigeria.

JUNE 2016 MISSION TO GATUNDU

Our journey took us to Gatundu – 90 minutes' drive from Nairobi. We were based at Gatundu District Hospital, a public level 4 health facility.

Our Team had 6 members: General Surgeon and team leader Aleksander Stanek, Austrian General Surgeon Leo Mittregger, Spanish General Surgeon Rocio Santos, Swiss Urologist Greg Wirth, Surgical Trainee Cristina Croitoru and Victoria Carswell, a Foundation Doctor (both from the UK). Several members were Hernia International veterans. This was the second Hernia International mission to Gatundu and with each mission, new equipment was brought along.

Over the course of 5 days we performed 48 operations on 46 patients aged between 2 and 95. Our team and the local doctors and nurses worked side by side, 12 hours a day. There were 23 inguinal hernias, 11 umbilical, 6 epigastric, and 4 incisional hernia repairs performed. Additionally, our team performed one orchiectomy, one hydrocele repair, one seroma aspiration and one excision of an abdominal lesion.

AFRICAN PUZZLES

In order to present the flavour of this work, we have made a compilation of unusual cases.

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Case 1. Returning to the basics.

Without a CT scan or any other type of imaging, can you make a diagnosis? If you can determine that what you see is an inguinal hernia, can you say what it contains? Having done that, can you repair it with a mosquito net and the instruments contained in just two suture kits?

Fig 1. Inguino-scrotal hernia

Figure 1 documents a 34-year old tailor, father of four children, presenting with a right inguinal-scrotal swelling which was present for all of his life. The swelling had significantly increased in size over the last few years. Poverty made him postpone treatment, gradually restricting walking and leading to pain levels which were barely manageable. He was taken to theatre and found to have a hernia containing almost the entire small bowel; it appeared to be a pantaloon scrotal hernia with one direct and one indirect congenital hernia. The right testicle was atrophied and was removed. The hernia was then repaired with a mosquito net in accordance with Lichtenstein protocol (excess skin was also removed). He made a good recovery and was discharged on day 4 postoperatively.

Case 2. Abdominal mass

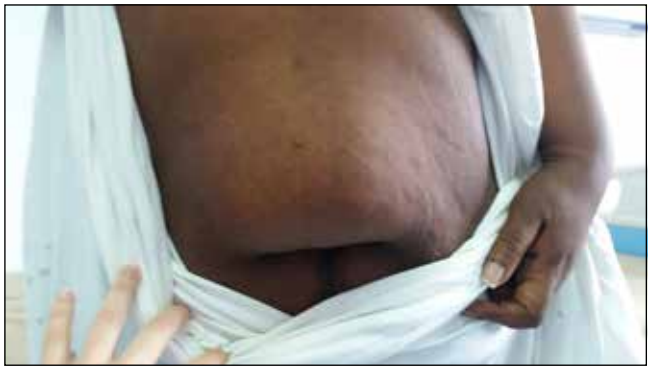

Fig 2. Para umbilical mass –pre-operatively

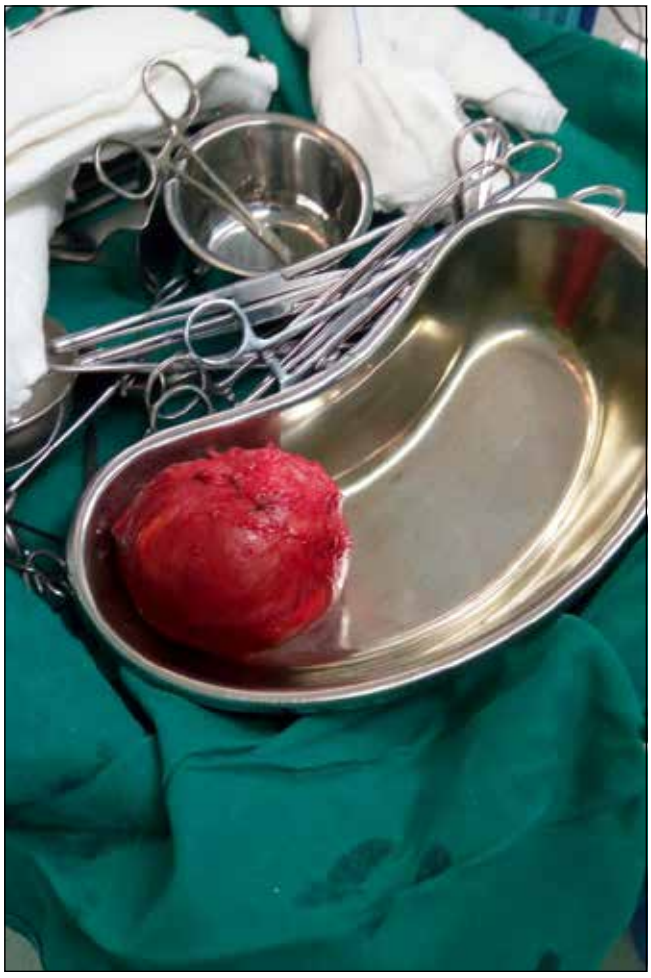

Fig 3. Para- umbilical mass - excised

The patient presented with a large firm lump just above the umbilicus which appeared a short while after she underwent incisional hernia repair in the United States. Her hernia appeared following an emergency C-section and got bigger. On examination it was well defined and irreducible. An abdominal ultrasound was inconclusive but clearly described an abdominal wall defect of 2 cm diameter, suggestive of a recurrent, incarcerated, incisional hernia. To our surprise we removed a firm mass, 7 cm in diameter. An abdominal wall defect was closed with non-resolvable stitches and covered with a mosquito net.

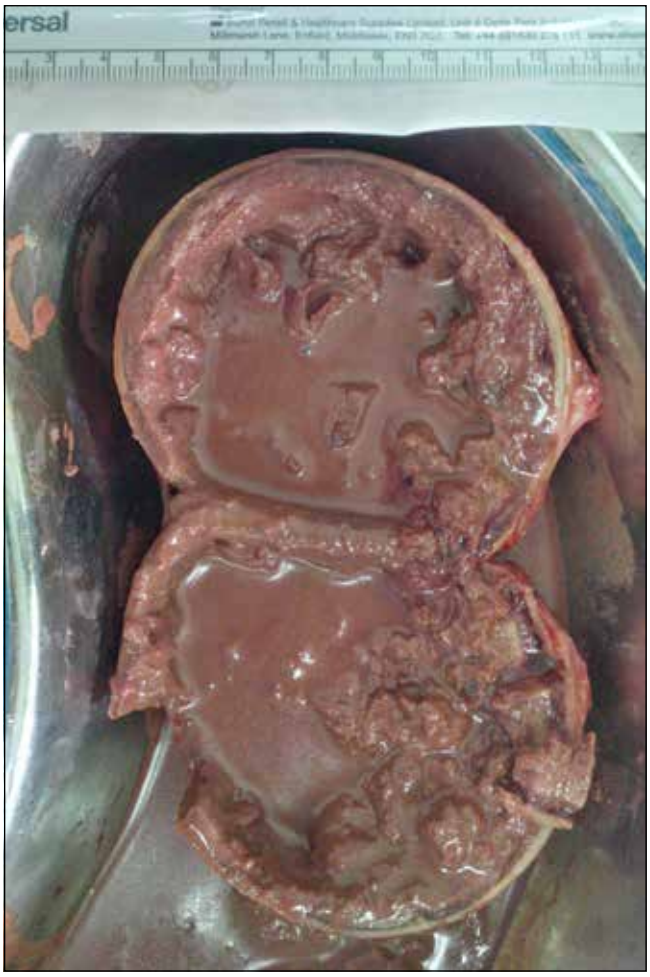

Fig 4. Section through the para-umbilical mass

The final histopathology report confirmed morphological features (…) of a benign simple cyst.

Case 3. (Six) fingers crossed for surgery

Despite our focus on hernias, some pathologies are frequently encountered in Africa. The picture below shows polydactyly, which is a common congenital abnormality - this patient has 6 fingers on both hands.

Fig 5. Bilateral Polydactyly

Through its volunteers, Hernia International has managed to bring hope to some of the most remote parts of the world. Feeling that you are part of something that makes a difference in the global community is one of the most powerful motivators for the team. Though we come from different cultural backgrounds, we all share the same passion for our profession. Surgery is our common language and working together through 12-hour-days with great people creates unbreakable bonds.

Northern Ireland will continue to be part of the Hernia International family through some of the medical professionals working here as well as the kind donations made by local people and institutions.

MY AFRICAN SURGICAL EXPERIENCE IN NIGERIA AND KENYA

By Aleksander Stanek

For those who lack experience of working outside the Western system, working in underdeveloped countries can seem like a different reality. I have worked in 2 African countries – Nigeria and Kenya. Many consider Africa a homogenous continent, but I found the 2 very different.

I spent 2 years in Nigeria where there is almost no public health system and most people pay for health care. In Kenya however, significant numbers in the National Hospital Insurance Fund scheme (NHIF) are treated for free, or at least have the option of public sector surgery. Being the only consultant surgeon in a city of almost 1 million was a big challenge, made more difficult by the lack of radiological and diagnostic backup. There was a poor-quality chest/abdominal X - ray and an unreliable ultrasound scanner which offered black and white patches on a 5' inch screen (it was frequently broken!). There was an extremely basic biochemical laboratory with turnaround of 24 hours for blood electrolytes. The two surgery theatres, working every day, were shared with the Gynae/Maternity ward but suffered nearly permanent blackouts covered by generators, but only if oil was available. Torches were necessary even during the day.

A shortage of surgical instruments was a serious problem at the beginning of my stay. I quickly found out that it was routine to keep all the 'sterile' instruments on one big table covered with an 'ever-sterile' drape, then take whatever was needed to prepare for the forthcoming procedure, irrespective of how long the instruments had been on the table. Thankfully the Medical Director, a German lady doctor with more than 35 years' experience of medicine in West Africa, gave me the opportunity to set up new laparotomy, hernia incision and drainage sets from high-quality German instruments, which she meticulously kept in her personal storage. Each instrument was marked to prevent them from misallocation to other sets during sterilisation, or simply 'vanishing'. Vanishing instruments are a well-known problem in African healthcare!

Other theatre resources were limited, such as the single diathermy machine. The machine was held in a massive cage with a monstrous padlock to prevent it from being stolen.

Despite such measures, the machine "vanished" within the first six months. Surgical theatres were equipped with air conditioning units, but most of the time these were either broken or switched off (particularly during the colder, rainy season). Another climate-specific problem in the OR was the ever-present equatorial African dust which is at its worst in the second half of the year because of Harmatan - a north wind from the Sahara Desert.

The staff were very devoted but there was a need to maintain a strict work etiquette so as not to lose continuity of care. Sometimes malaria, which was endemic in this region, disorganised the work in an unpredictable way. Sometimes, I was the only team member fit to work, operating through flare-ups my own malaria. The malaria prophylaxis eased symptoms, but relief was limited as I was not able to take bed rest for longer than 2 days at a time due to staff shortages. After several episodes of malaria during my stay in Nigeria, I didn't know which was worse - the malaria or the side effects of quinine, which I resorted to when other medicines failed to work.

TB and HIV were both common, often in the same patient. Surprisingly, the most common surgical procedure for TB was chest drainage for pleural effusions, resulting in liters of whitish, characteristically smelling pus. During my first ward round, I saw a junior doctor attempting tube insertion on a patient standing up in the dressing room. The patient cried out with pain as no local anaesthesia was given!

I immediately stopped this but a lack of anaesthesiologists was a serious problem. As in other less developed countries, the only available effective anaesthetic was ketamine. Unbelievably, this agent makes it possible to perform major procedures such as partial gastrectomy, cholecystectomy, small and large bowel resection without endotracheal intubation!

During my time in Nigeria, no endoscopy was available locally. The nearest service was in Lagos or Ibadan, but given a cost equivalent to 6 months' salary, endoscopies were not an option for most.

Double gloving, impermeable, thick rubber aprons, goggles and masks were all compulsory. The unlimited working time caused by permanently being on-call made this job radically different from the European Working Time Directive and NHS standards.

Does tropical surgery sub-specialisation really exist in its own right? The answer is both Yes and No!

Yes, as there are many conditions almost never seen in the West such as sickle cell disease, tropical ulcers, keloids, chronic lymphoedema and pyomyositis. Some conditions are known in the West, but in Africa, they have more diverse clinical presentations such as breast and abdominal TB, ascariasis, amoebiasis and typhoid fever. In Africa, disease and trauma related to animals are not uncommon; bites from wild animals - lions, hyenas and crocodiles, as well as peri-domestic creatures- monkeys, snakes and rodents. In some areas, insects may cause injury by bite, sting or simply skin contact - scorpions, ticks, fire ants and spiders all inhabit the region. Another local epidemic was trauma due to road traffic accidents.

No is also correct. Regardless of pathology, surgical skills and instruments remain the same. Malnutrition, bare-foot walking, limited access to medical care influenced pre-existing conditions, and managing adverse factors was as important as managing hernias. In 2002, I had received meshes for tension free hernia procedures. A group of 30 patients was successfully operated on with the mesh. Subsequently, only one patient developed wound infection which was treated conservatively with antibiotic. This patient was a 101-year old farmer who died the next year after hip replacement. On the morning of his hernia procedure, special precautions were taken, including a shower a short while before surgery (which was not easy considering the water shortages). These inguinal hernia mesh repairs were probably the first ever performed in West Africa, several years before the Operation Hernia Project was commenced by Professor Kingsnorth and colleagues in Ghana.

My Nigerian experience was not easy, but I was rewarded immeasurably by grateful patients and medical staff. The positive reinforcement I received from patients and staff has stayed with me for the rest of my life. Of course, I have never expected to be back to Africa but….

In 2012, while reading the British Journal of Surgery, I stumbled on an advert for Operation Hernia. The Gambia mission team for December 2012 was already assembled but I organised a mission for the next year. The location was Eruwa, a big village in Oyo State, Nigeria, very close to my old hospital. Dr. Oluyombo 'Yombo' Awojobi, a well-known Nigerian surgeon, ran a Hernia Clinic and hospital there.

Fig 6. Evening surgery with DIY equipment in Eruwa, 2013. Insects are on their way!

Based at newly built premises sponsored by Spanish surgeons, Yombo equipped his clinic with operation lamps which he constructed from basins and 150W bulbs! He used simply constructed operating tables instead of commercial ones due to limited financial resources. They did the job (Fig 6). Lack

of proper insulation of the windows made surgery impossible after sunset due to insects flying towards the lamps and swamping the operating tables and surgeons. Lessons learnt from this experience were invaluable to us.

Most cases were performed under local anaesthetic but rarely huge 'Nigerian' inguino-scrotal hernias were operated under spinal anaesthesia provided by a Nigerian anaesthetist - a team member available for only two days during the mission. As no general anaesthesia was available, we did not operate on big incisional hernias. We operated on up to 18 patients a day on the 3 tables with significant help from local junior doctors from Yombo's team. Patients underwent surgery over a period of 6 days, with 100% discharge within 24 hours and no immediate complications. We established a sound working pattern and an efficient process beginning every morning with a clinical review of all patients and producing an optimal running order according to anaesthetic requirements and pathology.

We were privileged to work with Baba Karim (Yombo's chief theatre nurse) and his staff, without whom day to day functioning would not have been possible. In addition to providing high quality surgical care, our team also taught the local surgical registrars tension-free mesh (mosquito net) repairs. By the end of the mission, 3 of the residents could successfully perform the procedure from start to finish. We were delighted to learn that 5 surgical registrars were inspired to continue using the newly learnt techniques at the hernia centre on a weekly basis outside of their regular duties.

Accommodation in Eruwa was the best our hosts could provide but lacked even a single-star rating. Electricity and running water were quite sporadic. Thankfully mosquito nets were available to us (not just to the patients!). We survived and left Nigeria safely without being assaulted by robbers (which is not uncommon), impressed with Dr Oluyombo Awojobi's warm attitude as well as the enthusiasm of his medical staff, and the perfect cooperation at all stages, including a simple Yoruba language lesson prior to our arrival. What else impressed me in Eruwa? The presence of 3 cash-machines in the middle of nowhere!

I also organised 2 missions to Gatundu, Kenya in 2015 and 2016. Uhuru Kenyatta (son of Jomo, the first Kenyan president, who was also incumbent at that time) owned a house in the village, as well as a large amount of land around it. The hospital in Gatundu, where the HI missions of 2015 were organised, was upgraded by the Chinese government for 2016. Generally, it looked good, but left us wishing for more facilities. For example, in one of the 2 theatres, a lamp has been attached in a fixed position one meter above the operating table without any possibility of changing this arrangement (thank God there was more than one lamp!).

Although our team left lots of instruments behind in 2015, they 'vanished'. Luckily an English team working in April 2016 left behind a diathermy machine along with some surgical instruments. We supplemented this with the diathermy machine donated by Tyrone County Hospital. I also received a lot of valuable medical items from manufacturers - gowns, gloves, sutures, diathermy pads and pencils. As usual, British Airways gave us a huge free baggage allowance to transport the equipment. This was greatly appreciated as many other European flight carriers refused.

Fig 7. Our "amazing" operating lamp 90 cm above the operating table in the new hospital, Gatundu

Compared with Nigeria, Kenyan infrastructure is more advanced, with an airport, buildings and roads built to a truly European standard and functioning with a high degree of safety. Our hotel was a 4-star establishment and was fenced, gated, with 24-hour security. We were charged a local rate which made our stay relatively cheap. Average temperature was around 20-25 degree Celsius. There were no issues with electricity and hot water. We commuted for 45 minutes to Gatundu hospital, ready to commence an operating day at 8.00 am.

Fig 8. Dr Ruth Muiri and Dr James Kariuki next to the diathermy machine donated by TCH, Omagh.

In Gatundu, we were privileged to work with the thoroughly professional and enthusiastic Kenyan anaesthetist Ruth Muiruri, who arranged our work very efficiently. There was only one SHO doctor – James Kariuki, who at first assisted us then went on to perform hernia repair under supervision. Quite often, a lack of scrub nurses meant we had to work alone, but this was not a problem.

For five days we were expecting to meet the Hospital Superintendent, who originally invited us out. He finally found a very brief moment to see us in his office on the top floor of the new building towards the end of our last day. His office was far away from the theatres. During this appointment we felt as though we were meeting a local Chieftain rather than a fellow doctor - far away from Yombo's attitude… far away from the NHS.

The next mission will go to Tanzania in 2017.

With special acknowledgements to Aleksandra Stanek .

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Clinical Paper

Hip Hemi-Arthroplasty vs Total Hip Replacement for Displaced Intra-Capsular Hip Fractures: Retrospective Age and Sex Matched Cohort Study

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Keywords: hip hemi arthroplasty, THR, fractured neck of femur, GIRFT, hip fracture database

ABSTRACT

Introduction: The Royal Victoria Hospital in Belfast is the largest volume hospital in the UK Hip Fracture Database. Management of displaced intra-capsular hip fractures is evolving in light of NICE[2] and BOA guidelines[3], with more patients receiving total hip replacement (THR) over hemi-arthroplasty. With current rationing within the NHS, it is vital that principles of the 'Getting It Right First time' (GIRFT) report[4] are implemented and the correct treatment choice made. Our aim was to assess Barthel scores[5], complication rate, blood transfusion rate and post op functional ability in two age and sex matched cohorts to see if our patient selection was appropriate.

Methods: Between January and December 2013, 2 age and sex matched cohorts each containing 46 hip fracture patients were retrospectively identified. The first group underwent Hip Hemi-Arthroplasty (HHA) and the second group underwent THR. We looked at complication rate, blood transfusion rate, pre- and post-operative locomotor ability as well as Barthel score[5].

Results: Average age in the HHA group was 69.7 with an average ASA grade of 2.61, compared to 71.2 and 2.43 respectively in the THR group. Complication rate in the HHA group was 45.6% with 2/3 due to chest sepsis or urosepsis. The THR group had a complication rate of 8.7% with 3/4 due to venous thrombembolism, reflecting the better pre-morbid physiological function in this cohort. Blood transfusion rates were similar in both groups. Barthel scores[5] showed average reductions of 2.67 in the HHA group and 0.30 in the THR group.

Conclusions: The application of the NICE guidelines[2] for arthroplasty choice in hip fracture management has led to judicious patient selection for THR. The THR group had a significantly lower complication rate ($p<0.05$) and better Barthel scores[5] ($p<0.05$) compared to the HHA group. In addition, having a higher ASA score (III or IV) or lower Barthel score[5] pre-operatively were independent predictors of complication occurrence.

INTRODUCTION

Neck of femur fracture is an increasingly common injury[1]. Fifty percent of these fractures will be intra-capsular[1] and the treatment option in the elderly population is arthroplasty. This raises an important question in every trauma unit; 'is Patient X a THR candidate?' Previously the answer to this question was largely down to individual operator preference and subjective impressions of fitness, however in 2011 the National Institute of Clinical Excellence (NICE) published guidelines[2] on arthroplasty choice in this patient cohort.

The Royal Victoria Hospital in Belfast is the largest volume hospital in the UK Hip Fracture Database. The management of displaced intra-capsular hip fractures is evolving in light of NICE[2] and BOA guidelines[3], with more patients receiving THR over HHA. In our unit, the NICE guidelines[2] on hip fracture management are used to direct our decision making of HHA vs THR. These guidelines state that THR should be offered to patients with displaced intracapsular hip fractures provided they can; mobilise independently with the aid of no more than a stick, are not cognitively impaired and are medically fit for anaesthesia and the procedure[2].

With current rationing within the NHS it is vital that the principles outlined by Professor Tim Briggs in the 'Getting It Right First time' (GIRFT) report[4] are implemented and the correct treatment choice made.

Our aim was to assess Barthel score[5] changes, complication

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Table 1.

Baseline Demographics and Clinical Parameters

Variable	*HHA Group (n=46)*		*THR Group (n=46)*		*P value*
Gender (Count)					
Male	7		7		1
Female	39		39		
ASA class (Count / %)					
I/II	18	39.1%	26	56.5%	n/s
III/IV	28	60.9%	20	43.5%	
Barthel Index at admission (count/%)					
<19	10	21.7%	1	2.2%	**0.004**
>=19	36	78.3%	45	97.8%	
Mean Age	69.7		72.0		
Mean Hb levels (Mean g/dl)					
Pre-op	12.25		12.87		**0.02**
Post-op	10.44		10.57		n/s
Lowest	9.2		9.12		n/s

rate, blood transfusion rate and post op functional ability in two age and sex matched cohorts to see if our patient selection for THR was appropriate.

METHODS

A retrospective case-control study was performed on 92 patients; 46 undergoing HHA and 46 who underwent THR. HHA cases were matched with controls of corresponding age and gender who underwent THR. The patients undergoing HHA had their surgery performed via the anterolateral approach. An Exeter stem with either a mono-block or bipolar head was used. In our unit, HHA was generally performed by a senior core trainee or junior registrar with consultant supervision.

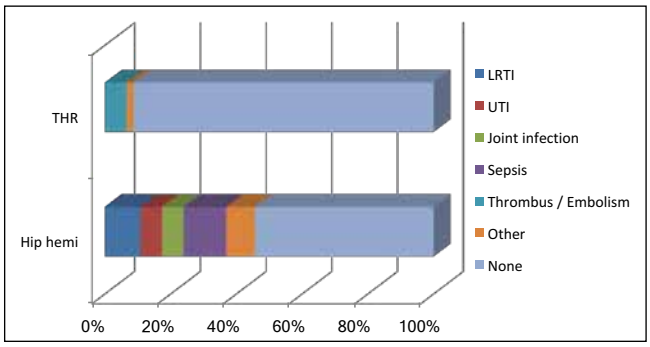

Fig 1. Demonstrates the complication rate in both groups. The majority of patients (90%) in the THR group did not suffer any complications. The range of complications in the HHA group was greater. Common complications in this group were respiratory tract infection, urinary tract infection and joint infection.

The total hip arthroplasties had their procedure performed via the posterior approach to the hip with capsular and piriformis repair on closure. The implants used were a cemented Exeter stem with either a cemented or cementless acetabular component. In our unit these surgeries are performed by a consultant or a senior registrar under consultant supervision.

ASA scores were recorded in both groups pre-operatively. Barthel Index[5] was measured pre-operatively and after 3 & 12 months in both groups to assess post-operative functional recovery. The number and nature of comorbidities and complications were also recorded. The rate for blood transfusion was also recorded in both groups.

The primary outcome measure for this study was the Barthel score[5] at 3 and 12 months post-operatively. Secondary outcome measures included requirement for blood transfusions and complication rate in both groups.

Statistical analyses

Data were entered into Excel and analyzed using SPSS 22 for Windows. Continuous variables were expressed as mean/standard deviation while categorical variables were expressed as count/percentage. Univariate analyses were performed using Pearson's Chi-Square or Fisher-Exact test for categorical variables. Shapiro Wilkov test was used to assess the normality of continuous variables. Normally distributed variables were compared using student t-test and ordinal/non-normal variables were compared using Mann-Whitney test. Unadjusted p-values were then calculated and a p-value less than 0.05 was considered statistically significant.

Multivariate logistic regression with a conditional forward approach was performed to account for the effect of the confounders and the multiple explanatory variables on the occurrence of surgical complications and the requirement for blood transfusion. Adjusted odds ratio and P values were calculated for the explanatory variables that were associated with each of the previous outcomes using univariate analysis. Continuous variables were recoded as categorical variables so that they could be integrated into a model to determine the independent predictors of surgical complications requirement for blood transfusion.

RESULTS

Baseline data

Baseline demographics, clinical and biochemical parameters for the all patients are shown in Table 1. The majority of study participants were females (84.4%). The mean age for patients in the HHA group was 69.7 ± 8.23 years, while patients in the THR group had a mean age of 72.02 ± 8.49 years. Both groups were matched for age and gender (P>0.05). Although the proportion of patients with ASA scores III/IV was higher in the HHA group, it did not reach statistical significance (P= 0.095). The majority of the participants were non/ex-smokers (80.4% in the HHA groups and 84.8% in the THR group, p=0.582). There was no significant difference in the drinking habits between both groups. The number of comorbidities was not significantly different between the groups; however pre-op haemoglobin levels were lower in the HHA group (12.25 ± 1.4 vs. 12.87 ± 1.1 in the THR group, p = 0.02) although this difference was very small and unlikely to be clinically relevant. Postoperative haemoglobin levels did not show such a difference. Another parameter that showed a significant difference between both groups was the Barthel score at admission. The proportion of patients with a Barthel score[5] above 19 was significantly higher in the THR group with only one patient having a score less than 19 (97.8% of THR group had Barthel scores 19 or higher). By contrast, only 36 patients (78.3%) of the HHA group had Barthel scores[5] of 19 or higher (p= 0.004).

Complication rate, Blood transfusion rate and Reduction in Barthel Score; Hip Hemi-arthroplasty vs Total Hip Replacement

There was no significant difference between both groups with regards requirement for blood transfusion (Table 2), as 11 patients in each group needed one or more units of packed red cells during or after surgery (23.9% in each group). Although mortality was higher in the HHA group (4 patients after 12 months vs. none in the THR group), this difference was not statistically significant (p= 0.117). However, complications were more common in the HHA group; 21 patients (45.7%) versus four patients in the THR group (p=0.000068). Complications in the HHA group included hospital and community acquired pneumonia, urosepsis and joint infection, while most of the complications in the THR group were due to venous thromboembolism (Table 2). There was one dislocation in the THR group. The THR group had a smaller reduction in their Barthel score at 3 and 12 months post-op. After 3 months, the mean reduction in the Barthel

TABLE 2.

Transfusion requirements, mortality, complications and Barthel scores; Hip Hemi vs THR

	HHA Group (n=46)		*THR Group (n=46)*		*P value*
Transfusion needed					
Yes	11		11		
No	35		35		
Mortality at 12 months (Count / %)					
Alive	42	91.3%	45	100%	0.117
Deceased	4	8.7%	0	0	
Complications (Count / %)					
Yes	21	45.7%	4	8.7%	**6.8 x 10-5**
No	25	54.3%	42	91.3%	
Complication according to class (Count/%)					
Respiratory tract infections	5	10.9%	0	0	
Urinary tract infection	3	6.5%	0	0	
Joint infection	3	6.5%	0	0	
Sepsis	6	13%	0	0	
Thrombus/Embolism	0	0	3	6.5%	
Other	4	8.7%	1	2.2%	
None	25	54.3%	42	91.3%	
Mean reduction in Barthel index at 3 months	1.95		0.196		**0.000125**
Mean reduction in Barthel index at 12 months	1.21		0.311		**0.051**

score was 1.95 in the HHA group compared to only 0.195 in the THR group (p= 0.000125, Table 2). After 12 months, the reduction in score was still higher in the HHR group (Table 2) although the difference was marginally significant in this case (p=0.051).

Requirement for Blood Transfusion

High ASA score and low preoperative haemoglobin level were associated with requiring blood transfusion post-operatively. Patients with ASA III / IV were 4x more likely to require blood transfusion than those with ASA score of I/II (95% CI 1.38 – 13.68) (Figure 2). Patients with preoperative haemoglobin less than 12.5 also had a higher chance of requiring blood transfusion (OR 4.11, 95% CI 1.48 – 11.44) (Table 3). Multivariate logistic regression showed that both ASA scores and preoperative haemoglobin level were independent predictors for requiring blood transfusion.

TABLE 3.

Association between demographics, biochemical parameters, clinical parameters and requirement for transfusion

Variable			Required transfusion	
		No.	No.	Percentage
ASA	I / II	44	5	11.4%
	III / IV	48	17	35.4% (p = 0.07)
Age	<70	34	6	17.6%
	>70	58	16	27.6% (p = NS)
Pre-op Haemoglobin (g/dl)	<12.5	39	15	38.5%
	>12.5	53	7	13.2% (p = 0.005)

Complications during/post-surgery

Univariate analysis showed that males were more likely to experience complications peri-operatively (p=0.051) although the association was marginally significant (Table 4.) Nearly half of patients who underwent hemi-arthroplasty experienced complications (45.7%) compared to only 8.7% of those who underwent THR (p=6.8 x 10^{-5}). Moreover, the requirement for blood transfusion was associated with developing surgical complications (45.5% vs. 21.4%, p= 0.027). This is further illustrated in Figure 3.

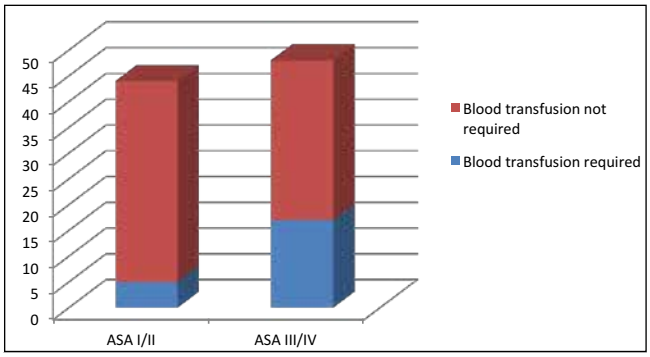

Fig 2. ASA score as predictive of requiring blood transfusion

TABLE 4.

Association of demographics, biochemical and clinical parameters with occurrence of surgical complications

Explanatory Variable			*Occurrence of Complication*		
N			*N*	*Percent*	*Significance*
Gender	Male	14	7	50%	
	Female	78	18	23.1%	**Yes** (p = 0.028)
Surgical procedure	Hip Hemi	46	21	45.7%	
	THR	46	4	8.7%	**Yes** (p = 0.0002)
Transfusion	Yes	22	10	45.5%	
	No	70	15	21.4%	**Yes** (p = 0.018)
ASA	I/II	44	7	15.9%	
	III/ IV	48	18	37.5%	**Yes** (p = 0.02)
Age	<70	34	10	29.4%	
	>=70	58	15	25.9%	No
Barthel score	<19	11	7	63.6%	
	>=19	81	18	22.2%	**Yes** (0.008)
Co-morbidities	<2	34	9	26.5%	
	>=2	58	16	27.6%	No

Having an ASA score of III/IV was also associated with an increased risk of complication (p=0.02, Table 4). The number of comorbidities alone was not associated with developing surgical complications (Table 4), however a lower Barthel score[5] at admission (<19) did have a significant association with complication occurrence (p= 0.008, Table 4).

In summary, multivariate logistic regression identified gender, nature of surgery and requirement for blood transfusion as independent predictors of developing surgical complications. Patients who underwent HHA were more likely to experience complications after surgery (OR 12.1, 95% CI 3.3 – 45.35), as were males (OR 0.17, 95% CI 0.035 – 0.822) and those requiring blood transfusion (OR 0.21, 95% CI 0.056 – 0.767).

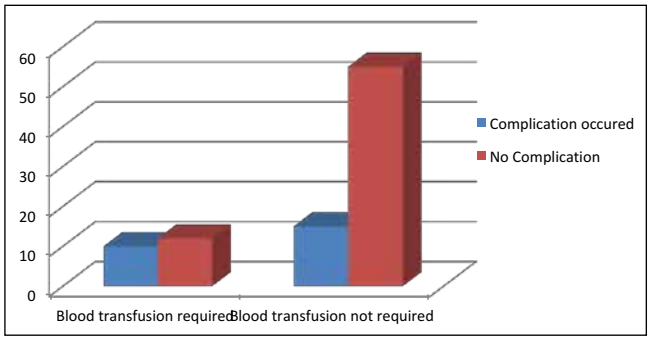

Figure 3. Complication rate according to requirement for blood transfusion

DISCUSSION AND CONCLUSION

The results demonstrated significant differences in the post-operative recovery in these two patient cohorts. Interestingly the mean age in the HHA group was younger than in the THR group which is perhaps the opposite of what would have been expected. There were a larger proportion of ASA III/ IV patients in the HHA group which reflects the frailer nature

of this cohort. The fact that this difference did not reach statistical significance may indicate that the sample sizes in this study were not large enough.

The complication rate in the HHA group (45.7%) was significantly higher in comparison to the THR group (8.7%). This may be explained by a poorer physiological condition in this cohort upon admission. There were also a greater proportion of patients in this cohort with a Barthel score[5] <19. In our experience, patients with a poorer mobility baseline are slower to rehabilitate and mobilise post-operatively and are thus more vulnerable to chest and urinary infection. This may have contributed to the high rate of chest and urosepsis in this cohort. Another factor which may have contributed to the higher complication rate is the grade of operating surgeon. In our unit, HHA is generally performed by a senior core trainee or junior registrar under consultant supervision. Procedure time may have been longer than if a senior surgeon was operating.

Of note, there was only one dislocation in the THR group. This would be considered a low rate of dislocation given that the THRs were being performed in the setting of trauma. It is well documented that the rate of dislocation in THR performed following a fractured neck of femur is significantly higher [6].

We found patients with ASA grade III or IV were nearly 4x more likely to require blood transfusion than those with ASA scores of I or II. This may be explained by a poorer haematopoietic potential in frailer patients with more co-morbidities.

There are some weaknesses in this study. Firstly, the sample sizes may not have been large enough as certain expected differences between the cohorts such as mean ASA score and mortality rate did not reach statistical significance. There were also different grades of surgeons operating on each cohort which may influence operative time and thus complication rates.

In our experience, the application of the NICE guidelines[2] for arthroplasty choice in hip fracture management has led to judicious patient selection for THR. In this study, the THR group had a significantly lower complication rate ($p<0.05$) and better Barthel scores[5] ($p<0.05$). With the trend toward performing greater numbers of THR surgeries in the hip fracture population, it is important to emphasise careful patient selection. It is important that we do not tip the balance and over-select patients for THR as this may led to frailer patients undergoing a more invasive procedure which may bear out in higher complication rates and increased mortality.

Large, appropriately powered studies are required to further define pre-morbid criteria to enable appropriate patient selection for THR.

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FURTHER READING

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Clinical Paper

ESCAPE to Reality, Post-Trial Outcomes in an ESCAPE Centre: A Retrospective Case-Control Study.

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ABBREVIATIONS

IV-tPA	Intravenous tissue plasminogen activator		**MCA**	Middle cerebral artery
ASPECTS	Alberta Stroke Program Early CT Score		**mRS**	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale		**IQR**	Interquartile range
ICA	Internal carotid artery		**TICI**	Thrombolysis in cerebral infarction

ABSTRACT

Introduction The Royal Victoria Hospital, Belfast provides the regional neuroendovascular service for Northern Ireland and was an enrolling centre for the ESCAPE endovascular stroke trial. Our aim was to assess outcomes for patients presenting with acute stroke following discontinuation of trial enrolment at our centre.

Methods We collected data on all patients presenting with acute stoke between Nov-1st-2014 and Oct-31st-2015 who received endovascular treatment or received IV thrombolysis (IV-tPA) alone. ESCAPE eligibility of each patient was assessed. Primary outcome was modified Rankin Score (mRS) at 3 months.

Results 129 patients presented with acute stoke symptoms during the time period; 56/129 (43.4%) patients in the intervention group and 73/129 (56.5%) patients in the control group. In the interventional group, 42/56 (75%) were considered ESCAPE eligible and 14/56 (25%) were considered ESCAPE ineligible. 30/42 (71.4%) ESCAPE eligible patients had a positive functional outcome at 3 months compared to 9/14 (64.2%) ESCAPE ineligible patients. In the control group, 37 (50.7%) had identifiable thrombotic occlusion and 13/37 (35.1%) were considered eligible for intervention. 4/13 (30.8%) achieved functional independence (mRS<3) at 3 months.

There was a statistically significant difference in functional independence in those who underwent endovascular therapy compared to the control group (p= 0.04).

Conclusion ESCAPE eligible patients in our centre had favourable outcome rates superior to the published trial data. ESCAPE ineligible patients tended to do slightly less well, but still better than the favourable outcome rates achieved with IVtPA alone. There is potentially a wide discordance between the threshold for futility and trial eligibility criteria when considering endovascular treatment for acute ischaemic stroke.

INTRODUCTION

Endovascular therapy for acute ischemic stroke is now accepted as the standard of care for selected patients with anterior circulation occlusion following publication of five positive randomized trials; MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME and REVASCAT.[1-6] The Royal Victoria Hospital, Belfast, UK was one of 22 international centres to enrol patients into the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial.[3] Enrollment into the ESCAPE trial was stopped in October 2014 following unplanned interim analysis triggered by release of the MR CLEAN trial results which showed superior efficacy of endovascular therapy. The safety monitoring board advised stopping the study as the prespecified boundary for efficacy had been crossed.[3]

It is estimated that 5-10% of patients with ischaemic stroke may benefit from endovascular therapy.[7] The RVH serves

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a population of approximately 400000 people and treats an estimated 120-150 acute strokes per year with IV-tPA and/or thrombectomy. At our centre, routine imaging work-up when endovascular therapy is available includes unenhanced CT brain, CT angiogram from the aortic arch and CT perfusion. Patients who are transferred from other units for endovascular therapy will have been initially triaged by the stroke team and interventional neuroradiologist following imaging review via the regional NIPACS (Northern Ireland Picture Archiving and Communication System) service. Imaging will then be repeated upon arrival (CT brain and CT angiogram) to assess continued eligibility for thrombectomy. We prospectively evaluate the ASPECTS score in all patients, which is a 10-point scoring system to determine the extent of early ischaemic changes in the middle cerebral artery territory.[8] A maximum of 10 reflects normal and 1 point is deducted for every abnormal region. ASPECTS ≤ 5 is considered to be the threshold for futility. Clot location and perfusion mismatch is also documented. We regard the ESCAPE trial eligibility criteria as a guide, but not prescriptive when considering endovascular therapy and it does not define our boundary for endovascular treatment.[3] For patients receiving endovascular therapy we prospectively document procedural times and recanalization success. Baseline and discharge NIHSS is also recorded routinely in all admitted stroke patients. Our stroke research nurse evaluates 3-month mRS via clinic appointment or telephone assessment.

The purpose of this study was threefold; first to ensure that patients meeting eligibility criteria for the ESCAPE trial continued to have outcomes comparable with the published data. Second, to evaluate outcomes in patients receiving endovascular treatment who would not have been eligible for ESCAPE as per the trial inclusion criteria. Lastly; to evaluate the outcomes in all patients who underwent medical treatment for acute ischemic strokes. Considering the service for endovascular treatment remains time limited, we were particularly interested in the outcomes of patients who were potentially eligible for endovascular treatment according to the ESCAPE trial eligibility criteria but received thrombolysis only.

MATERIALS AND METHODS

This retrospective case-control study was conducted on clinical records of all patients admitted to the Royal Victoria Hospital, Belfast from 1st November 2014 to 31st October 2015 who were treated for acute ischaemic stroke (n=129). The clinical records of 56 patients who underwent endovascular treatment with or without IV-tPA were "intervention cases". The remaining clinical records of 73 patients who received IV-tPA only served as "controls" for the study. Within each of the intervention and control groups patients were stratified by those considered ESCAPE eligible and those considered ESCAPE ineligible. The major ESCAPE trial eligibility criteria are presented in Table 1. For all patients treated via endovascular therapy we collected demographics including baseline NIHSS, baseline mRS, ASPECTS on initial unenhanced CT, clot location, administration of IV-tPA, CT to groin puncture time, groin puncture to recanalization time, TICI score, procedural complications, discharge NIHSS and 3-month mRS.

For patients treated via IV-tPA alone we collected demographics including baseline mRS, ASPECTS on initial unenhanced CT, clot location, discharge NIHSS and 3-month mRS. Patients were grouped into those considered ESCAPE eligible and those considered ESCAPE ineligible if an occluding thrombus was identified. Patients without an identifiable thrombus were evaluated separately

As this was a service evaluation study informed consent was not obtained.

Outcome measures. The functional outcome in each patient at 3 months after treatment was evaluated by the mRS score.

Statistical analysis. Descriptive statistics were computed and compared between the intervention and control groups. A chi squared test was applied to determine whether there was any statistical significance in functional outcomes between the control and intervention groups, between ESCAPE eligible and ineligible in the intervention group and between ESCAPE eligible patients in the control and intervention groups. The following assumptions were made for the analysis; a positive outcome[1] resulting in functional independence was defined as an mRS of <3 at 3 months and a negative outcome[2] defined as an mRS of ≥3 at 3 months. We hypothesise that for the intention to treat population (ITT), endovascular treatment has more positive outcomes than medical therapy alone. We also hypothesise that for the endovascular treatment population (ETP), ESCAPE eligible patients would also have more positive outcomes than non-eligible patients. Statistical significance was set at the p = 0.05 level.

RESULTS

Demographic and clinical characteristics for both the ITT and ETP are reported in Figure 1 and Tables 2 & 3. Overall 129 patient clinical records were identified that met the inclusion criteria of the study. There were 56 intervention and 73 control cases. Patients who had intervention and no intervention appear to be relatively homogeneous with regards to age, sex, baseline NHISS Score and basline

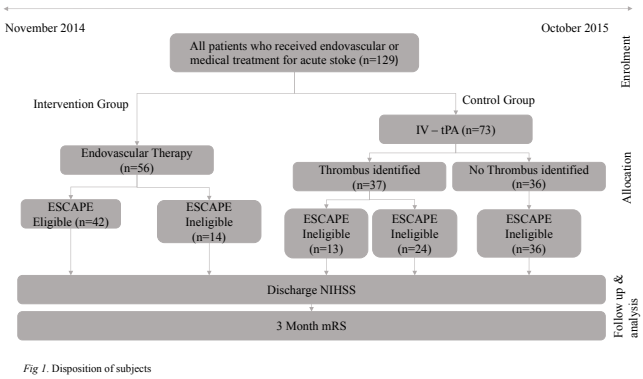


Fig 1. Disposition of subjects

Fig 1. Disposition of subjects

Table 1.

ESCAPE trial eligibility

Criteria	Description
1.	NIHSS score >5
2.	<12 hours onset of symptoms
3.	Adult (>18 years). No age limit
4.	Good pre-morbid status (baseline mRS ≤2)
5.	CT brain: ASPECTS Score >5
6.	CT angiogram showed occluded proximal artery in the anterior circulation.
7.	CT angiogram showed good collateral circulation

ASPECTS on CT. All subjects in the control group were treated with IV alteplase.

Intervention group. Of the 56 cases treated via endovascular therapy, 42 (75%) were considered eligible for intervention using the ESCAPE trial eligibility criteria and 14 patients (25%) were considered ineligible. These patients appear to be homogenous with regards to age, NHISS Score, treatment with IV alteplase and ASPECTS on CT. There were more females in the eligible group 24 (57.1%) compared to the ineligible group 4 (28.6%). The reasons for ineligibility included 6 (43%) patients with basilar artery occlusion and 8 (57%) patients with solitary M2 level occlusions. Twenty-one (37.5%) cases underwent endovascular therapy following transfer from another stroke centre in Northern Ireland. Median time from CT to groin puncture was 26 minutes (IQR: 21-32) and median groin puncture to recanalization was 35 minutes (IQR: 25-65) in the ESCAPE eligible group. For the ESCAPE ineligible group, median time from CT to groin puncture was 18 minutes (IQR: 15-34) and for groin puncture to recanalization was 43 minutes (IQR: 24-85). Recanalization success as defined by TICI 2b/3 was 33/42 (78.5%) in the ESCAPE eligible group and 12/14 (85.6%) in the ESCAPE ineligible group. Median discharge NIHSS score was 9 (IQR:2-15) in the ESCAPE eligible group and 9 in the ESCAPE ineligible group (IQR: 3-15). Functional independence as defined as mRS 0-2 was 30 (71.4%) in the ESCAPE eligible group and 9 (64.2%) in the ESCAPE ineligible group. The following post procedural complications occurred; 3 (5.4%) patients developed intracranial haemorrhage and 1 patient developed a common femoral artery pseudoaneurysm.

Table 2.

Baseline Characteristics and Process Measures

Variable	**Intervention (n=56)**	**Control (n=73)**
Demographics		
Age -yr		
Median	71	72
IQR	61-78	67-84
Female – no. (%)	28 (50%)	37 (50.7%)
Clinical characteristics		
NIHSS Score*		
Median	16	11
IQR	11-20	6-18
Treatment with IV alteplase no. (%)	27 (48.2%)	73 (100%)
Imaging Characteristics		
ASPECTS on CT	9(7-10)	10(8-10)

**Scores on National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits*

Table 3.

Baseline Characteristics and Process Measures within Intervention Group

Variable	ESCAPE eligible (n=42)	ESCAPE ineligible (N=14)
Demographics		
Age -yr		
Median	71	67
IQR	62-78	40-77
Female sex – no. (%)	24 (57.1%)	4 (28.6%)
Clinical characteristics		
NIHSS Score*		
Median	16	14
IQR	(11-20)	(5-18)
Treatment with IV alteplase no. (%)	21 (50%)	6 (43%)
Imaging Characteristics		
ASPECTS on CT	8 (7-9)	10 (8-10)

**Scores on National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits*

Control group. 73 cases were treated with IV-tPA, 37 (50.7%) had identifiable thrombotic occlusion (via CT angiography or the presence of a hyperdense vessel on unenhanced CT). Of these 23 (62%) patients had proximal anterior circulation occlusion (ICA/M1), 11 (30%) had M2/A2 occlusion and 3 (8%) had posterior circulation occlusion. 13/23 proximal anterior circulation occlusion cases would have be considered eligible for endovascular intervention based on the ESCAPE eligibility criteria. 12 (92.3%) of these patients who were considered ESCAPE eligible presented out of hours when the clot retrieval service was not available. Overall, median door to needle time was 48 minutes (IQR: 33-65) among IV tPA patients. Median discharge NIHSS score for ESCAPE eligible patients treated with IV tPA was 19 (IQR: 14-22). For ESCAPE ineligible patients with thrombotic occlusion median discharge NIHSS was 8 (IQR: 3-15*)* and for patients without thrombotic occlusion median discharge NIHSS was 3 (IQR:0-5). In patients with thrombotic occlusion, functional independence as defined by mRS 0-2 at 3 months was 4 (30.8%) among ESCAPE eligible patients compared to 9 (37.5%) among ESCAPE ineligible patients. Table 4 summarises the outcomes of the intervention and control

TABLE 4.

Clinical Characteristics in Intervention and Control Groups

	Endovascular Therapy n=56		IV-tPA Thrombus Identified N=37		IV-tPA No Thrombus Identified
Clinical characteristics	ESCAPE Eligible (N=42)	ESCAPE Ineligible (N=14)	ESCAPE Eligible (N=13)	ESCAPE Ineligible (N=24)	ESCAPE Ineligible (N=36)
3 Month mRS 0-2 – n (%)	30(71.4%)	9(64.2%)	4(30.8%)	9(37.5%)	25(69.4%)
Discharge NIHSS Score* - Median (IQR)	9 (2-15)	9 (3-15)	19 (14-22)	8 (3-15)	3 (0-5)

**Scores on National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits*
n: Number of patients with outcome. N: Total number of patients within group.

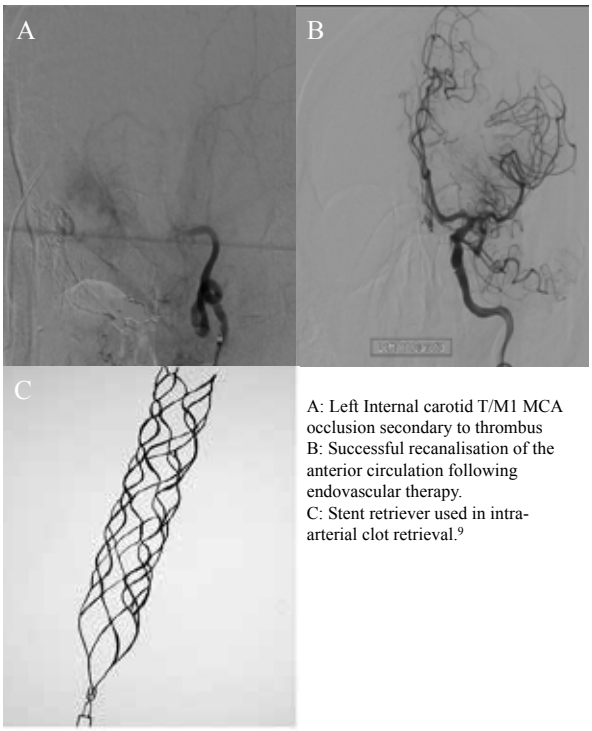
groups.

Analysis. The chi squared analysis showed a statistically significant difference in functional independence (mRS<3) in those who underwent endovascular therapy compared to the control group, χ^2 (1, n=129) = 4.0742 p= 0.04. Eligibility criteria was also considered as a factor that could influence functional outcomes within the intervention group but was not statistical significant. An additional analysis showed a statistically significant difference in functional outcomes in patients who were ESCAPE eligible and underwent intervention and those who were ESCAPE eligible and received IV-tPA only, χ^2 (1, n=55) = 6.9531 p = 0.008.

DISCUSSION

Our study showed that patients with acute ischemic stroke and proximal anterior circulation occlusion with a small core infarct who were treated with endovascular therapy had improved functional outcomes at 3 months compared to those treated with IV-tPA only (p=0.04). Good outcome rates were superior to ESCAPE results (71.4% versus 53.0%) and support the benefit of endovascular therapy in the treatment of acute stroke.[3] Our higher good outcome rates may be accounted for via our faster documented procedural times (median CT to recanalization of 68 minutes versus 84 minutes) and slightly better documented recanalization rates (TICI 2b/3 78.5% versus 72.4%) An example of successful recanalisation is shown in Figure 2. The rate of post procedural haemorrhage was slightly higher in our centre compared to the trial (5.1% versus 4.2%).

Despite high level evidence supporting endovascular therapy in acute stroke, there is heterogeneity among the intention to treat population.[2-6] For example, two trials enforced age limits on potentially eligible patients (SWIFT PRIME and EXTEND IA) and the onset of treatment of endovascular therapy varied among studies (within 6, 8 or 12 hours).[4,5] Baseline imaging to evaluate vessel occlusion and salvageable brain tissue, presenting ASPECTS, baseline NIHSS score, and contraindications to thrombectomy varied between trials. Consensus regarding the inclusion of solitary M2 occlusions also differed. Although MR CLEAN and REVASCAT included solitary M2 occlusions, the overall numbers were small and a recent meta-analysis of the five trials published in the Lancet did not demonstrate significant benefit for intervention for these distal occlusions.[2,6,10] Firm evidence for thrombectomy in this location may remain elusive given the difficulty in distinguishing (and inconsistency in classification) between the M1 and M2 segments and the greater anatomical variability with the M2 segment.[11] The limits for intervening in basilar artery occlusion may also be difficult to define, given the otherwise high rate of death and dependence among survivors with conservative management.[12]



A: Left Internal carotid T/M1 MCA occlusion secondary to thrombus
B: Successful recanalisation of the anterior circulation following endovascular therapy.
C: Stent retriever used in intra-arterial clot retrieval.[9]

Fig 2. An example of successful recanalisation

In our centre, the ESCAPE eligibility criteria do not strictly define our boundary for treatment, with approximately one quarter (14/56, 25%) of our endovascular cases being outside eligibility criteria. The overall outcome at 3 months for these patients was slightly worse compared to the ESCAPE eligible group (64.2% compared to 71.4%). However, these results

were not statistically significant (p=0.61) accepting the null hypothesis that there is no difference in functional outcomes when selecting patients for endovascular treatment using the ESCAPE eligible criteria. Although patients deemed ESCAPE ineligible represent a very heterogeneous patient group, as the interventional cases in this study had solitary M2 (8/14) or basilar artery clots (6/14).

As this is a relatively new and evolving service, our endovascular stroke service continues to be time limited to 'office hours' with only ad hoc out of hours availability. In our study, there was a statistically significant difference in functional outcomes in ESCAPE eligible patients within the intervention group compared to ESCAPE eligible patients within the control group who presented outside office hours (p=0.008). These patients treated solely via IV-tPA but deemed ESCAPE eligible had very similar 3-month outcomes to the control group (30.8% versus 29.3%). There is a clear imperative to deliver an effective and accessible 24/7 thrombectomy service. Indeed, given the effective outcomes with thrombectomy it is not surprising that this treatment is cost effective within the NHS.[14] It should also be noted that 21/56 (37.5%) patients treated with thrombectomy were transferred in from other units which cover 78% of the Northern Ireland population (NI population – Belfast Trust population/NI Population x 10). Equity of access to this service must also be addressed.

There are limitations to this study. The overall numbers are small, data presented has not been independently verified and assessment of 3-month mRS was not carried out by a blinded assessor. It will be useful to collect additional data to assess outcomes between those presenting directly to the RVH compared to those who are transferred from other units. 32.4% (35/108) of actively treated acute ischaemic strokes within the Royal Victoria Hospital received thrombectomy during this period. It would be useful to compare with other units that rely on transferring patients to access the endovascular service for the purposes of future planning.

Further research addressing thrombectomy in basilar clots and single M2 occlusions is needed. Research to compare intravenous lysis plus endovascular treatment versus endovascular thrombectomy alone is also limited.

CONCLUSIONS

The primary purpose of this study was to demonstrate outcomes in our centre following discontinuation of patient enrolment into the ESCAPE trial. In real world practice, outside of trial participation, our centre has demonstrated outcomes better than the published data from ESCAPE. Patients treated via endovascular therapy but considered ESCAPE ineligible also had overall outcomes better than those treated via IV-tPA alone. However, given the extent of heterogeneity in this group, defining the absolute boundary of futility will likely prove difficult and in practice the decision to intervene will remain a judgment call.

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Clinical Paper

Age adjusted D-dimer in the Belfast Health and Social Care Trust: A retrospective study

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ABSTRACT

D-dimers combined with clinical pre-test probability (PTP) scores are used to determine the likelihood of a venous thromboembolic event (VTE). It is recognised that with advancing age, d-dimer values increase, leading to a cohort of patients with a d-dimer above the standard cut-off of 500μg/L. A recent systemic review, examined the accuracy of an age-adjusted D-dimer in those aged > 50 years with a low clinical risk of a VTE. This showed an increase in specificity without loss of sensitivity. Our study, aimed to examine a population of patients, who between 2011 and 2014 underwent ultrasound Doppler studies of lower limbs. By applying a corresponding age-adjusted D-dimer, we determined the sensitivity and specificity and compared this to use of conventional D-dimer.

INTRODUCTION

D-dimers are fibrin degradation products which result from plasmin activated fibrinolysis. Their presence suggests activation of the coagulation system.[1] D-dimers are used in conjunction with clinical pre-test probability (PTP) scores to determine the likelihood of a venous thromboembolic event (VTE).[2] A commonly used pre-test probability scoring system is the Wells' Score.[3] The Wells' score is used in ambulatory patients and calculates the likelihood of VTE, such as deep venous thrombosis or pulmonary embolism. This practice is supported by NICE guidelines on diagnosing VTE.[4] If the PTP score is low, a corresponding negative D-dimer rules out the need for imaging, as the likelihood of a VTE is low. If however, the D-dimer is elevated, then ultrasound Doppler imaging is required.[4] It is recognised that D-dimers increase with advancing age, leading to a high proportion of patients with d-dimers above the standard cut off value of 500μg/L with no underlying VTE.[5,6]

A recent systematic review assessed the accuracy of age adjusted D-dimer in those >50 years of age with a low PTP for a VTE event. It suggested there was an increased specificity without loss of sensitivity of age-adjusted D-dimer versus conventional D-dimer.[7] This would infer benefit in using age adjusted d-dimer in determining which patients require ultrasound Doppler. An age-adjusted D-dimer is calculated based on age (years) x10μg/L.

Lapner et al published evidence refuting the role of age-adjusted D-dimer, suggesting that the increased specificity is a result of a non-specific increase in the average D-dimer threshold used to exclude VTE.[8]

In our study, we aimed to assess the potential role of age adjusted d-dimer, its reliability and the potential impact it could have on both the patient journey and radiology services within the Belfast trust. If evidence supported age-adjusted D-dimer, it could potentially reduce the number of ultrasound Doppler requests, resulting in time and resource savings.

METHODS AND MATERIALS

The radiology department of the Royal Victoria Hospital provided data on all ultrasound Doppler of lower limbs performed in the department between 2011 and 2014. This included both inpatients and those attending A&E (either self-presentation or referral from primary care).

A search was then conducted through hospital laboratory records for the corresponding d-dimer result. This left us with a cohort of 350 patients, aged >50 years, with a recorded d-dimer who underwent Doppler ultrasound imaging of lower limbs. Using this data, we calculated the sensitivity and specificity using age-adjusted d-dimer versus conventional D-dimer in four different age categories; 51-60 years, 61-70 years, 71-80 years and > 80 years of age. A cohort of patients aged less than 50 years were also included as a comparator group.

PTP was not consistently recorded in inpatient records or on radiology requests to allow for any reliable, accurate statistical information to be calculated from this.

RESULTS

Demographics of the group are detailed in Table.1

Specificity of conventional D-dimer is known to be between

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Table1.

Patient Demographics

Patient Demographics			
Age Group (years)	Total	Male	Female
51-60	69	37	32
61-70	85	42	43
71-80	107	69	38
>80	89	60	29

49-67% in those less than 50 years and anything between 0-18% in those over 80 years.[7] The specificity of age-adjusted d-dimer in our cohort was higher than that of conventional d-dimer in all age groups recorded. The sensitivity was maintained above 75% in all categories with use of age-adjusted d-dimer. These figures are shown in Table.2.

Table2.

Specificity and Sensitivity of age-adjusted and conventional D-dimer

Age Group (years)	Specificity (%)		Sensitivity (%)	
	Age-adjusted	Conventional	Age-adjusted	Conventional
<50	N/A	41	N/A	68.8
51-60	39	23	92	92
61-70	33.8	23	80	80
71-80	32	16.5	78.6	100
>80	36.4	8.1	80	100

N/A – Not applicable

Hypothetically, if those with a low PTP had a corresponding negative age-adjusted D-dimer, application of age-adjusted d-dimer cut-off value could have prevented 59 (16.6%) inappropriate Dopplers in our cohort.

With use of age-adjusted D-dimer across the whole cohort, there were 14 false negatives. Of these, four Dopplers revealed non-occlusive clot in keeping with an old VTE and not an acute episode, reducing this to 10 false negatives. Of these ten episodes, only five had a corresponding PTP recorded. Three patients had low risk scores while the remaining two had scores suggesting high likelihood of DVT. It is difficult to draw conclusions from this data due to its limited nature.

DISCUSSION

Our findings are in keeping with those of Schouten et al; the use of an age-adjusted d-dimer cut-off value of age (years) x 10μg/L, increases the specificity of the test, when used in conjunction with a low risk PTP score. Patient care could be improved with a reduction in the number of unnecessary tests and time spent at hospital. Unnecessary low molecular weight heparin administration whilst awaiting diagnostic imaging would not be required, again improving the patient experience

Sensitivity was maintained in the 51-60 and 61-70 age groups, but there was a reduction in sensitivity in the older age groups when compared to conventional d-dimer group. Our small numbers may have contributed to this. Those with a high PTP, a Well's Score of two or more, do not require a D-dimer if imaging is performed within four hours.[4] It could be inferred that those high risk of a VTE as per their PTP score would not have had a D-dimer performed and therefore would not be in our cohort of patients

The false negative results are notable, the consequences of not diagnosing a new VTE having the potential to be fatal. To examine the false negative cohort within this study requires access to the PTP which unfortunately is not available for informative conclusions to be made. In line with recommendations regarding interpretation of PTP, it should only be those patients considered low risk for VTE that should have had a D-dimer performed.

One of the study's strengths is the standardised calculation of the D-dimer, using the Innovance latex assay, as part of the standard operating procedure in our laboratory. The main limitations of this study are its small numbers and that this was a retrospective study. The lack of data on the pre-test probability scores reduces the reliability of the results.

CONCLUSION

Age-adjusted D-dimer is more specific for those with a low risk pre-test probability for VTE, when aged > 50 years. Sensitivity in our cohort was reduced which may be the result of small numbers and the retrospective nature of the data. Although the results are similar to those of Schouten et al, they do not support the role of age-adjusted D-dimer, as increased specificity with age-adjusted D-dimer is secondary to increased over-all average D-dimer threshold, as proven by Lapner et al.[8] Further studies are necessary to optimise the diagnostic role of the D-dimer in VTE.

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Clinical Paper

Microvascular Decompression for Trigeminal Neuralgia: A regional unit's experience

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INTRODUCTION

Trigeminal neuralgia (TN) is a rare chronic pain disorder, characterised by paroxysms of severe, lancinating pain in the distribution of the trigeminal nerve. Most commonly, the second and third branches of the trigeminal nerve are affected. Paroxysms of pain may be related to tactile stimuli such as hair combing, shaving or a cold wind against the patients face. The pain associated with TN is so severe that reports of patients committing suicide have been published in the literature. [1]

The estimated annual incidence of TN is 27 per 100,000 person years, with peak incidence between the ages of 50 and 60.[2] The vast majority of TN cases are due to microvascular compression of the root entry zone of the trigeminal nerve by vascular structures. [3] TN is seen with increased frequency in patients suffering from Multiple Sclerosis (MS), where it has an estimated prevalence of 1%-6.3%, and in MS patients the condition may be bilateral. [4,5] TN may also occur secondary to space occupying lesions at the cerebello-pontine angle such as epidermoid cysts, meningiomas or vestibular schwannoma. [6]

The diagnosis of TN is a clinical one, based on history and examination, with criteria for diagnosis recently published by the International Headache Society. [7] However, 3D volumetric MRI studies may be used to investigate for microvascular compression of the nerve, and for rarer, secondary causes of TN. [8] The first line treatment of TN involves medical management with carbamazepine or other anti-epileptic drugs, which have been demonstrated to be effective for pain reduction in patients with TN. [9] Although medical management has been demonstrated to be effective, 75% of TN patients ultimately undergo a surgical procedure for the relief of their pain. [10] The most commonly performed surgical procedure is microvascular decompression, where the vascular loop overlying the trigeminal nerve is displaced away from the root entry zone. Other surgical options for the treatment of TN include balloon compression of the nerve root, radiofrequency thermocoagulation, glycerol rhizolysis and stereotactic radiosurgery. [11]

The aim of this paper is to report the outcomes of patients treated with microvascular decompression in a small volume regional neuroscience unit at the Royal Victoria Hospital, Belfast between October 2011 and November 2014, and to compare these outcomes with those published in the literature.

MATERIALS AND METHODS

We retrospectively reviewed electronic records and operation notes of patients who underwent MVD by the senior author for TN between October 2011 and November 2014.

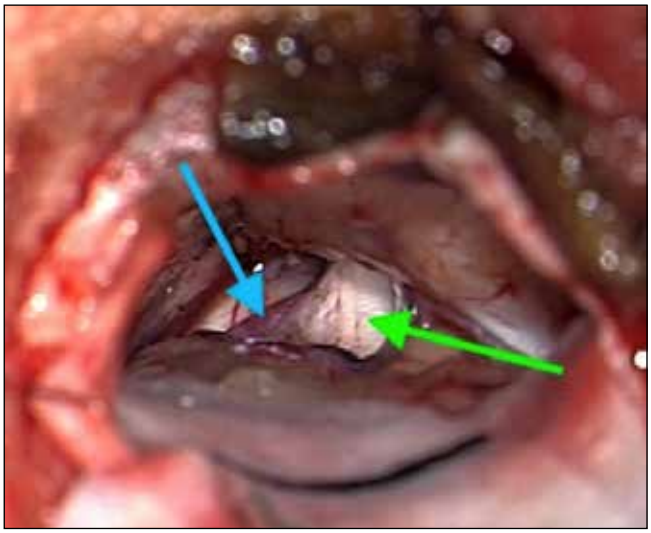

Fig 1. Superior cerebellar artery (blue arrow) in contact with trigeminal nerve ganglion (green arrow)

The procedure itself was performed under a general anaesthetic, with the trigeminal nerve ganglion accessed by means of a craniectomy over the asterion (located at the posterior aspect of the parietomastoid suture). Following this, the dura mater was opened to allow access to the cerebellopontine angle. The cerebellum was retracted, and the trigeminal nerve was identified with the use of a neurosurgical microscope. Following identification of the nerve, it was carefully inspected and any offending vessels are dissected off its surface: the superior cerebellar artery is most commonly implicated (Fig. 1), although compression by the anterior inferior cerebellar artery, as well as the superior

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petrosal veins have also been reported. [12] Following dissection of the vascular structures from the trigeminal nerve ganglion, Teflon® felt is interposed between the vessel and the nerve, to maintain separation. (Fig. 2). [13] In all but four cases in this series, intra-operative auditory evoked potentials were monitored, to aid in the prevention of post-operative hearing loss.

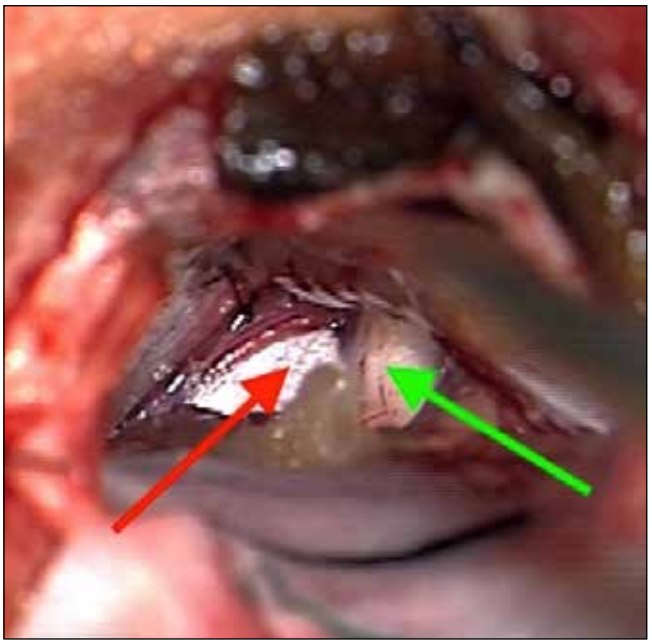

Fig 2. Interposition of shredded Teflon® (red arrow) between superior cerebellar artery and trigeminal nerve ganglion (green arrow)

Follow up clinic reviews were used for assessment of outcome measures in this study. A Barrow Neurological Institute pain score was calculated pre and post-operatively for all patients.

RESULTS

During a 37-month period, 32 patients underwent MVD for TN. All patients were operated on by the senior author. The patients included 21 females and 11 males, with a mean age of 54 years (range 29-72). The mean time from diagnosis to surgery was 6 years (range 0.18-16 years). The mean time from first neurosurgical clinic review and operation was 308 days (range 51-663 days).

28 of the patients had medical therapy alone prior to microvascular decompression; 3 patients had previous radiofrequency treatment and 1 had previous percutaneous balloon compression.

All but one of the patients had a vascular loop identified on pre-operative MRI. There was an average follow up of 254 days. A Barrow Neurological Institute pain score was calculated for all patients. Pre-operatively six (19%) patients had a score of 5, twenty-six (81%) had a score of 4. Post-operatively, at last clinic follow up, eight (24%) had a score of 4, five (16%) had a score of 3 and nineteen (60%) had a score of 1. A post-operative Barrow score of ≤3 was considered a satisfactory outcome.

Unfortunately, one patient reported the onset of contralateral pain following the procedure. In terms of other post operative complications (Table 1), 2 patients developed post operative hearing loss, 4 patients developed a cerebrospinal fluid leak, 3 patients developed minor wound infections treated with short courses of antibiotics and 1 patient developed a patch infection, requiring long-term antibiotic therapy (none of the patients required wound exploration to treat their infection). Also, 1 patient developed a minor cerebellar haematoma requiring readmission four weeks following their microvascular decompression.

TABLE 1.

Barrow Neurological Institute Pain Score

Score	Pain Description
I	Pain free, no medication
II	Occasional pain, no medication required
III	Some pain, adequately controlled by medication
IV	Some pain, not adequately controlled by medication
V	Severe pain or no pain relief

DISCUSSION

Microvascular decompression is a surgical procedure, undertaken following failure of medical therapy, or when medical therapy has intolerable adverse affects, for TN. All of our patients have an MRI pre-operatively, to assess for the presence of a vascular loop abutting the trigeminal nerve ganglion: the identification of a vascular loop compressing the trigeminal nerve has been shown to be associated with an improved outcome following MVD. [14]

In addition to the open approach, fully endoscopic microvascular decompression has also been described-allowing a less invasive approach to this procedure, without an increased risk of complications according to some published evidence. [15]

Due to the proximity to cranial nerve VIII, post-operative hearing loss is a possibility, with a reported incidence in the literature of 1.1-1.3%. [13,16] Brain-stem auditory evoked responses can be monitored intra-operatively in an effort to prevent hearing loss. [17] As described above, all of our patients underwent intraoperative auditory evoked potentials. However, both of the patients who experienced deafness post-operatively had normal auditory evoked potentials up until skin closure. Other potential complications include facial palsy, facial sensory loss, postoperative haemorrhage, CSF leak and meningitis. [13]

In this study, at an average of 254 days post-operatively, 24 patients (76%) had a satisfactory outcome (Barrow score ≤3), while 8 (24%) reported an unsatisfactory outcome (Figure 3). A 2010 study of 372 patients treated with microvascular decompression between 1982 and 2005 for TN refractive to

medical therapy reported that 84% of patients were pain-free, without the need for medication, at one year, and that 71% were pain-free without the need for medication at 10 years post-operatively. [14]

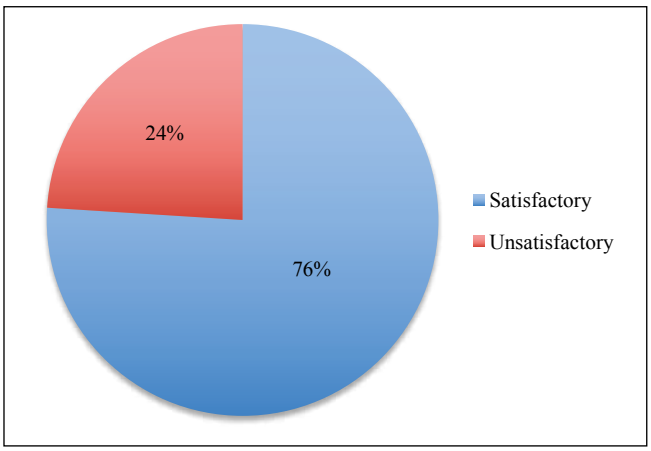

Fig 3. Trigeminal Nerve Decompression: Microvascular Surgical Outcomes.

A further study followed up 1185 patients treated with microvascular decompression in a major North American neurosurgical centre over a 19-year period, and found results more comparable to the results we are reporting. At one year, 75% of patients reported a complete response to surgery, with a further 9% reporting a partial response. Ten years post-operatively, 64% of patients reported complete relief, and 4% reported partial relief. [16]

In terms of post-operative complications (Table 2), those most commonly encountered in this cohort of patients were; CSF leak (4 patients, 12%) wound infection (4 patients, 12%), hearing loss (2 patients, 6%). There was one minor post-operative cerebellar haematoma that did not require neurosurgical intervention. No patients developed a facial palsy following their operation.

The limitations of this study are the small sample size, the retrospective nature of the study and the relatively short follow-up period. The reason for the disparity between the results of our centre and those reported in the literature may be: the method used to evaluate our outcomes; patients with a long duration of pre-operative symptoms may be skewing the data- the average time from diagnosis to surgery in our cohort of patients was 6 years, with one patient suffering from TN for 16 years before undergoing microvascular decompression-there is clear evidence from a number of longitudinal studies that long duration of TN prior to surgery is a negative prognostic factor. [16, 18-19]

Although we consider MVD to be gold standard treatment option in patients with TN refractory to medical management or who have not responded to MVD, alternative, less invasive procedures are available, and can be considered in the elderly patient with significant co-morbidities or in patients with MS, who often have poor results following MVD. [20] Balloon micro-compression is a procedure undertaken percutaneously, under fluoroscopic guidance, aiming to crush the nerve against the skull base, as it passes through the foramen ovale. The main disadvantage of this procedure is that it often leads to facial numbness that some patients may not be prepared to accept. Long term outcomes are not as favourable as those with MVD: a large retrospective analysis of 901 patients treated with balloon micro-compression described pain relief with no need for medication in 67% of patients at one year and 48% of patients at sixteen years post procedure. [21]

TABLE 2.

Post-Operative Complications

Complication	Number (%)
Death	0
Facial Palsy	0
Hearing Loss	2 (6%)
CSF Leak	4 (12%)
Minor Wound Infection	3 (9%)
Patch Infection	1 (3%)
Haematoma	1 (3%)
Contralateral Pain	1 (3%)

A further treatment modality utilised when MVD is not considered suitable is the use of stereotactic radiosurgery, delivering targeted radiation to the trigeminal nerve root entry zone. It is less effective than MVD, with rates of pain relief, without the use of medication, at ten years reported in a recently published series to be 51.5%. [22] There is also a delay in the onset of pain relief following the procedure, compared with MVD and balloon compression, that should lead to relief of pain immediately after the procedure.

CONCLUSION

In conclusion, it is clear that microvascular decompression is an effective treatment for TN refractory to medical management. However, the rates of post-operative pain reduction in patients undergoing this operation in our centre are not as high as those reported in the literature from two-long term outcome studies involving high numbers of patients. This may be due to a higher proportion of patients with negative prognostic factors pre-operatively (e.g., long duration of TN prior to operation), or due to discrepancy in outcome measurement. Neurologists and other physicians involved in the management of TN should consider prompt referral to a neurosurgical unit following the failure of medical therapy.

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Case report

Insulin Autoimmune Syndrome: a rare case of hypoglycaemia resolving with immunosuppression.

Hunter A[1], Graham U[2], Lindsay JR[1]

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Key words: Hypoglycaemia, autoimmune, insulinoma, hyperinsulinism

ABSTRACT

We report a case of a 58-year-old male presenting with confusion and hypoglycaemia. There had been no prior exposure to oral hypoglycaemic agents or insulin. He was found to have inappropriate endogenous hyperinsulinaemia. Insulinoma was excluded by detailed endocrine assessment. Insulin antibodies were positive in keeping with a diagnosis of insulin autoimmune syndrome (IAS). He was treated with prednisolone 5mg once daily and nutritional supplements leading to resolution of acute confusion and hypoglycaemic episodes.

The patient also had severe psoriasis and following discharge was treated with a variety of immunosuppressant therapies. This was associated with disappearance of insulin antibodies after twelve months of follow up. While it is possible that there was spontaneous resolution of insulin antibodies, we speculate that his prednisolone and immunosuppressant therapy may have suppressed insulin antibody production.

There are several well recognised associations with IAS and autoimmune conditions, including Grave's disease, systemic lupus erythematous and rheumatoid arthritis. To our knowledge this is the first reported case of insulin autoimmune syndrome, resolving with immunosuppressant treatment of psoriasis.

CASE REPORT

A 58-year-old male presented to the emergency department (ED) with new onset confusion. He had a history of learning difficulties and his family had found him to be confused and disorientated. The patient gave a one day history of feeling unwell and reported unsteadiness. He had no recent weight loss and his appetite had been normal. He was brought to the emergency department via ambulance having been treated for hypoglycaemia (capillary blood glucose (CBG) 1.9 mmol/L) with glucagon and intravenous glucose by the paramedic team. On arrival in ED, his CBG was 11.9 mmol/L. He was admitted for further investigation and monitoring. Past medical history included psoriasis, epilepsy and stroke. Medications at presentation were acitretin, coal tar solution 5%, oilatum, sodium valproate, carbamazepine, simvastatin and clopidogrel.

Capillary blood glucose was closely monitored during admission and he had recurrent episodes of late night and early morning hypoglycaemia, treated with a variety of oral glucose preparations and long acting carbohydrates.

During an episode of hypoglycaemia, bloods were sent for laboratory analysis revealing plasma glucose 2.6 mmol/L, serum insulin >1000 mU/L (reference range 2.6 -24.9 mU/l), serum C-peptide 17.4 ug/L (reference range 1.4 -4.4 ug/l). Sulphonylurea use was excluded by a negative drug screen. Adrenal insufficiency was excluded following a short Synacthen test (serum cortisol T0= 408 nmol/l and T30 = 1008 nmol/l).

He proceeded to a formal 72 hour fast to exclude endogenous hyperinsulinaemia. The fast was stopped at 23 hours (see Table 1) as CBG fell to 2.3 mmol/L and he was symptomatic with sweating and dizziness. Hypoglycaemia was confirmed on plasma glucose testing and insulin and C-peptide remained significantly and inappropriately elevated.

Table 1

Plasma glucose, 3-OH butyrate, insulin and C-peptide data during 72 hour fast.

	Time of blood test			
	18.30	06.20	09.10	15.45
Glucose (mmol/L)		3.5		2.3
3-OH butyrate (mmol/L)			0.01	0.32
Insulin (mU/L)	>1000	>1000	>1000	>1000
C-peptide (ug/L)	17.0	20.7	*	19.6

(*missing data)

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TABLE 2

Serum insulin levels undertaken during calcium stimulated selective venous sampling of localisation study

Time (seconds)	Gastroduodenal insulin (mU/L)	Proximal splenic insulin (mU/L)	Distal splenic insulin (mU/L)	Hepatic artery insulin (mU/L)	Superior mesenteric artery insulin (mU/L)
0	6950	7150	7250	6850	*
30	7050	7000	7500	7100	7550
60	6700	7950	7050	6750	7500
90	6850	7150	7300	6700	7450
120	6900	6900	7700	6950	7550

(*missing data)

His 72 hour fast results were in keeping with endogenous hyperinsulinemia, potentially arising from an insulinoma. CT scanning of the abdomen and pelvis showed subtle changes in a small area at the head of the pancreas. The case was discussed at a Multi-disciplinary meeting with an agreed plan for localisation studies with calcium stimulation testing and endoscopic ultrasound (EUS) of pancreas. EUS was undertaken and identified a poorly circumscribed hyperechoic abnormality in the tail of the pancreas measuring 13x11mm. Fine needle aspiration showed benign pancreatic acini cells only, with no features of insulinoma.

A calcium stimulated localisation study with venous sampling was non-localising with no focal area of increased pancreatic insulin production (Table 2). Pancreatic hormones were also normal, again making pancreatogenous hypoglycaemia unlikely (Table 3).

TABLE 3

Fasting gut hormone screen

Hormone	Level
Gastrin	<30 ng/L
Pancreatic polypeptide	75 ng/L
Somatostatin	18 ng/L
Total chromogranin A	14 U/L
Vasoactive peptide	34 ng/L
Neurokinin A	11 ng/L

Initial insulin assay measurements were initially undertaken at the Regional Endocrinology laboratory using the Roche electrochemiluminescence (ECLIA) insulin immunoassay, which is specific for human insulin. Samples were also analysed separately using the alternative Mercodia enzyme-linked immunosorbent (ELISA) iso-insulin assay at an external laboratory, which has 55% cross reactivity with proinsulin and several other exogenous insulin treatments. Both methods are standardised to 1st International Reference Preparation 66/304 for human insulin.

Inappropriately elevated insulin concentrations were also confirmed using the ELISA method at 124 pmol/L (Reference range <30 pmol/l) with proinsulin concentrations at 31 pmol/L (Reference range <10 pmol/l) while the patient was hypoglycaemic at 2.3 mmol/l.

In view of massively elevated insulin concentrations and positive insulin antibodies (confirmed on two occasions), Insulin Autoimmune Syndrome was considered the likely diagnosis. Due to recurrent persistent and disabling hypoglycaemia, empirical treatment with prednisolone 5mg daily was commenced alongside nutritional support with frequent small meals, particularly in the evening period. There was a good symptomatic and biochemical response to treatment, and he was able to return home with the help of his family who supported regular CBG monitoring.

LONG-TERM FOLLOW UP

After six weeks at review there was complete resolution of hypoglycaemic episodes. Non-fasting insulin concentrations measured at the local laboratory after 21 months had fallen to 41.5 mU/L. Three years from diagnosis insulin antibodies were no longer detected on blood sampling and insulin concentrations had fallen to 34 mU/L, in keeping with long-term remission.

Interestingly, this patient has severe psoriasis which had failed to respond to multiple systemic medications. His psoriasis became increasingly difficult to control from 4 months prior to presentation requiring the use of intermittent potent topical steroids and Acitretin, a synthetic aromatic analogue of retinoic acid. He started immunosuppressants eight months after presentation namely Methotrexate (April 2014 - December 2015), Ciclosporin (December 15 – June 16), Adalimumab (June 16 - November 16) and Ustekinumab (November 16 – present). Insulin levels over time are plotted in Figure 1.

DISCUSSION

We present an interesting case of hypoglycaemia arising from apparent insulin antibody mediated hypoglycaemia, which was treated successfully with prednisolone and nutritional supplements leading to resolution of symptoms and hypoglycaemia. Significantly, the patient was treated with a variety of immunosuppressant therapy for management of psoriasis, which was associated with disappearance of insulin antibodies after seventeen months of follow up. While it is possible that there was spontaneous resolution of insulin antibodies, his prednisolone and immunosuppressant

therapy appear to have reduced insulin antibody production as evidenced by a reduction in measured serum insulin concentrations and disappearance of insulin antibodies.

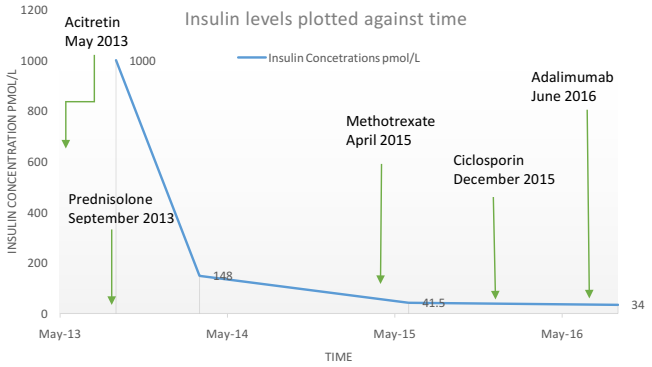

Fig 1. Insulin concentrations (mU/L) with time and immunosuppressant medication start times

There are several well recognised associations with insulin autoimmune syndrome (IAS) and autoimmune conditions, including Grave's disease, systemic lupus erythematous and rheumatoid arthritis. To our knowledge this is the first reported case of insulin autoimmune syndrome with resolution of markers of autoimmunity treated with immunosuppressant treatment of psoriasis.

Insulin autoimmune syndrome (IAS), or Hirata's Disease, was first described in 1972 in a Japanese patient who presented with hypoglycaemia. It is now recognised as the 3rd most common cause of hypoglycaemia in Asian patients. This follows insulinoma and non-pancreatic neoplasia as the first and second most common aetiologies respectively [1]. IAS has been increasingly recognised in Caucasian patients with several cases reported. It has a higher incidence in people who are HLA-DR4 positive or with other autoimmune conditions[2]. There have been published cases of IAS in patients with co-existent hyperthyroidism, systemic lupus erythematous and systemic sclerosis but to our knowledge none with psoriasis[3].

Triggers of IAS are drugs particularly those containing a sulfhydryl group[4] and exogenous insulin. This patient was never exposed to exogenous insulin, however he was taking clopidogrel, which is known to contain a sulfhydryl group, for a previous stroke,[5]. As clopidogrel was started two years prior to presentation it was not felt to be the trigger in this case and he remains on treatment. Virus exposure and myeloma are also potential causes of IAS, and these were excluded early in his assessment[1,6].

A variety of treatments of IAS have been reported in the literature, most commonly watchful waiting or removing the triggering medication. In most of cases stopping the culprit medication will induce spontaneous remission. Other treatments include high dose prednisolone (60mg once a day), azathioprine and 6-mercaptopurine[7]. Recently Rituximab was successfully used to treat refractory hypoglycaemia secondary to insulin autoantibodies in the absence of exogenous insulin being used[7]. Plasmapheresis has also been used in cases of refractory hypoglycaemia and in an extreme case, pancreatic surgery when immunosuppression was inappropriate due to sepsis[8].

An additional challenge in this case was that the patient had a learning disability and was unable to communicate his symptoms of hypoglycaemia or manage them independently. Empirical treatment with 5mg prednisolone once a day was used to alleviate hypoglycaemia symptoms. He responded well to treatment, which also included dietary adjustment with complete resolution of hypoglycaemia within weeks.

Seven months after insulin antibodies were identified he was commenced on further immunosuppressant medication under the supervision of his dermatologist. It is difficult to conclusively determine, which if any, of these treatments reduced insulin antibody generation in addition to impact of his prior course of oral corticosteroids. While it is also possible that spontaneous resolution of IAS may have occurred, he seems to have made good progress on treatment and his condition remains in remission with a reduction in measured serum insulin concentrations and disappearance of insulin antibodies.

In conclusion, insulin autoimmune syndrome is a rare but important differential diagnosis in individuals presenting with hypoglycaemia. This condition should be considered in patients with inappropriate endogenous hyperinsulinaemia in whom insulinoma has been excluded. Other factors including previous insulin treatment, exposure to sulfhydryl containing medications and extremely high serum insulin levels may point towards the diagnosis.

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Case Series

Sinoatrial Node Disease in Adults with Down's Syndrome.

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INTRODUCTION

Down's syndrome, also known as trisomy 21, is a common chromosomal abnormality associated with multiple co-morbidities, premature ageing and decreased life expectancy. We present four cases of individuals with Down's syndrome without congenital heart disease who presented with syncope and subsequently were found to have severe sinoatrial node disease, all requiring permanent pacemaker implantation. An association between the conditions has not previously been described and we postulate a possible increased frequency of sinoatrial node disease in adults with Down's syndrome. In addition, in each case there was a considerable delay in reaching the diagnosis of sinoatrial node disease; this was partly due to alternative differential diagnoses (particularly neurological) being considered first, partly due to difficulties in obtaining an accurate history of the syncopal events and partly due to decreased co-operation by the patients with regards to investigation of the underlying aetiology of their events.

CASE SERIES

Case 1. A 70 year old man with Down's syndrome was admitted following two syncopal events. He was placed on cardiac monitoring and had a number of episodes of sinus arrest of up to fifteen seconds. Nine months earlier, he had been admitted with a syncopal episode to another institution, where he had been uncooperative with medical staff, refusing all examination and had been provisionally diagnosed with a transient ischaemic attack. A permanent pacemaker was implanted on this occasion under general anaesthesia. Although he had no further syncopal episodes after implantation, he has subsequently died around a year later from an unrelated illness.

Case 2. A 54 year old man with Down's syndrome was referred by his General Practitioner following two episodes of syncope. He had been found lying on the ground. There was no seizure activity and he was noted to be pale. There was no tongue biting or urinary incontinence. He was assessed in an Emergency Department, with no abnormality found. He was referred to a neurologist in the first instance and the possibility of atonic seizures was raised and further investigation planned.

Resting ECG showed sinus rhythm with first degree atrioventricular block and incomplete right bundle branch block. Carotid sinus massage showed physiological slowing of heart rate only. Holter monitoring showed sinus rhythm, heart rate varying between 51 and 95 beats per minute. There were rare atrial and isolated ventricular ectopic beats but no arrhythmia was found to explain his presentation.

One year later, he presented as an emergency admission with four further episodes of syncope over a 48 hour period. He was placed on cardiac monitoring which demonstrated sinus pauses of nine and fourteen seconds. He subsequently had a permanent pacemaker implanted under general anaesthesia. He has not had any further syncopal events.

Case 3. A 56 year old man with Down's syndrome was referred with frequent syncopal events. He lived in residential accommodation and when staff noticed these events he was found to be very bradycardic. He refused to comply with wearing a Holter monitor or having an ECG performed. His radial pulse was 40 beats per minute by palpation. His case was discussed with a pacemaker implanter who felt that there was not enough evidence to support permanent pacemaker implantation.

Seven months later, he presented as an emergency with recurrent syncopal events. Sinus pauses of up to nine seconds were recorded. He has had a permanent pacemaker implanted under general anaesthesia with no further syncopal episodes to date.

Case 4. A 46 year old man with Down's syndrome was referred following assessment by a neurologist, who in turn had been referred the patient by an acute physician. There was a one year history of episodes of sudden collapse associated with pallor. There was a background history of epilepsy but the more recent episodes were felt to be different. A provisional diagnosis of atonic seizures had been made but the neurologist was not convinced. There were no abnormalities of 12-lead ECG and carotid sinus massage was normal. A patient activated monitor was fitted and when the patient was syncopal, sinus pauses of up to 15 seconds were documented. He subsequently has had a permanent pacemaker implanted under general anaesthesia and remains well.

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CONCLUSION

Down's syndrome, is a common genetic disorder with an incidence of around 0.1% of live births[1]. Individuals with Down syndrome have a higher risk of early death than the general population[2]. Following improved medical care life expectancy has increased[1]. About 10% of individuals with Down's syndrome but without congenital heart disease live to 70 years of age[3], the implication of which is that we have a greater prevalence of older individuals with Down's syndrome than in the past.

We present four cases of adult males with Down's syndrome, but without history of congenital heart disease, who have presented with syncope due to severe sinoatrial node disease requiring permanent pacemaker implantation. This raises the possibility of an association between the two conditions that has not been previously reported. We postulate that improvements in life expectancy in individuals with Down's syndrome will lead to an increased prevalence of patients with this condition presenting with sinoatrial node disease; further epidemiological data will be needed to confirm or refute this postulation.

In each case, there was a delay in making the diagnosis of underlying sinoatrial node disease. This was due to initial presentation and/or referral to specialties outside of cardiology, most frequently a provisional diagnosis of a neurological condition had been made. This was compounded by difficulties in obtaining an accurate history of the events and poor co-operation by the individual patients in regards to investigation. We suggest that underlying conduction tissue disease, most likely of the sinoatrial node, should be high on the list of differential diagnoses when considering unexplained syncope in adults with Down's syndrome.

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Medical History

FDR and American Military Deployment: "My" Armed Forces and their Health

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INTRODUCTION

The prevention and management of epidemic infections are a major responsibility of national leaders in peace and war. Belfast suffered outbreaks caused by meningococci in 1906,1907, 1908[1,2] and 1915[3]; Bordeaux, France, endured Spanish influenza in 1918[4,5]. In the UK, cerebrospinal fever became notifiable in 1912[6], so that epidemiologic data were collected for the World War I years[7,8,9]. Canadian troops brought meningococci to the UK in 1914-15; it spread to the civilian population[7,8]. Two to four percent of persons carry meningococcus in their pharynx but during an epidemic, the percentage of carriers may increase ten to twenty-fold. Four main groups can be identified by agglutination tests. A, formerly caused the majority of epidemics, while B was responsible for sporadic infections, until historically replaced by Group C as the predominant epidemic organism[7]. Group D rarely caused human disease[7,8,9,10].* The use of Flexner's serum during the Belfast outbreaks of 1906-1908 reduced mortality from 82 percent to 25-35 percent[2]. In the British military, mortality in 1915 approached 50% even with the use of serum[10]. In 1915, Regius Professor of Medicine at Oxford, Sir William Osler reported on recent outbreaks of cerebrospinal fever in military and naval camps and barracks, and the existence of a "meningitic type of poliomyelitis"[8].

John C. Slessor (JCS) had lived with William Osler's family in Oxford for 5 years just before World War I[11]. (Fig 1) In 1915, Professor Sir William Whitla[1,2] and Regius Professor Sir William Osler wrote authoritative reviews of the management of meningococcal epidemics[8].

The following year, 1916, the Oslers' only child Revere died of war wounds received as a gunner subaltern in the Ypres Salient. Harvey Cushing, a close family friend who had been married from the Osler's home, attempted to save his life and broke the sad news to the senior Oslers[11,13].

EDUCATION OF A PRESIDENT

After attending the Groton School in Massachusetts, Franklin Delano Roosevelt (FDR) wanted to attend the U.S. Naval Academy at Annapolis[14]. Roosevelt had been given for Christmas 1897, aged 15, A.T. Mahan's *The Influence of Sea Power upon History*. His distant cousin and close family friend President Theodore Roosevelt, and FDR's father, James, both advised "Harvard" as preferable. James died during FDR's freshman year at Harvard.

Fig 1. Twelfth Night, Oxford Preparatory School, 1909. JCS, in the front row (circled), was two years younger than the other actors. From the Archives of the Dragon School, Oxford, and reproduced with their permission. JCS lived in the nearby Osler house from which Harvey Cushing was married in 1911. Revere circled (top). Lady Osler left JCS in her will "a massive oak chest that belonged to her great-grandfather", Paul Revere of Boston, famous revolutionary, silversmith and coroner of Boston 1796-1801[12].

The following summer, FDR took his mother, Sara, to see Kaiser Wilhelm II. FDR sailed his mother in the Roosevelt yacht to Sorge, Norway, adjacent to the S.M.Y. *Hohenzollern*. Sara and her son FDR invited the Kaiser to tea. He accepted and reciprocated on the *Hohenzollern*[14].

On June 7, 1910 Theodore Roosevelt gave the Romanes Lecture at Oxford sponsored by Professor Osler[15]. In 1913, FDR was appointed Assistant Secretary, United States Navy[14,16]. He served 8 years with wide-ranging responsibilities which eventually affected Northern Ireland. FDR was in control of building the U.S. Navy's extensive installations along the Gironde, Bordeaux. FDR provided

* The Medical Research Council Report (9) and other contemporaneous sources use the Gordon Classification of Types I, II, III and IV.

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the impetus for the 1918 mine blockage from Scotland to Norway and the promotion of an effective U.S. Naval Air Service campaign against German U-boats[14,16]. FDR took two trips to WWI front lines in France and Italy. Wherever he went, he was treated like a Head of State. On his inspection tours, FDR's personal U.S. Navy Flag was the first U.S. flag raised and flown over the Royal Navy flags since the War of 1812.

Fig 2. Franklin D. Roosevelt, 44th Governor of New York State, 1929-1932. Oil on Canvas by Jacob H. Perskie (1865-1941) 122 cm x 97 cm, ca. 1932. From the collections of the State of New York, Hall of Governors, Albany, NY and reproduced with their permission.

Returning from Europe after his 1918 World War I trip, FDR was seriously ill with 'Spanish' flu and subsequent pneumonia. Upon arrival in Hoboken, NJ, he was transported by ambulance to his mother's home in Manhattan where he was nursed by his wife Eleanor, together with U.S. Navy nurses[14]. Post-Armistice, on his January 2, 1919 return trip to Europe, he was accompanied by his wife Eleanor, by authority of the Secretary of the Navy, Josephus Daniels[14].

The U.S. Navy in 1919 employed the largest airplanes in the world, the NC flying boats. NC4 was the first plane to be flown across the Atlantic, two weeks before Alcock and Brown, landing at Lisbon, Portugal on May 27, 1919 from Washington, D.C. via the Azores[14].

CATALINAS AND FDR

FDR became President and Commander-in-Chief of the United States on March 4, 1933[17] (Fig. 2). FDR let it be known that as Commander-in-Chief he would allocate U.S. heavy bombers. Within 6 months, Hitler became Chancellor of Germany[17]. In October 1933, the U.S. Navy contracted Consolidated, Martin and Douglas to build competing prototypes for a patrol flying boat[18,19]. Each Consolidated Catalina, winner of the competition, cost $US 90,000. Four thousand fifty-one were produced, of which approximately 200 were based in Northern Ireland during World War II[18,19,20].

FLYING FORTRESS AND FDR

On August 8, 1934, Boeing filed its proposal for the B-17 Heavy bomber[18,19,20]. Eleven months later a Boeing-financed Flying Fortress prototype flew from Boeing Field[18]. The U.S. Air Corps placed, with FDR's approval an order for 65 B-17 Flying Fortresses[18]. On the prototype's second flight it crashed and killed its pilots[18,19]. FDR told the RAF Tactical Planning Committee, which included JCS (see below) and Dowding (later victor of the Battle of Britain), that 12,000 B-17s would be built in the event of war with Germany. Otherwise the RAF and French could tender for them[21]. By July 1945, 12,731 had indeed been produced by Boeing[18,19,20].

JCS

Sir John (Jack) Cotesworth Slessor GCB 1948, KCB 1943, DSO 1937, MC 1916, later Head of RAF (JCS) was born in India on 3 June 1897, the son of Major Arthur Kerr Slessor of the Sherwood Foresters[22] . JCS married Hermione Guinness in 1923[22]. JCS was on the Air Staff, Air Ministry 1928-30, Instructor Staff College, Camberley 1931-1934; back to India 1935-37. He was in command of No. 3 Wing Quetta, 1935, Director of Plans, Air Ministry 1937-41, ADC to King

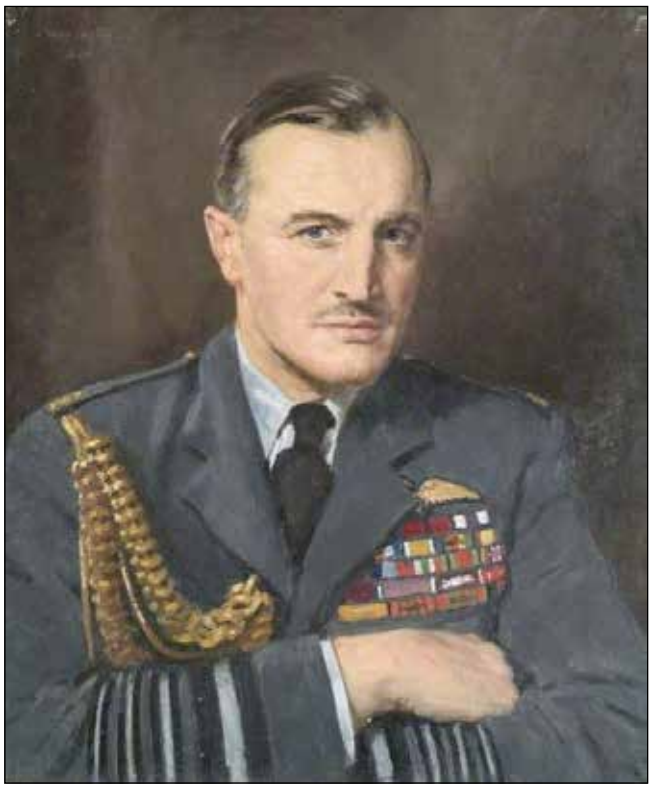

Fig 3. John C. Slessor, by Mary Eastman, 1947. Oil on canvas, 60.3 cm x 50.8 cm. From the collections of the Imperial War Museum, London, IWM Image no. ART LD 6512.

George VI, 1938, Air Representative to French Conversations 1938-39[21,22,23]. In 1940, he went to the USA, as sole RAF representative to the Anglo-American staff conversations and in US 1942, leaving Jan. 1943, then en route to the Casablanca Conference with FDR and Prime Minister Churchill[23,24]. JCS wrote much of the Final Report. Slessor flew from the UK to Washington DC seven times from 1940 through the end of 1943 and spent many weeks there[23,24] (Fig. 3).

JCS knew that FDR had been severely criticised for tardiness in deploying anti-sera to the large U.S. Navy base at Bordeaux, France[4,9]. JCS, despite his post-polio leg weakness, had become a war hero in the RFC and RAF. As a protégé of Lord Trenchard, JCS was given important planning posts for development of planes for the inter-war RAF[25]. In 1935 JCS was in command of the RAF group of squadrons at Quetta when the earthquake struck: thirty thousand died[26]. JCS and Donegal-born Lieutenant Colonel Bernard Law Montgomery arranged for the burial of the dead and the supply of vaccines, drugs, equipment, nurses, physicians and engineers[26].

In late 1940, JCS was sent as the sole RAF representative to prepare and take part in the American-British-Canadian (ABC) conference in Washington, D.C.[23,24]. There, Slessor met FDR at the White House and they worked out the U.S. proposed planning for Northern Ireland[24,27,28]. FDR insisted on Creevagh Hospital (Londonderry) being built for "My Navy". FDR recommended sending 30,000 U.S. workers from a still neutral U.S.A. to help local artisans build Creevagh Hospital, docks and airfields for "My Navy" and "My Army", since "My Bombers" needed a convalescent lodge and hospital therein. FDR likened Lough Foyle to the Gironde where he had supervised U.S. construction in 1917-1919. FDR knew of JCS's RAF plan M. He shared with JCS his own enquiries, projections and modus operandi[23,24].

JCS, with FDR's assistance, found 674 Hudsons, 91 Catalinas, 58 Liberators and 20 Flying Fortresses awaiting delivery to the UK[29,30,31]. JCS wrote to the head of the RAF; "The present system is whereby we bribe a few American pilots:….we want….at least 1,000 pilots.[29]" FDR intervened and arranged that the Fortresses be flown by RAF pilots from Seattle or Vancouver to Prestwick or Aldergrove. The other pilots were to be U.S., Canadian and British air-men. On arrival at Belfast hotels, the ten-gallon hats, high-heeled Texan boots and Canadian hooded parkas were certainly noticed. Sir Frederick Banting, of insulin fame, was the first civilian fatal casualty from a Hudson being ferried across the North Atlantic. He froze to death after surviving a Newfoundland crash[31,32].

As part of the ABC 1 and 2 plans of 1940 and early 1941, 26 airfields were planned for Northern Ireland. Langford Lodge was planned to be an American assembly, modification and repair depot[27]. Langford Lodge had a satellite airfield at Greencastle, County Down. Between 1942 and 1945, 48 aircraft accidents were directly related to Langford Lodge Air Depot[27]; the Medical, Dental and Nursing staff were U.S. citizens and Lockheed employees. The Station Surgeon was Major Samuel Blank[27]. In planning this hospital, both JCS and FDR knew of the 1907, 1908 and 1915 Belfast Cerebrospinal fever epidemics and the U.S. forces Bordeaux 1917-18 epidemics of cerebrospinal fever and influenza[1,2,3,7,8,9]. FDR also knew of JCS's Oslerian background and his 1935 Quetta earthquake experience: fly in or stock vaccines and drugs[11,26,33].

FDR and JCS strongly influenced Allied deployment in both Northern Ireland and elsewhere. Both were good at dealing with the US leadership of Ernest King, Commander of the US Navy and H.H. "Hap" Arnold, Commander of the US Army Air Force[34]. The US provided the majority of planes for RAF Coastal Command and the escort carriers of the Allies[34]. Why did JCS and FDR get on so well? Both had paralytic polio—JCS walked with one or two sticks and for cricket was allowed a runner; FDR employed leg braces and human aid. Each admired the other's charm and intellect. Slessor's wife, Hermione, was a Guinness and FDR's wife, Eleanor, was Theodore Roosevelt's favourite niece[14].

HUDSONS AND LOCKHEED

Early on 13 May 1938, leaving a crowd of journalists and aviation enthusiasts at Burbank, near Los Angeles, California, Waclaw Makowski flew a LOT purchased Lockheed Hudson L14 to Warsaw, Poland. The arrival in Warsaw was triumphant. A radio failure was due to faulty cable insulation short-circuiting at higher altitude [35]. Makowski later led RAF Squadron 300 to sink German invasion barges in the Battle of Britain. Conversion of 300 Squadron from Fairey Battles to Vickers Wellingtons commenced in October 1940. On March 23, 1941, Makowski led his squadron to bomb Berlin. Remarkably, no Wellington was lost. In 1984, Makowski was honoured by the U.S. Airforce together with Jimmy Doolittle (leader of the 1942 Tokyo raid), Chuck Yeager (breaking of the sound barrier) and Adolf Galland (Air Battle for Europe, Luftwaffe ace). At the USAF presentation of Great Moments in Aviation History, Makowski said "I am honoured to be… among aces…whose achievements surpass mine[35]".

By February 1939, Hudsons began to be delivered to RAF squadrons. At the outbreak of war, 78 were in RAF service[36,37,38]. During World War II the 2,000 Hudsons of RAF Coastal Command flew out of all 26 Northern Irish Airfields[36]. Two thousand nine hundred and forty-one Hudsons were produced by Lockheed between 1938 and 1943[19,20,23,37].

LIBERATOR B-24 JCS AND FDR

In May 1938, the French government issued a "specification to U.S. firm, Consolidated, for a heavy bomber"[39]. FDR approved this initiative. A contract for a prototype was signed on 30 March 1939[39]. On 29 December 1939 the Liberator B-24 made its maiden flight from the Lindbergh Field at the Consolidated plant in San Diego[39].

After the June 1940 French capitulation, 2 Liberators flew into Nutts Corner to form the genesis of RAF Coastal Command Liberators based in Northern Ireland. Approximately 300

of the 18,482 Liberators built saw service from Northern Ireland[28,36,39].

COMMANDER IN CHIEF

In 1940, FDR asked for an estimate of "overall production requirements… to defeat our potential enemies"[30]. As far as the Air Corps was concerned, 4 officers were named to "make a forecast of our needs". The veterans Harold George and Ken Walker were named to this panel along with Larry Kuter and H.S. Hansell, Jr., from the younger echelon of the U.S. Army Air Force. This was their estimate:

2,200,000 men

63,467 airplanes

239 combat groups; along with 108 separate squadrons not formed in groups.†"

"Our full-strength air offensive against Germany could not be developed before April 1944. The prophecy of that panel of four officers seems outstanding," wrote LeMay post World War II[30]. FDR kept this reply to himself and Hopkins[30].

The existing Slessor arrangement with FDR, had resulted from the ABC conversations of January to March 1941[21,24]. Although never formally approved (but initialed by FDR), the Slessor Agreement was essentially followed for six months after 29 March 1941[21,40]. The Slessor agreement with FDR "called for Britain to retain all the output from her own production, all U.S. produced aircraft from the British orders already in process." The Slessor Agreement included the now surrendered French orders and an allocation from the continuing American production as well as the "entire output" from any new U.S. expansion[24]. If the U.S. were to be drawn into World War II any new U.S. capacity would be allocated between the U.S. and the RAF on a 50-50 basis[21,24]. Between 1941 and 1945 18,482 Liberators were completed[39]. After Pearl Harbor the Slessor Agreement basically continued but FDR increased U.S. production of Liberators "to one every hour"[39].

MEDICAL COVERAGE

Typically, the RAF had 11 Medical Officers in Northern Ireland at any one time during World War II[41]. The practice of these MOs depended on the plane type being flown. For 502 Ulster Squadron (Limavady) many survivors had burns, fractures and head injuries from Whitley take off, landings and mountain crashes[42,43]. In 1941, one-half of the Limavady Whitleys were lost with the majority of their aircrew; many were drowned in the Atlantic and their bodies not recovered[44,45]. When 502 was moved to attack the 'U-boat choke point, the Bay of Biscay', medical coverage had to be expanded[41,46]. The RAF hospitals and EMS hospitals provided surgery for both RAF Coastal Command and for Ernest King's US Liberators[47,48]. Unfortunately, US Navy

† Here is what the U.S. Army Air Force and the U.S. Navy actually ended up with, as of 1945: 2,400,000 men, 80,000 aircraft, 243 combat groups[30]

Fig 4. Then Princess Elizabeth and her mother the Queen visited JCS in 1943 when he was Commander of RAF Coastal command. As Equerry to King George VI, JCS had helped organize the Royal visit of Their Majesties in June 1939 to FDR and his family at Hyde Park, New York.

Liberator navigation was inadequate, U.S. crews having been trained in the Gulf of Mexico[46]. King insisted that they be retrained by RAF Coastal Command. King then transferred them to Morocco[46]. With long range Liberators, some Africa-based, the Battle of the Bay of Biscay was won[47,48]. The US and Royal Navies also interdicted, with 502 Ulster Squadron's help, German blockade runners from Japan. During the Battle of the Bay the Germans learned presumably from captured aircrew, the sites of RAF hospitals at Torquay, near Truro and in Glamorgan. These were bombed by the Luftwaffe and nurses and RAF aircrew killed[41,49].

NORTH ATLANTIC TRANSFER

Approximately 10,000 U.S. manufactured aircraft were flown across the North Atlantic in World War II[31]. The Hudsons flew primarily to Aldergrove and the B-17 Flying Fortresses and B-24 Liberators to Prestwick[29,31]. Four percent were lost to the North Atlantic or crashed in Northern Ireland or Scotland[30,31]. The Catalinas flew to Lough Neagh, Lough Erne, Castle Archdale or Greenock on the Clyde[31].

Medical cover for the aircrew was provided by 11 RAF physicians and 50 Princess Royal RAF nurses at Castle Archdale, as well as the Emergency Medical Services (EMS)

in Northern Ireland[47,49]. By March 1943, Ballykelly had been opened and No. 120 Squadron had operational very long-range Liberators and Squadron 220, at Nutt's Corner, had U.S.–transferred Flying Fortresses in time for the successful victory in the Battle of the Atlantic late in 1943[47,48].

TRAINING AND CARE

My‡ father-in-law, George Waller joined RAF Coastal Command 502 Squadron (Ulster) in 1940[50,51]. In 1941, Waller became Staff officer for Air Vice Marshal Sir Geoffrey R. Bromet, D.S.O., AOC 19 Group in Plymouth; appointed in charge of training and safety, Waller deposited Bromet in the leaves and branches of a big oak[50,.51]. The Tiger Cub's broken propeller, converted to hold a clock, remains in the family. Bromet, in his role as Commander-in-Chief went on to conquer and occupy the Azores and in January 1943, Waller was transferred to the staff of JCS, newly AOC Coastal Command[50] (Fig.4). During 1944 and 1945, Waller remained at Coastal Command headquarters with Sir Sholto Douglas, MC, DFC, who succeeded JCS as AOC CC, 1944-45[52] (Fig. 5).

Fig 5. William Sholto Douglas, Marshal of the Royal Air Force, oil on canvas, 1940, by Sir Herbert James Gunn, RA (1893-1964), 72.2 cm x 63.5 cm. From the collections of the Imperial War Museum, Art.IWM ART LD 997, and reproduced with their permission exclusively for this Medical History.

JCS when summoned to meet alone in FDR's private White House office remembers FDR's extensive detailed knowledge and charm. "He appeared to know almost all details of performance and modifications to "My Heavy Bombers"[24], whether deployed in the RAF or 'My Navy's Air Force' or Hap Arnold's." India, Montgomery, the Guinnesses and the Oslers were also discussed with FDR during JCS's meetings in FDR's study.

Sholto Douglas wrote of being summoned in Cairo, Egypt to a one-on-one meeting with FDR. The guards were dismissed, and FDR gave an accurate and detailed "history of the Douglas clan and their relationships with FDR's Scottish grandmother"[53]. FDR "very nearly had me eating out of his hand" but when Allied Aegean policy was discussed, FDR left no doubt that he was in charge.

My father-in-law, now Wing Commander Waller, recalled a conversation with A/C/M Sir Sholto Douglas when playing bridge with him. "I made some remark slightly uncomplimentary about Air Marshal Dowding who had been Commander-in-Chief of Fighter Command during the Battle of Britain. Saying nice things about people was not one of Sholto's strong points, but when he heard my remark he said, 'Young man, never say anything like that again.' We all owe our lives to Dowding. Had it not been for his work in the years before the War we would have lost in 1940. I was only posted to succeed him as Commander-in-Chief Fighter Command at the end of 1940 because he was absolutely exhausted."

In late 1942, FDR's wife Eleanor flew to Langford Lodge, Northern Ireland to see the results of the planning and deployment of U.S. Forces[47]. Creevagh Hospital, U.S. Navy Overseas Hospital Number 1, had not had a fatality although busy with casualties from the war[47,54]. Nutrition and health of U.S. forces and their morale were most satisfactory[28]. Sholto Douglas states "I had been impressed by the forcefulness and alertness of her [Eleanor's] mind. She and her husband shared a great strength of character"[53]. After World War II, Sholto Douglas served as Military Governor of the British Zone in Germany, succeeding Field Marshall B.L. Montgomery. In 1948 he was created Lord Douglas of Kirtleside. In later years he was Scholar and later Hon. Fellow of Lincoln College, Oxford University[52].

FDR received a state funeral and is buried on the grounds of his Hyde Park, New York home overlooking the Hudson River. On JCS's death, his son, Group Captain J.A.G. Slessor received a letter from Lt. General Ira C. Eaker of the USAF which states, "It was a rare experience of a lifetime to have known and cooperated with Sir John Slessor. I shall never forget his friendship and never cease to admire his great qualities of mind and heart"[21,55]. JCS voiced, in 1943, similar feelings about FDR to my father-in-law.

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‡ This and any other first-person references refer to the first author.

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Medical Education

E-learning for medical education: reflections of learners on patients

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Provenance: internally reviewed
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ABSTRACT

Introduction There is a growing research interest in *how* healthcare professionals learn online. This paper reports an analysis of reflections that relate to patients from users of an e-learning resource, BMJ Learning.

Methods Healthcare professionals who use BMJ Learning are encouraged to reflect on their learning. Over one year, all of the learners' reflections that related to patients were captured by the programme's software and were analysed using thematic analysis.

Results A number of key themes emerged from this analysis: many learners reflected on patients in the context of their disease; many learners reflected on how they had put their learning into action or planned to put their learning into action for the benefit of patients; many learners reflected on how they would pass on what they had learned to patients; learners greatly appreciated patients contributing to the learning.

Discussion Learners predominantly reflect about patients in the context of their disease. The reflections demonstrate that learners are keen to put their learning into action for the benefit of their patients. Learners' reflections show a keen interest in the patient-centredness of the learning resources.

INTRODUCTION

E-learning is a modality that is being increasingly used in medical education.[1] In the early years of e-learning, there was a flurry of interest on whether e-learning "works" or "works better" than face-to-face learning.[2] The research evidence that has been developed shows that e-learning produces broadly similar outcomes as face-to-face education.[3] There is now a growing interest in *how* healthcare professionals learn online and *how* they think about the impact of their online learning on patients. This paper reports an exploratory thematic analysis of online learners' reflections that relate to patients.

The reflections of learners are important. According to Mann et al "reflective capacity is regarded by many as an essential characteristic for professional competence."[4] Reflection is now encouraged among learners at undergraduate, postgraduate and continuing medical education levels. Reflections of learners on patients are especially important. This is because patient centredness is important in healthcare professional education. Patient centredness is a value system that puts the agenda of the patient at the centre of the focus of healthcare.[5] Mead and Bower describe patient centredness as consisting of the following dimensions: "a biopsychosocial perspective, patient-as-person (understanding the patient's experience of their illness), shared power (therefore increasing patient involvement), therapeutic alliance, and doctor-as-person (self-awareness of their own subjectivity)".[6] The learners were users of an e-learning resource, BMJ Learning. BMJ Learning is the e-learning service of the BMJ. It contains a range of interactive and multimedia learning resources to help doctors stay updated. Its users include GPs, GP trainees, and junior and senior secondary care doctors. It covers clinical and non-clinical resources and is designed to help doctors learn practical knowledge that they can use in their day-to-day practice.

METHODS

Healthcare professionals who use the resources on BMJ Learning are encouraged to reflect on their learning when they have completed the resources. They are encouraged to articulate their reflections and to add them to a free text box at the end of the resources. Learners are not required or incentivised to write a reflection – they do this voluntarily. All of the learners' reflections between 01 June 2016 and 01 June 2017 were captured by the programme's software. The reflections that related to patients were analysed using thematic analysis.[7] This was used to allow new concepts and themes to emerge from the data.

RESULTS

Between 01 June 2016 and 01 June 2017, one thousand four

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hundred and sixty-one reflections mentioned patients at least once in the text. These reflections were subjected to thematic analysis. Six key themes emerged from this analysis.

Theme 1: Patients in the context of their disease

Many learners reflected on patients in the context of their disease. They stated how they had learned about various features of the patient and their disease – typically related to the diagnosis and management of the relevant disease. Learners often mentioned learning needs in relation to these patients – albeit in an informal way. One learner reflected: "It was worth reading. I deal with a lot of patients with cerebral palsy and it has given me brief overview (sic) of what the disease is and how it is managed."

Theme 2: Putting learning into action

Many learners reflected upon and articulated how they had put their learning into action or planned to put their learning into action for the benefit of patients. Learners did not see their e-learning activities as an academic exercise but rather had strong practical goals related to their actual patients. Sometimes they reflected that they had confirmed that their practice was correct and sometimes they reflected on how they had already changed their practice or planned to change their practice in the future. The changes to practice mentioned by the learners typically related to the clinical investigation, diagnosis and management of various diseases. Sometimes these reflections related to communication skills. One learner reflected: "Very good educational and informative topic which has enhanced my interviewing skills during doctor-patient consultation." Another reflected as follows: "Will definitely change my management of patients requiring anticoagulation."

Theme 3: Passing on knowledge learned to the patient

Many learners reflected on how they would pass on what they had learned to the patient. Many reflections from learners related to how they planned to use what they had learned to better inform their patients about their condition. Learners mentioned using the content as the basis of information for patients or on using the content to advise or educate their patients. Some learners suggested that the modules could be linked to patient information leaflets that they could give directly to their patients. Learners commented as follows: "Very useful to give more information to patients"; "I would find patient info (sic) leaflet useful".

Theme 4: Patients contributing to the learning

The resources often feature videos of patients speaking about their illnesses. We created these resources to ensure that the content is genuinely patient centred and that learners are learning about content that is important to patients. These were greatly appreciated by the learners. The learners felt that these videos brought the content to life and helped to break up the text. Many of them found that they gave a more meaningful insight into the condition under discussion and that this resulted in deeper learning. One learner commented: "Excellent description of migraine by the patient interviewed." Another reflected: "Thanks to patient. For giving us a perspective from the other side of the consultation."

Not all modules contain such videos and some learners stated that certain modules would benefit from these patient insights.

Theme 5: Patient scenarios

E-learning resources can feature interactive case-based patient scenarios – many of the learners commented on these and did so in a positive and constructive way. Many learners said that the resources could feature more of these scenarios or scenarios that were more complex or that were closer to real life. One learner reflected: "A very useful module, with excellent patient scenarios which makes you think laterally". Another reflected: "I think the use of clinical scenarios was very effective as I have met several patients in the emergency department with similar presentations as shown."

Theme 6: Learners need more knowledge about patients

Many learners reflected that, although the knowledge that they had gained was useful, they wanted even more detail. These learners requested more detail about the diagnosis and management of patients. Sometimes they asked for content to cover real life aspects of patient care in more detail or to deal with more complex situations. One learner reflected: "Excellent module. I wish though that perhaps they went into more detail about say clinical symptoms patients would have." Another commented: "A little bit more about managing patients who have a life expectancy of less than 10 years would help."

DISCUSSION

Learners predominantly reflect about patients in the context of their disease. The reflections demonstrate that learners are keen to put their learning into action for the benefit of their patients and sometimes this involves empowering patients by passing on their learning directly to patients. Learners' reflections show a keen interest in the patient-centredness of the learning resources – sometimes this is manifested in positive contemplations about patients contributing to the learning or patient scenarios that are grounded in real life experiences.

There are limitations to this analysis. All of the learners were users of a single e-learning resource (BMJ Learning): they may not be representative of users of other e-learning resources. Only reflections in the English language were analysed. Some reflective statements were incomprehensible – these were not analysed. Lastly these were all self-reflections that were articulated immediately after completion of the learning resources – we do not know what or how learners thought about patients in the long term.

This was an initial exploratory analysis. However, we plan to continue to analyse feedback to BMJ Learning that relates

to patients and to produce more resources that encourage such reflections – such as learning resources where patients contribute to the learning or learning resources that use patient scenarios grounded in real life experiences.

SOURCES OF FUNDING

None

ACKNOWLEDGEMENTS

None

CONFLICT OF INTEREST

Kieran Walsh is clinical director at BMJ

ETHICAL APPROVAL

This was not sought as this was not a trial.

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Letters

CHRONIC RING EROSION OF A FINGER

Editor,

Ring erosion of a digit is a rare injury that develops insidiously over many months or years.[1]The risk factors include psychiatric illness, poor social support and self-neglect.[1]The majority of patients deny direct trauma as a cause. We present a case of ring erosion of a digit with significant bone destruction.

A 59-year-old man was admitted for investigation of sepsis, following a fall. His comorbidities included obesity, recurrent lower leg cellulitis and restricted mobility. He had no psychiatric illness or known substance abuse. On admission, he was unkempt, pyrexial and tachycardic. The finding of an embedded ring on his right middle finger warranted plastic surgery review due to concerns that it could be the source of sepsis. On further questioning, the ring had been present for over 3 years and removal had been recommended. However, due to fear that it would result in finger amputation, the patient declined treatment.

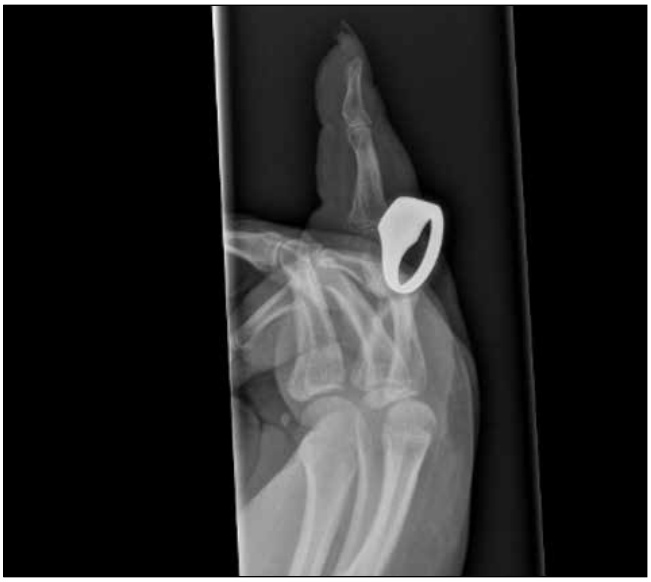

Fig 1: Photograph showing dorsum of right hand with the ring embedded in the middle finger.

The finger was swollen proximally without significant erythema or discharge. It was well perfused and had a reduced range of movement and stiffness. The ring freely rotated in the bony tract which had formed over the years. Radiographic examination of the affected finger showed significant bone erosion of more than 50 % of the proximal phalanx (Figure 1,2)

The external part of the ring was cut with a ring cutter and the internal part was then easily removed by rotating it out through the formed tract.

DISCUSSION

Ring erosion of a digit involves a combination of repetitive trauma over a long period of time and predisposing factors. Initially, oedema and skin hypertrophy develop distal to the ring, subsequently, an epithelial bridge forms over the ring on the palmar surface, leaving the dorsal surface intact.[1]The clinical picture at presentation is usually either chronic or acute-on-chronic with superadded infection and neurovascular compromise.

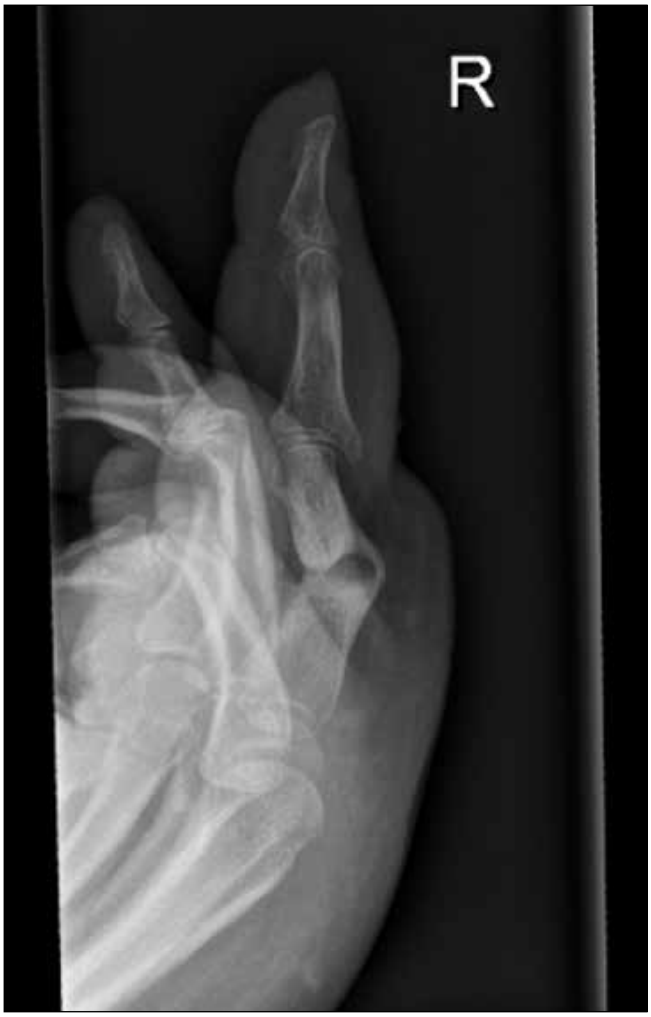

Fig 2: Lateral radiographs of the right hand showing erosion of the proximal phalanx of the right middle finger before and after ring removal

To our knowledge, there is no case of digital amputation in the literature as a consequence of ring embedment. This could be explained by the fact that the involved digits, develop collateral circulation around the rings.[2,3]

In one review of the literature in 2002, Leung reported 11 cases with a similar presentation. Over 50% of patients had a mental illness and 72% were female between the ages of 7-73 years. Another author reported multiple rings removed from the same digit without the need for amputation.[2]

The management entails removal of the ring and wound care.[1] It may be possible to remove the ring with a ring cutter as a minor procedure, especially when the ring is freely mobile within the tissue plane formed.[1,4] A foreign body granuloma

may develop if a saw is used for ring removal as small ring fragments can remain in the tissue.[5] In more complicated cases, a hand surgeon should be consulted for consideration of removal in a controlled theatre environment.[1,3] In advanced cases, exploration and reconstruction of the defect may be required.[1,3]

The learning point is that early intervention is the key to preventing the associated morbidity caused by chronic destruction and loss of function.[3]

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OUTCOME OF SUPRAVENTRICULAR TACHYCARDIA IN INFANCY AFTER 4-YEAR FOLLOW-UP

Editor

Supraventricular tachycardia (SVT) is the most common arrhythmia in children, with the majority of SVT episodes occurring in a structurally normal heart.[1]

Although there is a broad spectrum of research on method of management and short-term outcomes of SVT prophylaxis[2-3], there is little evidence on the long-term outcome of patients presenting with SVT. In fact, we were only able to locate one study of 15 patients.[4]

METHODS

The 'HeartSuite' database from the Royal Belfast Hospital for Sick Children (RBHSC) included 55 patients who were diagnosed and admitted into RBHSC or referred to out-patients' clinics across Northern Ireland.

Data were collected for children presenting with the first episode for infants under 1 year of age between 2006 and 2011 allowing at least 4 years' follow-up.

RESULTS

The major finding was that 48/55 patients (87.3%) after review were discharged or able to live without medication. Of the 55 patients surveyed, 36 (65.5%) were discharged and 12 (21.8%) were still being followed up but on no medication. Only 6 (10.9%) were still on medication. There was one intervention for catheter ablation of the accessory pathway. There was no mortality.

DISCUSSION

The study suggests that a large number of patients presenting with the first episode in the first year were discharged after four years.

One retrospective review[4] on the outcome for AVNRT (atrioventricular nodal re-entry tachycardia), a common form of SVT, in 15 patients also showed no mortality after 40+ months' follow-up. 9/14 asymptomatic subjects (64.3%) were no longer on medication in their study which is significantly lower than our findings (87.3%) and 5 (35.7%) were still on medication after 21 months' follow-up – higher than our figure of 10.9%. 2/15 in the study underwent radiofrequency ablation (13.3%), also higher than the 1.8% intervention rate we found. The small number of patients followed up in both studies may have contributed to these discrepancies. This study was also specific to patients diagnosed with AVNRT and it was published almost two decades ago.

Our study was on a small scale but specific to the population of Northern Ireland. The strength of this study is that there is at least a four-year follow-up for each subject, enabling us to provide information for the long-term outcome.

CONCLUSION

This study provides detailed information on SVT outcomes in Northern Ireland. It provides a larger sample of patients than previously reported for over a similar length of time. This study may give doctors a clearer plan for paediatric SVT patients in relation to prognosis and duration of review.

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CAUGHT RED HANDED- CONGO STAINING IN THE OROPHARYNX

Editor,

A 74-year-old retired mechanic and never-smoker presented with a two-month history of hoarseness and weight loss. On examination he was found to have a large right-sided oropharyngeal mass extending across the soft palate with an associated ipsilateral neck gland.

Contrast enhanced computed tomography (CT) showed a 4x3x6cm mass extending from the hard palate to the superior border of the hyoid bone with no infiltration. It was contiguous, infiltrated the soft palate and bilateral level 2 lymphadenopathy was noted.

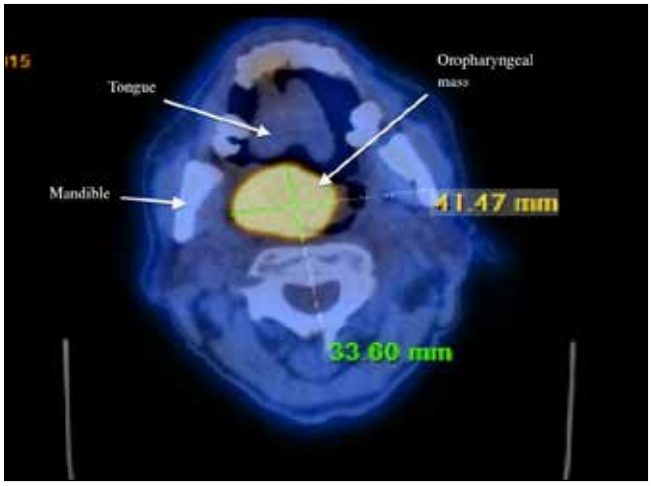

Fig 1: Axial PET CT image of mass in the oropharynx

Fine needle aspiration of the neck node showed abundant amorphous material which was representative of amyloid on Congo red stain and the washings showed polyclonal population on light chain stain- characteristic of amyloidosis. PET CT confirmed uptake in the oropharynx but showed nil else in keeping with systemic amyloidosis. (Fig 1)

This patient was managed jointly by ENT and the haematologists who commenced a short course of steroids with good symptomatic effect and by the otolaryngologists who performed carbon dioxide laser resection. A pre-operative tracheostomy under local anaesthetic and embolisation of the external carotid artery was performed as substantial bleeding was expected due to the rich blood supply and dense protein matrix in amyloid lesions, which prevents constriction of the blood vessels.

To date there has been no re-occurrence of the disease though some is expected, as full excision was not possible due to the location of the deposit. This patient remains under regular follow by the otolaryngologists, the haematologists and the National Amyloid center.

DIAGNOSIS

The diagnosis of amyloidosis is made by a combination of clinical symptoms and tissue biopsy to establish a definitive diagnosis. Bennhold introduced the Congo red stain in 1922 and showed the characteristic red staining of amyloid in normal light. (Fig 2) Apple-green birefringence with polarised light microscopy, however, is the gold standard for diagnosis. (Fig 3)[1]

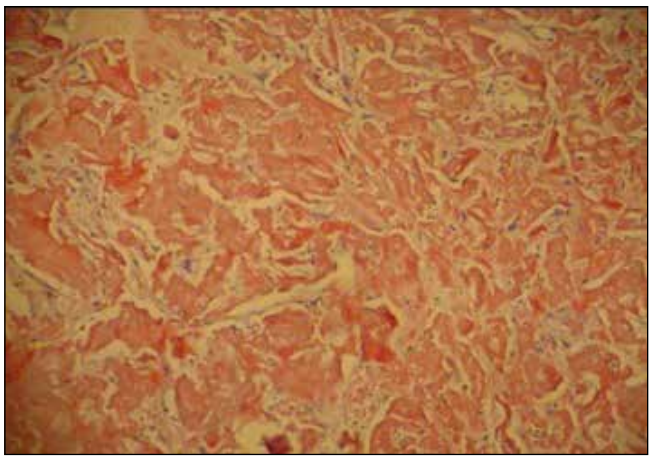

Fig 2: Slide with Congo red stain showing presence of amyloid

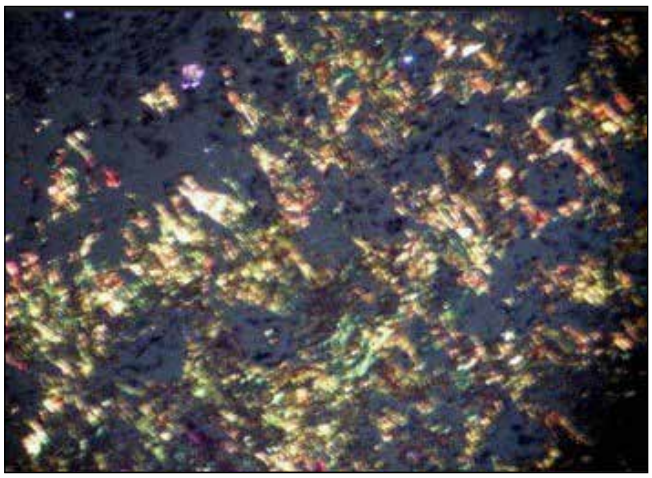

Fig 3: Apple green birefringence in polarised light-green colour demonstrates presence of amyloid

IMAGING

Computed Tomography (CT) and Magnetic resonance imaging (MRI) are useful to assist in surgical approach but are non-specific for amyloidosis. The presence of giant cells in localised amyloidosis enables (18) F-fluorodeoxyglucose (FDG) positron emission tomography/ computed tomography (PET/CT) to be used in the differentiation between systemic and localised disease. Scintigraphy following administration of radio-labelled serum amyloid P component (SAP) is a specific imaging technique which enables quantification of amyloid deposits. This investigation is only available in a few centres in the United Kingdom including the National Amyloidosis Centre.

DISCUSSION

Amyloidosis is a heterogeneous group of diseases that can present with diverse symptoms according to the predominant site(s) of protein deposition. Although a rare disease, is not

uncommon, with head and neck involvement in 19% of cases.[2] It is important differential diagnosis for oropharyngeal masses as the management and prognosis varies significantly from malignant disease.

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FOUNDATION DOCTORS' AUDITS: EFFECTIVE OR NOT?

Editor,

The UK Foundation Programme (FP) curriculum recommends that Foundation doctors (FD) develop experience in 'managing, analysing and presenting at least one quality improvement project and using the results to improve patient care'[1]. While the Maltese FP follows the UKFP recommendations, little emphasis is placed on completion of the audit cycle. The authors devised a questionnaire to assess the proportion of audits performed by FDs at Mater Dei Hospital (MDH) that completed the audit cycle, implementing changes in clinical practice.

METHODS

All audits registered on the Maltese FP audit register between January 2012 and August 2015 were included in the study: a total of 110 projects. The questionnaire was forwarded to the main author of each registered project by electronic mail, and responses collected over 6 months.

RESULTS

57 questionnaires were completed (52%). Most FD embarked on an audit so as to influence practice (79%) or improve the curriculum vitae (72%). 66.6% of respondents felt satisfied with the outcome of their project, while 71% felt supported in performing the audit. 77% of respondents felt encouraged to present their findings. Only 5.2% of audits reached the final, re-audit stage of the audit cycle. The most common reasons for failing to complete the audit loop were time limitations (46.9%), administrative difficulties (25%) and a move to a different department (50%). Of the 94.8% of responders who failed to complete the audit cycle, only 8.9% handed over their work to a colleague to complete.

DISCUSSION

Audits done by FD in Malta were rarely completed, with only 5.2% of the registered audits reaching the re-audit stage. This compares with 24% in a similar study in London[2]. 21% of junior doctors from Leeds perceived their audit projects to have a negative effect on the department[3] the degree of support from audit staff, and the perceived value of the resulting audits. This contrasts with our data showing a relatively high rate of satisfaction with the outcome of the audits performed, regardless of the stage of the audit cycle that was reached. This could indicate a poor appreciation of the potential for audit to influence practice. Also sobering is the fact that of those failing to complete the audit cycle, 91% did not plan to handover their results to a colleague to complete the cycle, and almost 50% had no plans to complete the audit. In these cases, it appears that potentially influential data has gone to waste.

The authors propose a handover system for FD to pass on their collected data for a colleague to act upon. This could avoid useful and hard-earned data from going to waste, and lead to improvements in practice. Encouraging multiple FD to work as a team on a single project can also help them overcome time limitations[4]. FD need to be made aware of the value of a completed audit: part of the responsibility for this falls on Educational Supervisors within the FP. Helping junior doctors to contribute by implementing change will motivate them and encourage them to undertake further audit projects in the future.

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CENTRIFUGATION IN GP PRACTICES - CAN IT IMPROVE DIAGNOSTIC EFFICIENCY?

Editor

Potassium (K) is one of the most frequently tested analytes in the biochemistry laboratory. Because of its critical role in both cellular and electrical function it is vital that hypo and hyperkalaemia are promptly communicated to clinicians. A delay in sample centrifugation is a common cause of pseudohyperkalaemia. The follow up of pseudohyperkalaemia consumes valuable health care resources and can result in patient care delays.

The purpose of this trial of sample centrifugation at source was to verify the positive impact on the quality of potassium results (ie the number of samples requiring follow-up) reported within the literature[1] and measure user satisfaction

TABLE 1:

Proportion of results per concentration category

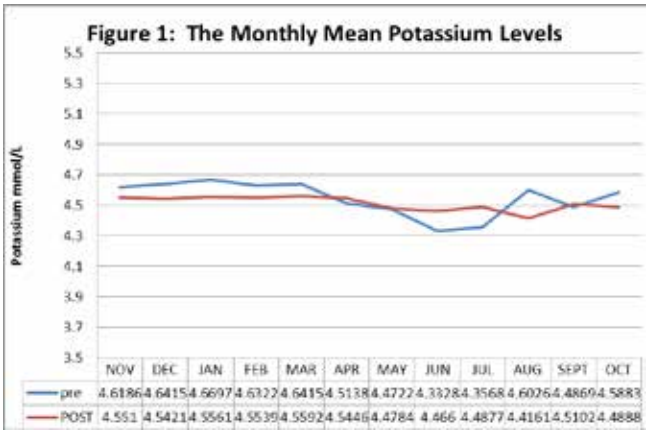
	Pre implementation		Post implementation	
	Number of samples	% of total sample number	Number of samples	% of total sample number
Dashed out	434	10.68	32	0.77
<3.5	38	0.93	39	0.94
Normal range	3365	82.78	3912	94.54
>5.3-6	210	5.17	140	3.38
>6	18	0.44	15	0.36
TOTAL	4065		4138	

A Heraeus Labofuge 300 centrifuge fitted with an 8 swing bucket rotor was installed in the Dromore GP surgery treatment room and safety checked by the supplier. To ensure the safety of patients and staff a comprehensive training program was delivered by the laboratory Biomedical scientist.

The pilot officially started in November 2014. To minimise the chances of erroneous potassium results due to samples being mistakenly re-centrifuged[2], the practice placed all centrifuged samples in a special labelled bag. Potassium results for the Dromore practice during the pilot period and retrospective data from November 2013 to October 2014 were extracted from the Laboratory information system and analysed by Microsoft EXCEL. User satisfaction was accessed by a post pilot questionnaire.

The total numbers of potassium requests during the pre-implementation and implementation periods, presented in Table 1, were similar. There was a 2% increase in requests. This increase in activity is consistent with the long term activity trend for biochemistry analysis.

Centrifugation at source improves the quality of Potassium result in 2 ways. Firstly, as evident in figure 1 and previously reported by Turner et al (2012) it reduces seasonal variation. Secondly as we see in table 1 it increases the proportion of results within the normal range thus reducing the need to follow up abnormal results. The proportion of results in the <3.5 mmol/L category was unaltered therefore the improvement is primarily due to a reduction in the elevated and dashed out categories. It is noteworthy that only in the post implementation period were values exceeding 7 reported. In these 2 patients previous results had been dashed out due to delayed separation.



Feedback from Dromore treatment room staff was extremely positive. The additional time spent centrifuging samples was offset by the flexibility of collecting samples at any time of the day rather than organising collections to coincide with the delivery vans. The footprint of the centrifuge did not significantly impact on the space within the treatment room and the noise level was not intrusive. General practitioners indicated a reduction in the time taken to review lab results and a reduction in the risk posed by alert fatigue. The Practice would encourage other practices to consider installing a centrifuge.

Centrifugation at source or an alternative such as phlebotomy centres must be an integrated component of the Pathology modernisation strategy[4].

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Abstracts

20th Meeting of the Irish Society of Human Genetics

Friday 15th September 2017 Croke Park, Dublin

ORAL PRESENTATIONS:

S01. DEVELOPING AN MDT MODEL IN NEUROFIBROMATOSIS TYPE 1 (NF1) AS A PARADIGM FOR ENTRY INTO A EUROPEAN REFERENCE NETWORK (ERN).

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Neurofibromatosis (NF1) affects 1/2500 people throughout the world. Children with NF1 require a multidisciplinary service ideally, delivered on a single site. NF1 is a very variable condition with children requiring the expertise of genetics, paediatricians, ophthalmologists, dermatologists, neurologists and other specialities as required. Building such a service concentrates expertise, facilitates coordination of care and fosters ideal opportunities for research.

Aims: 1) To develop a service ensuring children had access to a multidisciplinary clinic on an annual basis. 2) Hold monthly clinics offering ophthalmology, medical, developmental and dermatology follow up. 3) To create a registry of patients which captures the incidence and prevalence of NF1 in Ireland. To offer best possible care for the children attending the service by following international consensus guidelines. 4) To liaise with NF1 Association, families and research authorities.

Methods**:** 1) Appointment of a CNS/CNM2 in Neurofibromatosis as funded by the NCH Foundation. 2) Visit to the complex NF1 Clinic in Manchester's Children's Hospital and learn from their service, MDT and guidelines. 3) Establish links with genetics, oncology, radiology and orthopaedic depts. in OLCHC. 4) Create a referral pathway for HCPs to ensure children with NF1 are referred to most appropriate service in a timely fashion. 5) To register the service on Orphanet and gain entry into an ERN as a multi-site service in conjunction with OLCHC.

Results/Conclusion: To date, the service has been running for 9 months. The CNM2 provides telephone service and coordinates clinics. The Clinic has been registered in Orphanet and the process has begun to create a patient registry and enter the service in the ERN.

S02. TUMOUR RISKS AND GENOTYPE-PHENOTYPE ANALYSIS IN AN IRISH COHORT OF PATIENTS WITH GERMLINE MUTATIONS IN THE SUCCINATE DEHYDROGENASE SUBUNIT GENES SDHB, SDHC AND SDHD

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Germline mutations in the succinate dehydrogenase subunit genes SDHB, SDHC and SDHD are the most frequent causes of inherited phaeochromocytomas and paragangliomas. Patients presenting with these tumours are usually offered genetic testing for these and other genes as part of standard clinical investigations. However, the information regarding penetrance and phenotype genotype correlations associated with SDHB/C/D mutations is variable, making it difficult to determine an optimum management strategy for this group.

In order to address this issue we undertook a retrospective cohort study of patients who underwent genetic testing for SDHB, SDHC or SDHD. 195 patients were identified through the Irish Genetics laboratory electronic database as having had a genetic test for SDHB, SDHC or SDHD and referral source, referral reason and genetic test outcome were analysed.

Analysis of penetrance and phenotype presentation was determined through a Clinical Genetics chart review of 147 patients from 40 separate families. Analysis of age-related tumour risks according to relevant gene and mutation type (for SDHB and SDHD) provided estimates of penetrance and genotype-phenotype correlations.

Increased knowledge of the molecular basis of phenotypic variability commonly observed in individuals with germline SDHB/C/D mutations will facilitate the development of age-appropriate management protocols based on gene specific tumour risks.

S03. CATALOGUING INHERITED DISORDERS AMONGST THE IRISH TRAVELLER POPULATION

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Irish Travellers are an endogamous, ethnically Irish population of ~40,000. Consanguinity is common. Knowledge of Traveller disorders exists but mainly in specialised Irish centres. Most Traveller disorders are published but ethnicity is not explicit, hampering diagnoses, particularly if the patient is overseas where knowledge about this population is poor.

Aims: To catalogue inherited Irish Traveller disorders through identifying the disorders, detailing mutations, use of coding, (OMIM, Orphacodes & ICD10), publications, and help develop a database to facilitate diagnoses.

Methods: A literature review was undertaken. Key national and international Clinician/scientists were contacted to identify relevant disorders and publications. Laboratory and clinical databases were searched to retrieve disorders & mutations. Annotations were updated. An Excel database was established listing each disorder, its appropriate code, associated mutation and relevant publication.

Results: 86 distinct rare genetic disorders resulting in 75 phenotypes were identified; 78/86 were autosomal recessive; 4 of these were dominant disorders presenting only in the recessive state. Seven dominant disorders with no recessive phenotype were included as > one affected individual existed. One common 17q12 duplication was included, presenting in two unrelated families. Homozygous mutations were found in all recessive disorders bar one. The genetic basis of 78/86 was established. A further 2/76 have common haplotypes; the genetic basis of six disorders remains unclear. Linkage disequilibrium was observed in 4 families with co-existing McArdles disease and microcephaly & 11 individuals have co-existing Friedreich's ataxia & galactosemia.

Conclusion: Our work is the first step towards cataloguing inherited Irish Traveller disorders. Future challenges include development of an online mutation database.

S04. MUTATIONAL ANALYSIS IN A COHORT OF ADULTS WITH A BIOCHEMICAL DIAGNOSIS OF TRIMETHYLAMINURIA ATTENDING AN IRISH METABOLIC UNIT

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Primary Trimethylaminuria (TMA)(OMIM 136132), is an autosomal recessive rare disorder which results in diminished capacity to oxidise the dietary derived amine trimethylaminuria to its odourless metabolite Trimethylamine-n-oxide (TMA-n-Oxide). Severe primary TMA has been defined as the percentage of unmetabolised free TMA in urine being >40% and mild/moderate TMA range is 10-39%. More than 30 variants of the Flavin monooxygenase 3 (FMO3) have been reported to cause primary TMA. Diagnosis of primary TMA has implications for management of the patient in relation to treatment and genetic counselling.

We sequenced the entire FMO3 gene coding region in 10 patients who had a biochemical diagnosis of TMA made in the past 5 years. Three of the patients had severe TMAU (% TMA range 39.4 to 45), (Group A) and 7 had mild to moderate TMAU (%TMA range 10-30), (Group B).

We identified causative (loss of function) in 5/10 individuals. Homozygosity for loss of function mutations was detected for 2/3 cases with severe TMAuria (Group A).

3/7 of the patients with mild to moderate TMAuria biochemically had a genetic diagnosis. Two were homozygous for Glu158Lys/Glu308Gly and the other was compound heterozygous for P153L and A232T.

Primary TMAU is rare in Ireland and mutational analysis should not replace biochemical diagnosis.The rate of detection of pathogenic mutations was low using the recommended biochemical cut-offs. The E305X mutation the first *FMO3* mutation described in OMIM (136132.0001) in an Irish Australian family may be an Irish Mutation.

Two new apparent *FMO3* mutations are described in this Irish population. A cut- off of free TMA levels higher than that suggested on the Gene Utility card may be more beneficial in directing genotyping.

S05. TARGETED NEXT-GENERATION SEQUENCING FOR THE MOLECULAR CHARACTERISATION OF HEREDITARY RENAL DISEASE

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Background: As part of the Irish Kidney Gene project, 2000 people with renal disease were surveyed and >30% of participants reported a family history for their condition. This strongly suggests an underlying genetic component for the development of kidney disease. Blood and urine tests as well as kidney biopsies are frequently used to inform on aetiology of the disease. However, in around 10% of cases, aetiology is simply unknown, making it difficult for physicians to provide a clear diagnosis or prognosis to these patients.

Aim: This project aims to utilise genomic sequencing to stratify patients with hereditary renal disease (HRD). In doing so we seek to aid clinical diagnosis, provide insight into pathogenesis and in some cases point to specific therapies.

Methods: We developed a custom, targeted NGS panel for inherited kidney diseases which we have applied to 48 HRD patients. The panel includes 11 genes which are established causes of polycystic kidney disease, von Hippel Lindau syndrome, renal cysts and diabetes syndrome and Alport syndrome. The NimbleGen Heat-Seq kit was used for library preparation and samples were sequenced using an Illumina MiSeq platform at Beaumont Hospital. Data was analysed using a custom bioinformatics pipeline and variants were classified according to the ACMG guidelines.

Results/Conclusions: To date, this panel has identified candidate pathogenic variation in a third of samples studied. Future work in this project will include the development of a larger targeted panel including >100 known renal disease genes.

S06. IDENTIFYING NOVEL INHERITED BREAST CANCER MUTATIONS IN AN IRISH POPULATION

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Breast cancer is the most common female malignancy worldwide. Up to 10% of cases are the result of an inherited monogenic mutation, while a further 25% appear in familial clusters. Only 30% of hereditary breast cancers are attributed to mutations in BRCA1 and BRCA2, identified as high-risk genes through linkage analysis. While BRCA mutational status is highly informative, and allows clinicians to modify surveillance, prevention and therapeutic strategies, the risk conferred by mutations in other genes is more difficult to define in light of variable penetrance. Next-generation sequencing has been rapidly evolving to advance testing sensitivity and throughput in a cost-effective manner. This progression

has made multi-gene testing a practical option when looking to identify inherited mutation(s) in a clinical setting. However, current clinically available multi-gene panels generate many variants of unknown significance in genes that are presently not considered clinically useful. The aim of our study was to design a multi-gene panel to enable the detection of rare, probably pathogenic variants contributing to the susceptibility of breast cancer in an Irish population. An extensive literature review was conducted in order to generate a list of 282 genes with potential association to breast cancer. Targeted DNA enrichment and multiplexed next-generation sequencing was performed on a cohort of 167 samples from the west of Ireland. 90 breast cancer patients and 77 geographically-matched controls were included in this study. Bioinformatic analysis was performed following GATK best practices workflow. Variant data for our 282 selected genes will be presented and discussed.

S07. BENEFICIAL EFFECTS ON PSYCHOSOCIAL AND COGNITIVE DEVELOPMENT OBSERVED IN CHILDREN FOLLOWING *IN UTERO* FOLIC ACID SUPPLEMENTATION TRACK WITH CHANGES IN THEIR DNA METHYLATION

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Increasingly accurate surveys of human health throughout the life course has led experts to propose that stresses on the developing child whilst in the mother's womb can affect the individual's health later in life. Such long-term effects on health are thought to be mediated by a semi-permanent trace on the genes called an epigenetic mark, mediated by processes such as DNA methylation. DNA methylation patterns may be altered by the mother's diet, particularly folate – a key component in the DNA methylation cycle. Currently, mothers are recommended to supplement their diet with 400μg folic acid/day as a preventative measure against neural tube defects prior to/during the first trimester. However, there remains no clinical recommendation as to whether mothers should continue supplementation during the latter two trimesters and the potentially heritable effects. Thus, we analysed cord blood samples (n=93) from the Folic Acid Supplementation in the Second and Third Trimesters (FASSTT) randomised control trial for genome-wide DNA methylation. Offspring exposed to folic acid in later pregnancy had fewer highly methylated genomic regions and more intermediately methylated sites. Upon further interrogation, gene ontology analysis revealed these sites are enriched for genes associated with cognition and neurological system processes, and tissue analysis revealed enrichment of affected genes associated with the brain. Cognitive and psychosocial testing of the children at age 7 years, using standardised tests (WPPSI, TEIQue-CSF, RASP), showed that the children supplemented during pregnancy scored significantly higher for emotional intelligence, resilience and verbal IQ. Thus, this study offers a potential biological mechanism linking maternal folate levels with childhood cognition.

S08. THE IMPACT OF MTHFD1L EXPRESSION ON FORMATE LEVELS AND THE CELLULAR PROTEOME IN A CELL LINE MODEL.

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Introduction: We previously identified the mitochondrial 10-formyltetrahydrofolate synthase enzyme, MTHFD1L, as a risk factor for human Neural Tube Defects (NTD). This association was further supported by a mouse model of mutant *mthfd1l*, that exhibited an NTD and was rescued with maternal formate supplementation. The abundance of MTHFD1L is also increased in a range of cancers. MTHFD1L performs the last step in mitochondrial one carbon metabolism to produce formate for transport into the cytoplasm.

Aim: Given the pivotal role of MTHFD1L in human disease, we sought to decipher the cellular response to the expression level of MTHFD1L in HEK293 cells.

Methods: Human MTHFD1L was overexpressed in a stably transfected line using a pcDNA3.2 vector and knocked down using two inducible shRNA constructs that were clonally selected. Cells were grown and sampled over a five-day period. Expression level was confirmed by RT-qPCR. Intracellular and media formate levels were measured using GC-MS. Proteomics analysis was performed on whole cell lysates using LC-MS/MS on an Ultimate 3000 nano LC system coupled to a LTQ Orbitrap XL.

Results: Intracellular and media formate levels directly correlated with expression level of MTHFD1L compared to controls within an approximately 1.5 to 3 fold range. Our proteomics analysis showed that MTHFD1L expression level had an effect on proteins involved in DNA synthesis, replication and repair.

Discussion: We have demonstrated that MTHFD1L expression level has a direct impact on both intra- and extra-cellular levels of formate and may act as a signal for uncontrolled cell proliferation.

S09. THE IRISH DNA ATLAS; REVEALING FINE SCALE POPULATION STRUCTURE AND HISTORY WITHIN IRELAND.

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Ireland has remained relatively isolated from mainland Europe, notwithstanding historical migrations including the Norse-Vikings, Anglo-Normans, and the British Plantations. Although previous studies have shown the Irish to have elevated levels of homozygosity compared to mainland Europe, the extent of genetic structure within Ireland, and the genomic impact of historical migrations, is largely unknown. Here we illustrate fine-scale genetic structure across Ireland that follows sociological boundaries and present evidence of admixture events into Ireland. Utilising the 'Irish DNA Atlas', a DNA cohort (n = 194) of genealogically described Irish individuals with four generations of ancestry linked to specific regions in

Ireland, we analysed in combination with 2,039 individuals of regional British ancestry (the PoBI dataset) and show that the Irish population subdivides into 10 distinct geographically-stratified genetic clusters; three of shared British/Irish ancestry, and seven of predominantly 'Gaelic' Irish ancestry. This structure is remarkably homogenous, and is associated with very little gene flow barriers within Ireland. Additionally, using a reference of 6,760 European individuals and two ancient Irish genomes, we quantified the ancestry of these Irish clusters within the context of Europe as well as ancient Ireland. We show high levels of north-west French-like and Norwegian-like ancestry within Ireland, and homogenous levels of ancient Irish ancestry in our 'Gaelic' Irish clusters. Finally we detect admixture events into Ireland, coinciding with the Plantations of Ulster, as well as Norse-Viking activity within Ireland. Our work informs both on Irish history, as well as the study of Mendelian and complex disease genetics involving populations of Irish ancestry.

S10. A MOLECULAR ANALYSIS OF SDCCAG8, A SCHIZOPHRENIA RISK GENE THAT FUNCTIONS IN THE CENTROSOME

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Schizophrenia affects 1% of adults and is a major global health problem. I am interested in the potential role of the centrosome in schizophrenia. The centrosome, an organelle within cells, plays a crucial role in brain development where it directs cell shape, polarity and motility. The centrosome also seeds the growth of antenna-like signalling structures called primary cilia. Rare mutations in centrosome genes cause disorders that present with severe cognitive deficits and variable neuropsychiatric phenotypes.

GWAS data has implicated many genes in schizophrenia. We have shown that seven schizophrenia risk genes encode proteins with centrosomal functions. Of these, SDCCAG8 is also associated with educational attainment in GWAS and the genome-wide significant SNPs for the two phenotypes are in high linkage disequilibrium indicating a pleiotropic effect. We have found that a schizophrenia risk SNP in SDCCAG8 is significantly associated with poorer performance in a social cognition task, in a large Irish dataset of schizophrenia patients and controls (p=0.001).

To analyse the molecular function of SDCCAG8 we have used genome editing to knock it out in neuronal and retinal cells. Preliminary data shows that loss of SDCCAG8 impairs cells' ability to make primary cilia and that their capacity to repair genome damage is reduced. Current work is addressing whether SDCCAG8 affects activities that may contribute to schizophrenia, including cell migration and cell signalling. This could identify molecular mechanisms by which SDCCAG8 mutations contribute to schizophrenia risk and cognition, and help uncover the processes that implicate centrosome genes in neurodevelopmental phenotypes.

S11. POLYGENIC RISK SCORE AS A DETERMINANT OF RISK OF NON-MELANOMA SKIN CANCER POST-TRANSPLANTATION

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Multiple genetic loci have been identified for non-melanoma skin cancer (NMSC) in the general population. Polygenic risk score (PRS) was defined as the sum of all alleles associated with a trait weighted by the effect size of that allele as determined by a previous genome-wide association study (GWAS). We tested whether PRS, calculated using a GWAS of NMSC in a non-transplant population, can be used to determine risk of developing and time to NMSC post-transplant.

Post-kidney transplant NMSC cases (n=155) and controls (n=442) were collected from Tennessee, Ireland and Scotland. Genetic variants that reached pre-defined levels of significance were chosen from a squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) GWAS, both conducted in non-transplant populations. Using these GWAS results, BCC and SCC PRSs were calculated at each p-value threshold (pT) for each sample. PRSs were tested as a predictor of case:control status using logistic regression and time to NMSC post-transplant in a survival model.

SCC PRS calculated at pT $1x10^{-6}$ was the most significant predictor of case: control status of NMSC post-transplant (OR per 1 stdev increase in PRS=2.3; corrected P (P_c)=0.04). When NMSC was subdivided into SCC and BCC, SCC PRS pT $1x10^{-6}$ significantly predicted case:control SCC (OR=2.5, P_c=0.02) and BCC status (OR=7.6, P_c=0.02). SCC PRS pT $1x10^{-5}$ also significantly predicted time to BCC (P_c=0.007, HR=1.8) and SCC (P_c=0.05, HR=1.4).

PRS of non-transplant NMSC can be used to predict case:control status of post-transplant NMSC, SCC and BCC as well as time to developing BCC and SCC post-transplant.

POSTER PRESENTATIONS:

P01. ESTIMATING THE NUMBER OF RARE DISEASE PAEDIATRIC PATIENTS SEEN BY A SINGLE NATIONAL GENETICS CENTRE BORN IN THE YEAR 2000.

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Introduction: Rare diseases are diseases, which affect a small number of people compared to the general population. In Europe, a disease is considered rare when it affects no more than 5 per 10,000 individuals. A disease can be rare in one region but common in another. The objective of this study was to derive a proxy estimate the number of childhood onset rare diseases through referrals to the country's only Genetics center, as the Republic of Ireland does not have a centralized rare disease registry.

Methods: A retrospective review of referrals to cytogenetics and clinical genetics for the years 2000-2016 for patients born in the year 2000 was undertaken. Anonymized data was catalogued into rare, common, normal, likely rare & unclassifiable by review of records, and assigned Orphacodes based on diagnosis. Census live birth data was used as the denominator.

Results: 54,7891 live births were recorded by the census in 2000. 1872 referrals to Genetics (representing 1749 individuals born in

2000) were retrieved for review. 1007 had cytogenetic testing only, of which 51 had rare chromosomal anomalies. Review of 742 referrals to clinical genetics yielded 581 with a rare disease (78%), 7 with a likely rare disease, 56 with a common disorder, 83 who were normal (at risk relative) & 15 unclassified (hadn't yet been seen). Of the 53/1749 who had died (3%), 51 had a rare disease with congenital malformations (24) the most common cause.

P02. A POPULATION STUDY OF TUMOURS IN NEUROFIBROMATOSIS TYPE 1 PATIENTS IN NORTHERN IRELAND

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Neurofibromatosis type 1 (NF1) is a relatively common autosomal dominant genetic condition, with an incidence of around 1 in 3000. All NF1 patients attend our regional NF1 clinic intermittently and our departmental database records clinical details. Currently, we have 468 living patients affected with NF1 in Northern Ireland. NF1 is caused by mutations, or occasionally deletions, of the neurofibromin tumour suppressor gene, which leads to over-activation of the RAS-MAPK pathway, and tumour formation. These vary from benign lesions, such as neurofibromas, through to malignant peripheral nerve sheath tumours (MPNSTs) and tumours in other sites, particularly the central nervous system, that can be associated with significant morbidity and mortality. MEK inhibitors have recently been shown to be an effective treatment modality in the tumours associated with NF1. We have studied our population to determine the number of patients with plexiform neurofibromas, who are at risk of MPNSTs, and the proportions of patients with tumours elsewhere. This will allow us to identify which patients could benefit from MEK inhibitors in the future.

P03. A COMPLETE POPULATION SURVEY OF EPILEPSY IN TUBEROUS SCLEROSIS PATIENTS IN NORTHERN IRELAND

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Tuberous Sclerosis complex (TSC) is an autosomal dominant genetic condition which results, in the majority of patients, from a mutation in the TSC1 or TSC2 genes. Many of the patients are affected by angiomyolipomas and sub-ependymal giant cell astrocytomas. There is evidence that mTOR inhibitors, particularly Everolimus, shrink such tumours. In addition, the recent EXIST-3 study showed that Everolimus led to a significant reduction in seizure frequency in TSC patients whose seizures had previously proved resistant to anti-epileptic drug treatment. Consequently, a European licence has been granted to prescribe Everolimus for this indication.

In order to determine the potential number of patients who may be eligible for consideration of this treatment, we undertook a complete population survey of epilepsy in our TSC patients. Information was extracted from our database and descriptive statistics were carried out. We were particularly interested in obtaining numbers of those whose seizures were poorly-controlled, defined as requiring 3 or more anti-epileptic drugs to manage their seizures, or requiring neurosurgical intervention. Many of the TSC patients with a diagnosis of epilepsy were also diagnosed with learning difficulties. The possibility of an association between degree of seizure control and severity of learning difficulties was explored. Finally, the annual cost of prescribing Everolimus to Northern Ireland's TSC patients with poorly-controlled seizures was estimated.

P04. ZYGODACTYLY (SYNDACTYLY TYPE A1) IS ASSOCIATED WITH CHARCOT NEUROPATHY AND DIABETES

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Charcot neuroarthropathy is associated with neurological deficit and is often seen in patients with a history of diabetes. Zygodactyly is a common congenital malformation with cutaneous webbing of the second and third toes.

To determine the frequency of Zygodactyly in midfoot (tarso-metatarsal) Charcot neuropathy due to diabetes, we analysed a prospective series of twenty-five patients with Charcot neuropathy referred to podiatry clinics from diabetes and vascular departments. Twenty-nine patients with diabetes (but no Charcot neuropathy) were used as controls. Nineteen of the twenty-five patients with type 2 diabetes, peripheral neuropathy, and midfoot Charcot neuroarthropathy, exhibited Zygodactyly as did one of the twenty-nine controls. There was a significant difference between the two groups (Chi squared test $p < 0.001$). None of the cases or controls had any dysmorphic features or other limb malformations.

Zygodactyly occurred in association with midfoot Charcot neuroarthropathy (diabetic neuropathy) in 76% of cases. No association between Zygodactyly, diabetes and Charcot neuropathy has previously been recognised. Genes such as OPG and RANKL affect foot and bone development and MSX1 and PLA2G6 affect spinal and distal nerve development. The possibility of a genetic contribution in patients who develop type 2 diabetes, peripheral neuropathy and Charcot neuroarthropathy must be considered. Zygodactyly may act as a predictive marker for Charcot neuropathy and further identification of regulatory genes may be possible. Until then, recognition of Zygodactyly may allow early intervention and a reduction of complications in patients with Charcot neuropathy.

P05. USING NEXT-GENERATION SEQUENCING STRATEGIES TO GUIDE PRECISION ONCOLOGY IN CASES WITH ATYPICAL CLINICAL PRESENTATION

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Development of an unusual clinical phenotype across both common and rare cancer types presents a significant challenge from a diagnostic and therapeutic perspective. We describe

two distinct cases involving an Ovarian adenocarcinoma and a Medullary Thyroid cancer (MTC) patient and wherein both patients presented with metastases at highly unusual locations, followed by development of an aggressive disease. In first case involving a patient diagnosed with ovarian adenocarcinoma presented with a rare solitary extracranial brain metastases with no other associated metastases after 2 years post-hysterectomy and chemotherapy. Despite surgical removal of the metastatic lesion and stereotactic radiotherapy, the patient showed a further relapse at the initial as well as two additional extracranial regions. Our current analysis of whole-genome sequencing of primary tumour and extracranial lesion, reveal a remarkable difference in the genomic aberration landscape between the primary tumour and the metastases. In addition, we also identify several structural variants including novel gene fusions as well as gross chromosomal abnormalities, which could be potentially utilized as targets for treating this patient further. In the second case, whole-exome sequencing of primary tumour and bone-marrow metastases in the MTC patient identified three germline single nucleotide polymorphisms (SNPs) within the *RET* proto-oncogene that remained undetected using routine hospital genetic testing procedures. More importantly, we report for the first time in thyroid cancer on the occurrence of a "chromothripsis-like pattern", which involved shattering of chromosome 4 leading to complete abrogation of normal chromosomal function, along with dramatic widespread copy number aberrations across both primary tumour and bone marrow samples. These results provide a rationale for the application of comprehensive genomic analysis of cancers presenting with unusual and aggressive phenotypes to facilitate more appropriate therapeutic options and diagnoses.

P06. CO-EXISTING TRANSIENT NEONATAL DIABETES MELLITUS TYPE 1 WITH CONGENITAL CHOLEDOCHAL CYST – COINCIDENCE OR CONNECTED?

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Transient Neonatal Diabetes (TNDM) is characterised by diabetes that develops in the first 6 weeks of life and resolves by 18 months. Approximately 70% of cases are classified as TNDM Type-1 (TNDM1), caused by methylation defects on chromosome 6q24.

It is associated with some congenital anomalies, however associated hepatobiliary abnormalities are not described. Choledochal cysts are congenital dilations of part or all of the bile duct, occurring in 100,000-150,000 live births. The 5 major types are classified according to the extent of hepatobiliary involvement. Surgical excision of the cyst is indicated to prevent complications such as stone formation, malignancy, cyst rupture and pancreatitis.

We describe a case of TNDM1 due to whole chromosome paternal uniparental disomy 6, with co-existence of a type 1a choledochal cyst in a female born following intrauterine growth retardation. Hyperglycaemia soon after birth led to insulin treatment and a diagnosis of TNDM1, with resolution of the diabetes by 4 months of life. Follow up of antenatal findings of a cystic anomaly demonstrated the presence of a type 1a choledochal cyst on ultrasound and magnetic resonance cholangiopancreatography. Sucessful surgical excision of the cyst and a roux-en-Y hepaticojejunostomy was undertaken at 6 months of age.

To our knowledge the co-existence of these disorders has not previously been reported. Further genetic analysis by whole exome sequencing is now in progress to determine if a mutation in the *PKHD1* gene, unmasked by the paternal UPD of the entire chromosome 6, explains the associated choledochal cyst in this case.

P07. PARENTAL MOSAICISM FOR A PATHOGENIC FBN1 GENE MUTATION IN 3 SIBLINGS AFFECTED WITH MARFAN SYNDROME : IMPLICATIONS FOR GENETIC COUNSELLING

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Mosaic mutations can go unnoticed, underlie genetic disease or normal human variation, and may be transmitted as constitutional variants to future generations. Marfan syndrome (MFS) is a clinically variable systemic connective tissue disorder involving ocular, skeletal, and cardiovascular systems. The risk to siblings of an identified *de novo* variant in a proband remains above population risk but less than the 50% risk attributed probands (~75%) who have an affected parent. This is due to somatic and germline mutations reported in rare cases.

We describe the phenotypic variability in three siblings with a confirmed heterozygous pathogenic exon 52 fibrillin1 (FBN1) gene variant with clinically unaffected parents Parental leucocyte DNA was tested and did not identify the FBN1 gene variant. Paternity has been unequivocally confirmed and subsequent testing of parental buccal samples failed to detect the variant.

One brother had aortic valve replacement and aortic aneurysm repair at 35 while another brother had surgery of aortic dilatation at the sinuses of Valsalva at 32. The brothers had variable joint hypermobility, patellar dislocations and ophthalmic presentations involving subluxed lenses, myopia and ambylopia. Early onset of varicose veins as a teenager in one and thoracolumbar scolosis in another brother were present. Their 42 year old sister has apparently normal aortic and cardiac imaging and ophthalmology but has mild Marfanoid facial features.

To our knowledge this is the first reported family in the literature of 3 siblings as a result of parental mosaicism for a FBN1 gene variant and highlights the impact for genetic counselling.

P08. TARGET 5000: A GENETIC CHARACTERISATION STUDY OF INHERITED RETINAL DEGENERATION (IRD) PATIENTS IN IRELAND.

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The inherited retinal degeneration (IRD) patient cohort used in the study has been obtained via a collaborative network of opthamoloogists whereby if an IRD is suspected given consent, a

DNA sample is taken and provided to a central laboratory for genetic analysis. The study seeks to detect previously identified, together with as yet undiscovered, pathological mutations in a panel of known retinal degeneration genes utilizing target capture next generation sequencing (NGS) for 264 IRD genes. The study to date includes over 700 IRD patients from more than 500 pedigrees.

While clinical trials are in progress for patients with IRDs, many such trials require patients to have a known causative mutation to participate in these trials. The Target 5000 research project aims to genetically characterise the estimated 5,000 people in Ireland with IRDs. To date, as part of Target 5000, over 10% of the Irish IRD population has been sequenced providing real insights into the genetic architecture of IRDs in Ireland. Target 5000 offers not only a chance to discover new relevant and pathogenic mutations, but is vital to providing patients with information regarding the underlying genetic pathogenesis of their disease.

Thus far, during the course of the study, genetic analysis of IRD patients has helped to resolve ambiguous phenotypes and to identify causative mutations in approximately 60% of IRD cases. The growing body of data from NGS studies of IRDs globally should facilitate better correlations between genotype and phenotype and refine methods for diagnoses and prognoses.

P09. UTILIZING DETAILED PHENOTYPING FOR INTERPRETING VARIANTS FROM WHOLE EXOME SEQUENCING IN PATIENTS WITH RARE OVERGROWTH SYNDROMES

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Overgrowth syndromes are characterized by tall stature, macrocephaly and other congenital features. These disorders typically arise sporadically through *de novo* dominant mutations in a growing list of genes. Although whole-exome sequencing (WES) allows us to examine all genes at once in a cost effective manner, we are left with a very large number of possible disease-causing variants to sift through. In addition, we must identify at least two patients with mutations in the same novel gene for the finding to be significant. To address this, we utilized detailed phenotyping of patients with undiagnosed overgrowth to group patients with significant phenotypic overlap and to help us interpret and prioritize the variants identified via WES.

We performed WES for 12 undiagnosed patients from our overgrowth cohort. For most patients, there were no obvious causative variants in genes that were previously associated with human overgrowth. Therefore we analysed the participants' clinical records to look for phenotypic traits that may lead us to new candidate genes. After further mining of the WES data, we prioritized possible disease causing variants based on a number of factors including biological function of the gene, predicted effect on protein function and a minor allele frequency <1%. High-priority autosomal heterozygous candidate variants were identified. These variants are being validated via Sanger sequencing and tested in parental samples to assess inheritance.

We have found that detailed phenotyping is a useful tool for narrowing down the number of candidate variants for rare overgrowth syndromes.

P10. WHOLE GENOME SEQUENCING OF NATIVE HIGH ALTITUDE QUECHUA INDIVIDUALS FROM CERRO DE PASCO PERU, IDENTIFIES CLEAR SIGNALS OF POSITIVE SELECTION

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Living the 'high life' presents challenging conditions of extreme cold, hypobaric hypoxia and a restrictive diet that forces populations to adapt to survive.

The Quechua are an indigenous high altitude population of Peru and Bolivia. They have resided at altitudes greater than 2500 meters above sea level (m.a.s.l) for the past 10,000 years, following their arrival in South America. Previous studies have characterised their adaptive physiology and identified genes under natural selection (ref). However our understanding of their genetic adaptation to hypoxia is incomplete, as previous studies focused on common genetic variation and applied a limited number of selection tests.

To shed further light on genetic adaptation in the Quechua, we established a cohort of 43 Quechua individuals from Cerro de Pasco, Peru (4330 m.a.s.l). We performed whole genome sequencing to a mean depth of 34X. We detailed the demographic history of Quechua using principal components analysis, Admixture and Treemix. We performed five tests of selection, (iHS, XP-EHH, ΔiHH, F_{ST} and ΔDAF) on real, and simulated Quechua data incorporating details of the demographic history of the population. We performed a composite of multiple signals (CMS), which aggregates information from the five tests of selection, and identified robust signals of positive selection in high altitude Quechua individuals.

The Quechua appear as a relatively homogenous population, with 10% European ancestry. We report the top 1% of genes under selection identified by CMS. We identify putative hypoxia associated genes under selection as well as the previously reported well-characterised hypoxia gene *EGLN1*.

P11. THE CANCER TESTIS ANTIGEN AND REPLICATION-DEPENDENT HISTONE GENE CLASSES ARE HYPOMETHYLATED IN UHRF1 KNOCKDOWN CELLS, RESULTING IN INCREASED TRANSCRIPTIONAL ACTIVITY.

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DNA methylation is an important epigenetic mechanism of regulating gene expression that is affected in certain human diseases including imprinting disorders and cancer. In mouse, UHRF1 is an essential cofactor of DNMT1, the enzyme responsible for maintaining methylation patterns. To investigate the effects of loss of UHRF1 on methylation patterns in human cells, *UHRF1* levels were decreased in immortalized hTERT fibroblast cell lines using short hairpin RNA. Genome-wide effects on methylation were investigated by the Illumina Infinium HumanMethylation450 BeadChip array. Online bioinformatics software tools were used to identify FDR-significant hypomethylated gene classes, which were then verified by pyrosequencing. Transcriptional effects on these gene classes were investigated by the genome-wide Illumina

HumanHT-12 v4 Expression BeadChip array, and verified by RT-qPCR. While *UHRF1* depletion caused widespread demethylation, the replication-dependent histone gene cluster and the cancer testis antigen genes were identified as most significantly hypomethylated in *UHRF1* knockdown cells. Pyrosequencing confirmed hypomethylation in promoter regions of cancer testis antigen genes *TSPY2*, *MAGEC1*, *MAGEC2* and *MAGEA12*, and histone gene *HIST2H2AA4* in knockdown cell lines. Hypomethylation in these gene classes correlated with an increase in expression in the knockdown cell line. In addition, cells were rescued using *UHRF1* cDNA and showed a return to wild type transcription levels in the rescue cell line. We have shown that these genes are regulated by promoter DNA methylation, confirming the sensitivity of cancer-testis genes to demethylation, supporting possible use of methyltransferase inhibitors to boost antigen presentation in cancers, and the crucial role of UHRF1 in cell cycle regulation.

P12. AAV-MEDIATED GENE THERAPY IN A PATIENT-DERIVED FIBROBLAST MODEL OF RETINITIS PIGMENTOSA 2

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X-linked Retinitis Pigmentosa (XLRP) is a severe, early-onset form of inherited retinal degeneration (IRD). It is estimated that approximately 15% of XLRP cases are due to mutations in *RP2* (*Retinitis Pigmentosa 2*). The ubiquitously expressed RP2 protein is involved in ciliary trafficking of lipid-modified proteins – a process vital for photoreceptor function and survival. Most pathogenic *RP2* mutations are suggested to result in truncation or complete loss of the protein. The most common stop mutation, R120X, appears to trigger nonsense-mediated decay of the transcript. RP2 is therefore an excellent candidate for gene augmentation therapy.

In recent years, personalised cell models have emerged as invaluable tools for the elucidation of disease pathogeneses and have greatly enhanced pre-clinical proof of concept studies. Through the Target 5000 programme, a project focused on genetic characterisation of the 5,000 IRD patients in Ireland, a male patient harbouring the R120X *RP2* mutation was identified. A patient-derived dermal fibroblast cell model of the disease was thus generated and characterised. The transduction efficiencies of AAV vectors of various serotypes in fibroblasts were tested and compared, after which it was decided to proceed with an AAV2/2.CAG.RP2 vector to explore RP2 delivery in this patient-derived cell model. In addition, the effects of RP2 overexpression *in vivo* in murine photoreceptors and retinal pigment epithelium cells were analysed.

P13. DEVELOPMENT OF ASSAYS FOR EVALUATION OF MITOCHONDRIAL FUNCTION AND CANDIDATE THERAPIES

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Mitochondrial dysfunction leads to a lack of energy production and ultimately the death of the cell. Recently a number of disorders have been shown to have mitochondrial dysfunction including but not limited to; Multiple Sclerosis, Parkinson's and Leber's Hereditary Optic Neuropathy (LHON). In LHON, Complex I of the Electron Transport Chain (ETC) is affected which leads to a severe shortage of energy in the cell and eventually cell death. In particular retinal ganglion cells (RGCs) are affected, leading to retinal dysfunction and blindness. These observations have prompted interest in exploring innovative therapeutics to modulate mitochondrial disorders involving complex I deficiency.

The team has explored candidate gene therapies for complex I deficiency, which could classically be delivered via Adeno Associated Viruses (AAV) such as AAV serotype 2 (AAV2), among other vectors. As such the team has developed novel *in vitro* methods for the analysis of complex I deficiency and the evaluation of novel candidate therapies, allowing us to monitor the efficacy of these therapeutics. Assays include a suite of methods to enable evaluation of Complex I activity and oxidative phosphorylation efficiency among other mitochondrial biomarkers. Such assays in principle would be of value for future *in vitro* and or *in vivo* studies involving therapies directed towards targeting complex I deficiencies.

P14. WIDESPREAD RECOVERY OF METHYLATION AT GAMETIC IMPRINTS IN HYPOMETHYLATED MOUSE STEM CELLS FOLLOWING RESCUE WITH DNMT3A2

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Background: Imprinted loci are paradigms of epigenetic regulation and are associated with a number of genetic disorders in human. A key characteristic of imprints is the presence of a gametic differentially methylated region (gDMR). Previous studies have indicated that DNA methylation lost from gDMRs could not be restored by DNMT1, or the de novo enzymes DNMT3A or 3B in stem cells, indicating that imprinted regions must instead undergo passage through the germline for reprogramming. However new putative gDMR have recently been described, along with an improved delineation of the existing gDMR locations. We therefore aimed to re-examine the dependence of methylation at gDMRs on the activities of the methyltransferases in mouse embryonic stem cells (ESCs).

Method: We examined the most complete current set of imprinted gDMRs that could be assessed using quantitative pyrosequencing assays in two types of ESCs: those lacking DNMT1 (1KO) and cells lacking a combination of DNMT3A and DNMT3B (3abKO).

Results: Loss of methylation was approximately equivalent in both cell types. 1KO cells rescued with a cDNA-expressing DNMT1 could not restore methylation at the imprinted gDMRs, confirming previous observations. However, nearly all gDMRs were remethylated in 3abKO cells rescued with a DNMT3A2 expression construct (3abKO + 3a2). Transcriptional activity at the *H19/Igf2* locus also tracked with the methylation pattern, confirming functional reprogramming in the latter.

Conclusions: DNMT3A/B plays a vital role in methylation maintenance at imprints as the rescue with DNMT3A2 can restore imprints in these cells. This provides a useful system to explore factors influencing imprint reprogramming.

P15. GENE-SET ANALYSIS OF GWAS DATA IDENTIFIES A ROLE FOR SATB2 AND THE NURD COMPLEX IN SCHIZOPHRENIA AND EDUCATIONAL ATTAINMENT

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SATB2, *BCL11B* and *GATAD2A* map to regions containing genome-wide significant SNPs for schizophrenia and regulate key stages of neurodevelopment via epigenetic mechanisms. *SATB2* mediates the projection of neurons across the cerebral hemispheres by regulating the activity of *BCL11B* via the NuRD nucleosome remodelling complex, which contains. *GATAD2A*. We hypothesized that genes within the NuRD complex and genes regulated by *SATB2* in the pre- and post-natal brain may contribute to schizophrenia etiology. To test, we developed three gene-sets. 1.)Genes reported in mouse knockout studies of *SATB2* during cortical development (SATB2_Cortical). 2.)Genes mapping to *SATB2* ChIP-seq peaks generated from mouse cortices at E15.5 (SATB2_Pre-natal). 3.)Genes mapping to *SATB2* ChIP-seq peaks generated from mouse P0 hippocampal neurons (SATB2_Post-natal). We performed competitive gene set analysis (GSA) using MAGMA to test if genes within a gene-set were more strongly associated with schizophrenia than other genes in the genome. We applied GSA to schizophrenia GWAS (n=150,064). We also investigated these gene-sets for a genetic contribution to educational attainment (EA; proxy for cognition) using GWAS (n=405,072). After multiple test correction, we observed significant associations for (1)SATB2_Cortical with schizophrenia ($P=8.65x10^{-05}$) and EA (P=0.00049), (2)SATB2_Pre-natal with EA (P=0.0068) and (3)SATB2_Post-natal with schizophrenia (P=0.0069) and EA ($P=2.03x10^{-06}$). Further GSA established that effect sizes are stronger for these gene-sets when analysis is limited to genes that are highly expressed in neurons or at different key timepoints during neurodevelopment of the cortex or hippocampus. These data support a role for the NuRD complex and genes regulated by SATB2 in schizophrenia and EA

P16. COMPARISON OF DNMT1 INHIBITORS BY METHYLOME PROFILING IDENTIFIES UNIQUE EPIGENETIC SIGNATURE OF DACOGEN

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Background: Dacogen (5-aza-2'deoxycitidine) is currently used to treat Acute Myeloid Leukaemia (AML) and is in trials for myeloid dysplastic syndrome and some solid cancers. As a hypomethylating agent it is thought to act by inhibiting the enzymes which add methyl groups to DNA, chief among them DNMT1. Improved targeting has been hindered by a lack of understanding with respect to the exact mechanism of action on DNMT1 and of the gene targets affected by altered methylation following treatment.

Methods: We performed a comparative treatment of the same normosomic, non-transformed fibroblast cell line hTERT1604 over three days with either pharmacological 5-aza-2'deoxycitidine (Dacogen) or with SMARTpool siRNA directly targeting DNMT1. DNA was collected for analysis of methylation levels using Illumina 450k BeadChip methylation arrays. Data was analysed in R using the tailored RnBeads pipeline and in-house scripts.

Results: Both Dacogen and DNMT1 siRNA caused overall hypomethylation in the treated cells, with the latter proving more efficient at demethylation at genes in particular. Amongst the targets experiencing demethylation, some hypomethylated promoters were unique to Dacogen treatment and therefore off-target with respect to the reduction in DNMT1. However an unexpected phenomenon almost exclusively caused by 5-Aza-2'-deoxycytidine treatment was gain in methylation. Therefore we also compared our findings to an independent published 450k dataset of Dacogen treated AML cells (KG1a). Our results suggest Dacogen is also having an important effect on methylation unrelated to the inhibition of DNMT1 thus suggesting further avenues for therapeutic improvements.

P17. COMMON AND RARE RISK VARIANTS MAP TO GENES WITH SIMILAR CHARACTERISTICS IN BOTH SCHIZOPHRENIA AND EDUCATIONAL ATTAINMENT

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Disruptive, damaging ultra-rare variants (dURVs) are more abundant in schizophrenia (SZ) patients than controls and are more concentrated in neuronally-expressed genes with synaptic functions. dURVs in highly constrained genes influence educational attainment (EA; a proxy for cognition) in the general population. We used MAGMA to perform gene set analysis of the largest available GWAS datasets to investigate if association signals for SZ and EA similarly mapped to highly constrained genes and to neuronally-expressed genes with synaptic functions. We investigated if SZ and EA associations were enriched in brain regions at different timepoints from early development through to adulthood. Highly constrained genes (probability of being loss-of-function intolerant; pLI>0.9; n=3,230) are strongly enriched for association with SZ(p=3.14E-08) and EA(p=1.27E-09) in comparison to genes under less constraint (0.1<pLI<0.9; n=4,621; p=0.40 for SZ, p=0.34 for EA) or weak constraint (pLI<0.1; n=10,374; p=0.99 for both SZ and EA). Neuron-specific genes are strongly enriched in SZ(p=3.24E-09) and EA(p=1.33E-08) in comparison to oligodendrocyte- or astrocyte-specific genes. For neuronally-expressed genes, there is strong enrichment in the potentially synaptic gene set (p=4.53E-09 for SZ and p=2.74E-09 for EA) but no enrichment in non-synaptic genes (p=0.24 for SZ, p=0.17 for EA). The strongest enrichment for SZ and EA is in genes that are highly expressed during trimester 2 and this was consistent across all brain regions. Common and rare risk variants are mapping to genes with similar characteristics in SZ and EA but how they combine to influence an individual's risk of SZ or their cognitive function remains to be elucidated.

P18. IDENTIFICATION OF GENETIC MARKERS ASSOCIATED WITH SEVERITY OF TISSUE DAMAGE IN RHEUMATOID ARTHRITIS: AN APPROACH FOR PERSONALIZED MEDICINE

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Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease affecting 45,000 people in Ireland. Prolonged joint inflammation results in tissue damage with consequent reduced functional capacity and quality of life. Damage to the joints of hands and feet, assessed by x-ray, is an important outcome measure that has

genetic input of around 60%. Recent studies have identified single nucleotide polymorphisms (SNPs) in immune-related genes that are associated with severity of tissue damage in RA. One of our studies identified an association with C5orf30, a previously uncharacterized regulator of tissue damage and inflammation (1, 2). However a more comprehensive genome wide analysis is required to more fully characterize the genetic basis of RA severity. This project will identify genetic variants, and their synergistic combinations, that are associated with severity of RA. We will analyse genome-wide SNP data in 1,007 RA patients using state-of-the-art genetic epidemiology and computational techniques, including negative binomial modelling, to identify variants linked with joint damage severity. The study population is uniquely large and detailed clinical and genetic datasets will be used for validation studies using five European early RA cohorts. Simulations for statistical power indicate excellent power will be achieved for moderately frequent alleles, for effect sizes (IRR) over 1.4. The aim is to develop both a genetic prognostic score for RA, and to identify novel mediators of tissue destruction. The earlier identification of RA patients at risk of poorer outcome would facilitate patient stratification and inform therapeutic targeting with more aggressive regimes whilst avoiding such treatment in patients likely to have a better outcome

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P19. A MIR-330 MEDIATED GENOMIC SHIFT IN THE ENDOTHELIUM, TRIGGERING ENDOTHELIAL DYSFUNCTION FOLLOWING *S. AUREUS* INFECTION OF THE BLOODSTREAM

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Bloodstream infection and sepsis are often instigated by the bacterium Staphylococcus aureus. Upon accessing the bloodstream, S. aureus binds to the endothelium triggering vascular leakage, inflammation and oedema. These characteristics are difficult to treat pharmacologically as the nature of signalling guiding this host response remains unclear. microRNAs (miRNAs) regulate ~60% of the human genome through post-transcriptional silencing/degradation of target genes. Previously, bacteria were shown to profoundly affect miRNA expression via up-regulation of dendritic miR-99b elicited by M. tuberculosis infection.

This study investigates contributions of S. aureus induced endothelial miRNA dysregulation to sustained and excessive host responses in sepsis.

Sheared (10dynes/cm2) human endothelial cells were treated with plasma and TNFα to mimic sepsis conditions. Infection induced miRNA alterations were uncovered using Taqman cards to generate miRNA profiles of uninfected and infected cells (RQ = 2-ΔΔCt). Potential mRNA targets were established bioinformatically and confirmed by RNAseq, western blots and qPCR.

Following infection, 58 endothelial miRNA were significantly down- and 35 significantly up-regulated, including miR-330 ($p<0.05$). Bioinformatic analysis of RNAseq data identified 102 potential miR-330 targets that were down-regulated following both infection and miR-330 overexpression ($p<0.005$). Of interest were genes required for endothelial barrier integrity, including ADAM19 and ZO-1. Both S. aureus infection ($p<0.05$) and transfecting a miR-330 mimetic into uninfected cells caused increased permeability ($p<0.005$). Consistently, western blot analysis demonstrated down-regulated of these proteins following infection.

We propose that S. aureus infection leads to rapid dysregulation of endothelial miRNAs, contributing to degradation of the endothelial barrier potentially through down-regulation of junction proteins.

P20. DEPLETION OF DNMT1 IN DIFFERENTIATED HUMAN CELLS HIGHLIGHTS KEY CLASSES OF DEPENDENT GENES

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DNA methylation is a critical mechanism for regulating gene expression and ensuring genomic stability. However, loss of function mutations of methyltransferase enzymes such as DNMT1 in normal differentiated cells result in a lethal phenotype. Consequently, existing investigations have only assessed DNMT1 knockdowns in embryonic stem cells or cancer cell lines. Here, isogenic lines of hypomorphic, normal, immortalised fibroblasts have instead been generated via stable integration with short hairpin RNA. Enrichment analysis of epigenome-wide methylation arrays indicated widespread demethylation within promoter and gene body regions. In addition, four specific gene categories were highlighted as most affected; protocadherins, genes regulating body mass, olfactory receptors and cancer/testis antigens. Comparison of short-term siRNA and long-term shRNA-mediated depletion of DNMT1 indicated that many regions recover methylation as shRNA-containing cell lines adapt to lowered levels of DNMT1. Interestingly, polycomb-regulated genes are refractory to de novo DNA methylation in these cells following recovery, reinforcing the concept of mutually-exclusive domains that are regulated by these two major epigenetic mechanisms.

P21. EPIGENETIC EFFECTS OF RIBOFLAVIN SUPPLEMENTATION ON HYPERTENSION IN ADULTS SCREENED FOR THE *MTHFR* C677T POLYMORPHISM

[1,2]Amenyah S. D., [2]McMahon A., [1]Deane J., [2]Ward M., [2]McNulty H., [2]Strain, J.J., [2]Horigan G., [3]Purvis J., [1]Lees-Murdock D.

[1]Genomic Medicine Research Group, [2]Nutrition Innovation Centre for Food and Health (NICHE), Ulster University, Coleraine, BT52 1SA, [3]Department of Cardiology, Altnagelvin Area Hospital, Western Health and Social Care Trust, Londonderry, Northern Ireland

Background: The *MTHFR* C677T is a common polymorphism of the folate metabolising enzyme methylene tetrahydrofolate reductase (MTHFR) associated with hypertension. Riboflavin is a cofactor to MTHFR in the one-carbon cycle for generating methyl groups important for biological reactions such as DNA methylation. Supplementation with riboflavin has previously been shown to reduce blood pressure specifically in individuals with the homozygous *MTHFR* 677TT genotype. The mechanisms underlying the blood pressure lowering effect of riboflavin are currently unknown however aberrant DNA methylation has been implicated in the development of hypertension. The aims of this study were to

examine global DNA methylation on hypertension in adults stratified by MTHFR genotype and in response to intervention with 1.6mg/day of riboflavin in individuals with the *MTHFR* 677TT genotype.

Methods: Stored peripheral blood leukocyte samples from participants who had consented and participated in targeted RCTs at Ulster University's Nutrition Innovation Centre for food and HEalth (NICHE) and previously screened for the *MTHFR* C677T polymorphism were accessed for this study. Bisulphite conversion and pyrosequencing was used to analyse global and gene-specific DNA methylation.

Results: Preliminary results show that methylation at the repeat element, LINE-1, and imprinted gene, IGF2 was not significantly different between the *MTHFR* C677T genotypes at baseline. However, subsequent supplementation with riboflavin resulted in a decrease in global methylation and an increase in IGF2 methylation in *MTHFR* 677TT participants.

Conclusion: This is the largest study to date examining the interaction between the *MTHFR* C677T genotypes, riboflavin supplementation and DNA methylation. Riboflavin supplementation influenced repeat element and imprinted gene methylation in *MTHFR* 677TT genotype individuals. Further work will provide insights into the mechanism of riboflavin action in lowering blood pressure in these genetically at risk adults.

P22. MIR-199A-5P IS A MARKER OF BLOOD PRESSURE IN PREMATURE CARDIOVASCULAR DISEASE PATIENTS HOMOZYGOUS FOR THE MTHFR C677T POLYMORPHISM.

SM. Lynch[1], M Ward[2], H McNulty[2], G Horigan[2], J.J. Strain[2], J Purvis[3], M Tackett[4], DJ. McKenna[1]

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Background: microRNAs are small, non-coding RNAs which are potentially valuable markers of cardiovascular disease (CVD) risk, including hypertension. This novel investigation aims to profile circulating serum concentrations of microRNAs in premature CVD patients to identify microRNAs that correlate best with hypertension.

Methods: Serum samples from an existing cohort of 75 premature CVD patients were analysed for expression of 68 CVD-related microRNAs. Patients had been screened for the methylenetetrahydrofolate reductase (MTHFR) gene polymorphism C677T, a risk factor for hypertension. Samples had been collected at baseline and following intervention with riboflavin, co-factor for the MTHFR enzyme, as part of a placebo-controlled double-blind, randomized trial. The associations between miRNA expression and blood pressure at baseline and post-intervention were investigated. Comparisons of data between CC and TT MTHFR genotype groups, and in response to intervention, were assessed using ANOVA, Pearson's correlation and corrected t-test statistical analyses.

Results: microRNA expression was successfully detected and quantified in all samples. At baseline miR-199a-5p expression was inversely correlated ($r=-0.51; p<0.001$) with blood pressure in patients with the MTHFR TT genotype only. The decrease in blood pressure in those TT genotype patients who responded to riboflavin intervention was inversely correlated with miR-199a-5p expression ($r=-0.55; p<0.05$). In vitro and in silico analysis of miR-199a-5p function was also performed.

Conclusions: This is the first study to identify miR-199a-5p as a potential serum biomarker of blood pressure in a cohort of at-risk CVD patients. We propose that serum profiling of microRNAs could aid early prediction of CVD and may lead to improved treatment regimes

P23. INVESTIGATING THE LINK BETWEEN MIR-210 AND HYPOXIA IN PROSTATE CANCER

Z Angel, CP. Walsh, DJ. McKenna

Genomic Medicine Research Group, Biomedical Sciences Research Institute, Ulster University, Cromore Road, Coleraine, N. Ireland, BT52 1SA

Background: Hypoxia in prostate tumours has been associated with disease progression and metastasis. MicroRNAs are short non-coding RNA molecules which are important in several cell processes, but their role in hypoxic signalling is still poorly understood. miR-210 has been linked with hypoxic mechanisms, but this relationship has not been extensively studied in a prostate cancer setting. Therefore, in this study, we investigate the link between hypoxia and miR-210 in prostate cancer cells.

Methods: In this study we have used prostate cancer models of hypoxia to investigate the functionality of miR-210. Expression levels of miR-210 have been measured by qPCR in in vitro and in vivo samples. Functional bioassays were used to examine its effect on prostate cancer cell behaviour. Target genes have been identified and bioinformatic analysis has been employed to investigate a clinical significance for miR-210 in prostate cancer.

Results: miR-210 is induced by hypoxia in prostate cancer cells. Over-expression of miR-210 impacts upon target genes which in turn may affect cell proliferation. Data-mining of online repositories of clinical prostate sample data shows that miR-210 is significantly correlated with Gleason grade and other clinical markers of prostate cancer progression. Further in silico analysis of miR-210 cellular networks reveal that miR-210 plays a key role in a number of important cell processes, the dysregulation of which can promote the development of prostate cancer.

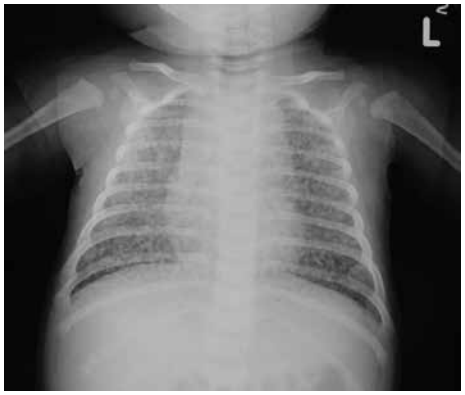
Conclusions: We propose that miR-210 is an important regulator of cell response to hypoxic stress and may play an important role in the pathogenesis of prostate cancer. Further study will focus on determining its function in prostate cancer and its potential as a biomarker in this disease.

Ulster Med J 2018;**87(1):**65-66

Curiositas (Global Health)

In this edition of Curiositas we have a global health perspective on a range of interesting topics.

POSTGRADUATE QUIZ



1. What is the most obvious abnormality on the chest x-ray of this child who has recently moved to the United Kingdom from Sub-Saharan Africa?
2. What is the most likely underlying diagnosis and how would you manage them?

Dr Benjamin McNaughten (Paediatric trainee), Dr Paul Moriarty (Consultant in Paediatric Infectious Diseases, Royal Belfast Hospital for Sick Children), Dr Andrew Thompson (Consultant Paediatrician, Royal Belfast Hospital for Sick Children), Dr Thomas Bourke (Consultant Paediatrician, Royal Belfast Hospital for Sick Children).

HISTORICAL QUIZ

1. Who is this well-known lady and where does she currently reside?

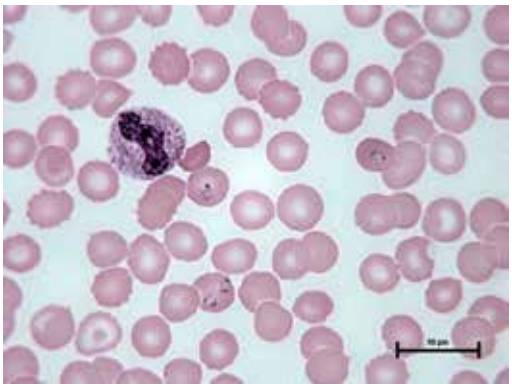
2. At what age did she die and what was most likely at the time to have been on her death certificate?

Dr Benjamin McNaughten (Paediatric trainee), Dr Thomas Bourke (Consultant Paediatrician, Royal Belfast Hospital for Sick Children, Dr Andrew Thompson (Consultant Paediatrician, Royal Belfast Hospital for Sick Children). ***Acknowledgements:*** *Picture supplied by Professor William Thompson (Retired).* ***Permission*** *of use granted by Mr Patrick McLain from National Museums NI (NMNI)*

UNDERGRADUATE QUIZ

A 27 year old male presents to hospital with a headache, fever and vomiting. He has recently returned from a holiday in Uganda. As part of his investigative workup, a blood film is performed.

1. What abnormalities can be seen on the blood film?



2. What is the most likely diagnosis?
3. How should this patient be managed?

Rachel Keown (4th year medical student, Queen's University Belfast), Anthony Thompson (Biomedical Scientist, Royal Belfast Hospital for Sick Children), Dr Paul Moriarty (Consultant in Paediatric Infectious Diseases, Royal Belfast Hospital for Sick Children), Dr Andrew Thompson (Consultant Paediatrician, Royal Belfast Hospital for Sick Children). ***Acknowledgements:*** *Blood films supplied by Anthony Thompson (Biomedical scientist, Royal Belfast Hospital for Sick Children)*

AND FINALLY….

1. What are these and why might you recommend feeding them to children in low-resource settings?

Dr Lynne Speirs (Paediatric Infectious Disease Fellow, GOSH, London), Dr Claire Waterson (Paediatric Infectious Disease Trainee, Royal Belfast Hospital for Sick Children). **Acknowledgements:** Pictures supplied by Dr Lynne Speirs *(Paediatric Infectious Disease Fellow, GOSH, London)*

ANSWERS See overleaf

CONSIDER CONTRIBUTING TO CURIOSITAS?
Please refer to '*Curiositas: Guidelines for contributors*' http://www.ums.ac.uk/curiositas.html and email *umj@qub.ac.uk* with your ideas and submissions.

Curiositas: Answers

POSTGRADUATE QUIZ

1. The most obvious abnormality on this chest x-ray is the presence of miliary nodules.
2. Miliary nodules are characteristic of miliary tuberculosis (TB). Miliary TB is an uncommon pulmonary manifestation of TB. It represents widespread haematogenous dissemination of Mycobacterium tuberculosis. Approximately 1.5% of patients with TB are estimated to have miliary TB. The disseminated nodules consist of central caseating necrosis and peripheral epithelioid and fibrous tissue. Radiologically they are not calcified. This contrasts to the initial Ghon focus which is often visible on chest radiographs as a small calcified nodule. In the absence of central nervous system (CNS) involvement the patient should receive isoniazid (with pyridoxine), rifampicin, pyrazinamide and ethambutol for 2 months followed by isoniazid (with pyridoxine) and rifampicin for a further 4 months.[1] Attempts should be made to culture the pathogen. Children with pulmonary TB have a low bacillary load and do not expectorate well, making diagnosis from sputum samples difficult. Early morning gastric aspirates and bronchial washings are alternatives. In miliary TB, mycobacterial blood cultures may yield a pathogen. If the patient had neurological symptoms or signs they should be tested to exclude CNS involvement. If there is evidence of CNS involvement the course of isoniazid (with pyridoxine) and rifampicin should be extended to 10 months.[1] Treatment should be modified according to drug susceptibility testing.

National Institute for Health and Care Excellence (2016). Tuberculosis. NICE guideline [NG33]

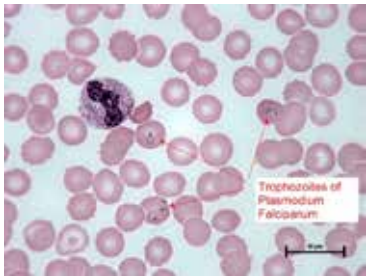
HISTORICAL QUIZ

This is Takabuti better known to most children growing up in Northern Ireland as the "mummy" in the Ulster Museum. She was first seen in the museum in 1835. From the inscriptions and hieroglyphs on the case it is known that she was a married lady of about thirty years of age who lived in the city of Thebes almost 2500 years ago.

Life expectancy in ancient Egypt was between 20 and 30 years but fluctuated at times of prosperity or famine. Females were more likely to die young due to complications of child birth. Cause of death was variable with infectious diseases and in particular tuberculosis claiming most lives. Water-borne infections such as typhoid and cholera were also endemic. If you managed to avoid war, starvation and infectious diseases there were always the snakes or Nile crocodiles to contend with!

UNDERGRADUATE QUIZ

1. Trophozoites of Plasmodium falciparum are noted within some of the erythrocytes.
2. The presence of trophozoites of Plasmodium falciparum in the blood film in combination with his non-specific clinical presentation and recent travel to a high-risk country makes malaria the most likely diagnosis. Malaria is the most commonly imported tropical disease in the UK with around 1300-1800 cases reported annually.[1] It is caused by the parasite Plasmodium with approximately three quarters of cases secondary to Plasmodium falciparum.



3. The patient should be admitted. Parasite count should be checked to assess the potential future severity of the disease. Malaria caused by Plasmodium falciparum can be divided into two main categories; uncomplicated malaria and severe/complicated malaria. The features of severe or complicated malaria include:

- Impaired consciousness or seizures.
- Renal impairment (oliguria <0.4 ml/kg bodyweight per hour or creatinine >265 μmol/L).
- Acidosis (pH < 7.3).
- Hypoglycemia (<2.2 mmol/l).
- Pulmonary oedema or acute respiratory distress syndrome (ARDS).
- Haemoglobin <80 g/L.
- Spontaneous bleeding/disseminated intravascular coagulation.
- Shock (algid malaria i.e. BP < 90/60 mmHg).
- Haemoglobinuria (without glucose-6-phosphate dehydrogenase deficiency).
- Parasitaemia >10%.

There are three main treatment options for uncomplicated falciparum malaria: Artemisinin combination therapy (ACT), oral atovaquone-proguanil or quinine plus doxycycline.[1] ACT has been proven to be the most effective for removing the malaria parasites and is often considered the drug of choice.[2] Parenteral artesunate has shown to be a superior treatment over intravenous quinine in patients with complicated/severe malaria[3]. The patient should be given advice regarding secondary prevention of malaria for future travels and public health should be informed.

1. Lalloo DG et al. UK malaria treatment guidelines 2016. *Journal of Infection* (2016) **72**, 635-649
2. Sinclair D, Ani B, Donegan S, Olliaro P, Garner P. Artemisinin- based combination therapy for treating uncomplicated malaria. *Cochrane Database Syst* Rev 2009; **(3)**. CD007483
3. Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. *Cochrane Database Syst* Rev 2012; **6**. CD005967

AND FINALLY…

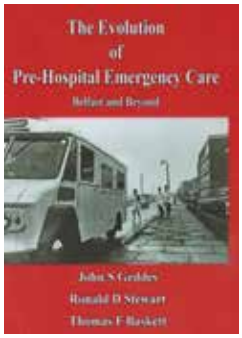
Entomophagy (the practice of eating insects) is increasing worldwide. Edible grasshoppers (*Ruspolia nitidula*) are a delicacy in Uganda and many other East African countries and, in season, are widely available[1]. Recently it has been demonstrated that as well as being a tasty snack, grasshoppers are important source of protein. In Uganda, *R. nitidula* is processed by either sautéing, deep frying, or boiling followed by drying. Studies of composition have revealed 36-40% protein, 41-43% fat and 10-13% dietary fibre. The moisture content is lower than other major protein sources such as fish and meat, making them a more concentrated source of nutrients.

5.9 million children under the age of five years died in 2015 and malnutrition is thought to be an underlying cause in up to half of these deaths[2]. Sharing knowledge of locally available protein rich food with caregivers is important to allow children to receive a balanced and healthy diet.

1. Ssepuuya, G., Mukisa, I., Nakimbugwe, D. Nutritional composition, quality and shelf stability of processed *Ruspolia nitidula* (edible grasshoppers). *Food Science and Nutrition*. 2017; **5(1)**: 103-112.
2. World Health Organisation. World Health Statistics 2016. Monitoring Health for the SDGs. WHO 2016. [Accessed online 23rd April 2016] Available from: http://www.who.int/gho/publications/world_health_statistics/2016/en/

Book Reviews

THE EVOLUTION OF PRE-HOSPITAL EMERGENCY CARE: BELFAST AND BEYOND



JS Geddes, RD Stewart and TF Baskett. Clinical Press 2017, ISBN 978–1–85457–093 –2. RRP £20.

The first thing to appreciate about this 191 page volume is that it is not a textbook. It was written to celebrate 2 events – the 50th anniversary of the publication in the Lancet of the famous Pantridge and Geddes paper entitled; "*A mobile intensive-care unit in the management of acute myocardial infarction*" and also the 20th anniversary of the development of a coherent system of emergency medical services in the rugged, rural Canadian province of Nova Scotia.

The 3 authors spent their formative years working in these 2 locations and the book is part history, part recollection of the people, times and places involved.

The story begins in 1950s North America, where the specialty of emergency medicine has not been invented yet and no self-respecting hospital doctor would willingly venture into the bear pit that was the "emergency room". The situation outside hospital was even worse, with no organised ambulance service – just volunteers – often the local undertaker whose long hearse could at least fit a stretcher inside (conflict of interest perhaps?).

Developments in cardiopulmonary resuscitation and large cabinet-sized defibrillators led to the introduction of coronary care units by the early 1960s but the technology contained within was not available to the "man on the street" suffering a heart attack.

The Vietnam War led to better trauma/surgical resuscitation training for doctors and the US Army began training ordinary GIs to act as medical "corpsmen" who could give intravenous fluids, relieve pain and stop bleeding right on the front line – no one is sure exactly how and when, but the corpsmen started to be known as paramedics.

The returning doctors and paramedics could see that the American pre-hospital and emergency department system was deeply flawed but administrators and legislators wouldn't change things without a proven intervention that could save lives.

The story then moves to Belfast and the recollections of Dr John Geddes, at that time SHO and then registrar working with Professor Frank Pantridge. The development of the portable defibrillator and cardiac ambulance are detailed – some facts were new to me – for example, Pantridge wrote to NASA asking for release of advanced miniaturised capacitors necessary for the electrical circuits in the portable defibrillator. NASA agreed and thus, Belfast stole a march on several American universities working on the same project!

Papers on the introduction of the cardiac ambulance system, successful pre-hospital defibrillation and autonomic disturbance early in myocardial infarction were produced but received a lukewarm reception in the UK.

In the USA however, this potentially life-saving innovation was exactly what was needed to persuade the authorities to upgrade and enhance the ambulance system and introduce trained paramedics to intervene on the scene rather than just drive the patient to the hospital.

The book then goes on to chart the pioneers who developed both prehospital coronary/trauma care in North America and modernised emergency departments in certain major cities before finally focusing in on rural Nova Scotia which covers a vast swathe of territory.

The final chapter is a short biography of Frank Pantridge.

I enjoyed the story of the early pioneers of CPR – I was familiar with some of the names but not their important work. The Belfast chapters were before my time in RVH Cardiology but I found myself laughing at medical and nursing staff being timed as they sprinted down from the ward to the ambulance pickup point – anyone too slow was expected to get fitter! It was also interesting to note that the original service was limited to GP phone calls only and the idea of the public phoning for this premium service was initially dismissed.

I was very much aware that the Belfast model did not really catch on in the UK but I truly didn't understand why it was embraced so much in North America until I read this book – the American system just needed one worthwhile intervention to modernise the entire system and make use of the returning veterans both medical and paramedical.

A worthwhile read for those with an interest in the history of Belfast Cardiology, CPR and pre-hospital care in the widest sense.

Dr John Purvis (Consultant Cardiologist, Advanced Life Support instructor and former BASICS Dr).

Book Case

Professor Jim Dornan recommends 6 books for the weary off-duty Medic to enjoy.

INTRO

While travelling life's journey, it is surely important to shape one's view of its every element as we encounter daily challenges. We are all open to potential impression by what we hear, observe and read. Of the hundreds of books I've read, I thought I'd choose six to share that either emboldened and empowered me, informed me or, better still, totally changed the way I thought.

I find fiction mostly not stimulating as I'm always convinced my own imagination would be better than that of anyone else! I do though relish scripts that describe human battles with the elements, whether it's climbing Everest, crossing the Atlantic, conquering Space or indeed I also enjoy avidly devouring books that are full of political intrigue.

But for my six I've chosen ones that changed or impacted on my views at the time, and enduringly.

A SPANIARD IN THE WORKS

John Lennon (Penguin 1981, ISBN-13: 978-0140049268. Paperback. Out of print)

As a teenager growing up in Bangor there was a make your mind up time. Were you a mod or a rocker? Some years later a lifelong friend commented, early in our relationship, that I was very impressionable. So, in reality, I became a bit of both. Deep down though I was a rocker, though I was more the Beatles than the Stones, importantly I was more Elvis than Cliff.

Rules, rules, rules dominated our lives at school, socially, certainly at home and most definitely on a Sunday. What people might think seemed more important to those around me than what was probably or necessarily correct. Rules meant power to those who set them. 'Hypocrisy rules OK' would have been a mantra for many.

Of course, we couldn't understand why we got caned for very little, why we had to wear our school cap at all times. Why our hair could never touch our collar. Why our trousers had to be more that 14 inches at the hem. Why our team couldn't play sport on a Sunday. Why our parents could not have a glass of wine with the neighbours. Why we would go to hell for ....well whatever sin was defined as at the time. Then fifty years later we find that these rules were now considered irrelevant without any actual rewriting of the Bible required. Fantastic and intriguing. Yet these rules were relevant and enforceable at the time, if not actually set in stone.

So, when we found a role model who supported us in trying to hold back and even actually turn the tide, we were going to embrace him. That was John Lennon. I so much admired him, his music of course, but his rebellious streak more than anything. He was empowered before I knew what the word meant.

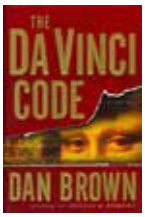
Lo and behold, after a constant school diet of Wordsworth, Shelley, Coleridge and their ilk, along came an anthology of poems by MY very own John Lennon. A Spaniard in the Works.

Maybe not a literary masterpiece, but he was my literary master.

John Lennon told it like it was. He took no prisoners. He wasn't impressionable, weak or hypocritical. A good man. A man who saw what was wrong in the world and tried to change it. When you've read this piece, google the words of "Imagine", or "All you need is Love". Both were and are away beyond their time. If they don't make you think, you're in the wrong profession or place.

Yes, reading this book made me dig the heels in a bit more. Fight for rights. Thanks John.

THE DA VINCI CODE



Dan Brown (Corgi, 2003, ISBN-13: 978-0552159715. RRP £7.99 paperback)

While waiting for my suitcase in Nairobi airport in early 2005, a paperback version of this book arrived alone on the carousel. All watching were bemused. I picked it up, and saw it as a sign, as I'd forgotten to pick a book at WH Smiths at Aldergrove.

I read it, and it's not so much the story itself that I learnt from, but Dan Brown's wonderful and inciteful evidence which revealed the view of women's place over the ages taken by all, and I mean all, of the main religions. The facts unearthed stimulated my research further and laid the basis for my Annual Oration delivered at Queens in 2011 which was entitled The Fall and Rise of (some) Women.

Brown highlighted how women were revered during the pagan era. Mother Earth was worshipped, as she was simply provided with a seed and produced the miracle of life. Religious men from the east weren't too impressed with this and as the various churches emerged and established, without exception patriarchy ruled. Men's rules prevailed, women were put in their place by the established church. Organised religion was all about male priests collecting taxes from hard working congregations with a view to securing a place in the afterlife. Even when Islam came along and took their opportunity to provide an alternative, they too focused on male dominance. They missed a huge trick.

Meanwhile in the dark ages, tens of thousands of midwives, herb growers and so-called witches were burnt at the stake by the Christian church in the name of God. Truly this was all news to me at the time of reading and my further research triggered by Brown has convinced me that to a great extent, the position of women in society today has been molded, coloured and shaped by the churches. It is little wonder, though sad that they appear to be so reluctant to relinquish their powers. But it's inevitable.

Symbolism, ceremony, secret societies and rituals act are the backdrop to Browns wonderfully crafted works, but buried within is his role as a truly contemporary feminist shining through. A life changing read… if you ignore the story.

FOUR-IRON IN THE SOUL.

Lawrence Donegan (Penguin, 1998, ISBN-13: 978-0140260144. RRP £9.99 paperback)

I have futtered at golf for many decades. Always loved the opportunity to get out into the fresh air and have a bit of craic during and after the round, but as to the occasion providing an opportunity for me to reveal my skills, prowess and competitive nature? Sadly no! Not yet! For you just can't go out without hope and I just know I'm going to get my handicap down to 16 someday!

Obstetrics when I was a boy required a lot of our time. Though when I look for sympathy from my wife, a fellow carer of women, by saying, "In my day...." she invariably stops me in my tracks and says "Jim, it's not your day". Sad, but true.

Anyway, I just don't know how some of my colleagues became so good at the blooming game, 'cause I have truly struggled.

In 2012, I retired from the NHS and vowed to crack this game once and for all. Professor Lamki, my lifetime friend and mentor stopped me in the corridor and said "Jim, I hear you're taking up golf," I concurred. He continued "I can hardly think of a game worse suited to your personality!"

So there you go. What hope did I, or do I, have?

Laurence Donegan in "A four iron in the soul" provided me with huge insight into what is required to be a successful golfer.

Donegan was a journalist and handy golfer who took a year off and acted as a caddy to a young pro golfer, Ross Drummond, on the circuit. This gave him the opportunity to determine the key qualities necessary to make the cuts and bring home the bacon. A fascinating insight into the personalities involved reveals that the best golfers are those with absolutely nothing in their heads, especially at the top of their back swing. I realised then what Harith Lamki was referring to!

Donegan noted that the best golfers were focused almost to the point of despair. Not for them the pint immediately on trudging off the eighteenth. Rather, straight round to the range for two or three hours getting the muscle memory established and the rhythm engraved in their soul.

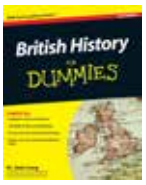
When they do reach the locker room and bar, the good ones truly don't know the difference between politics in North Korea and North Down, and tellingly, don't care.

My lack of ideal attributes hasn't stopped me trying though, and "A four iron in my soul" provided me with all the excuses I need.

In my retirement I have been a frequent playing partner with Brian Dean, the Doc's Doc from the Ormeau Road. He's tried and tried to talk and walk me round some fabulous courses. He almost has a face-saving expression for every one of my shots, and there are many, which I produce. In utter desperation recently, he caught my eye at the end of another gross swing and said, after a suitable interval and light blush, "I've run out of words!"

Need another golf book, with instructions this time.

BRITISH HISTORY FOR DUMMIES



Seán Lang (John Wiley and Sons, 3rd revised ed, 2011, ISBN-13: 978-0470978191.RRP £17.99 paperback).

My father was so keen to have a son who would study medicine I became aware of constant pressure to read anything scientific between the ages of 12 and 18. History, now one of my favourite subjects, was relegated to the bottom of the list, and while I did enough to get through, it was never presented to me in a fascinating manner to grab my interest. That all changed later in life when I bought myself British History for Dummies. Wonderful. Like Classic FM for those who didn't know classical music could grab their soul given the chance.

Dr Seán Lang was not a Grade A history student himself, but did go on to become a University History don. It's never too late to learn. He relates the major changes that have coloured our place in these Celtic islands in a fair and illuminating manner and provides logic, where possible, to explain the big moves that shaped our culture. Sadly, much (as was evident in Da Vinci Code) can be explained by too much misused testosterone running in the veins of our Lords and Masters.

I particularly liked how he explained how the Britannic knights tired of clamping up their maidens in chastity belts to keep the serfs at bay while they went off to the religious wars to fight for "Christianity" (something wrong there. Yes?) when over fifty percent of Britain's nobility got wiped out. Those who survived yet another cull met around the table one more time and decided...'I tell you what, let's invent armies, made up of our serfs, and we'll direct operations from behind the lines, with our maidens by our sides' Voila! The course of wars changed forever.

Those who knew my management style will realise that those delegation skills I gleaned from these books were key to my success as Clinical Director in RMH.

GEORGE BEST, A LIFE IN THE NEWS.

Richard Williams (Aurum Press, 2006, ISBN-13: 978-1845132019. Hardback. Out of Print).

There were times in my life when I thought of George Best on a daily, almost hourly, basis. As a teenager I was enthralled by him. In my early twenties, I lived his every twist, turn, shimmy, sprint, lob, shot and cross. When he beat two or three men in one move, so did I. I so admired his skills, I so cherished the fact that he played for my teams of Manchester United and Northern Ireland. He could do no wrong in my eyes. He was never admonished for faking. He rarely, if ever, retaliated. He scored for fun. He dribbled for show. As a young lad from Castlereagh, he literally slept every night with a football in his arms. I tried it in Bangor, with little effect.

We did have access to Match of the Day, but the rest of the time we mostly had to get by with direct observation of his appearances for NI. (And yes, he did score a great goal when he took the ball from Gordon Banks at Windsor and slotted it into the net - I was there.) However most of the time we had to make do with match reports and commentary from football journalists. And truly they were often better that the real thing. Reality TV is just that, but literature is reality PLUS the writer's added colour and texture.

This book, George Best, a Life in the News, truly brings to life all his great times. The reader is transported as if by magic to Old Trafford, Maine Road, Anfield, Wembley, and yes, even Windsor, and George's finely-honed skills are imprinted into my psyche as though I was there myself, indeed perhaps even more so.

As I young boy I think I got more pleasure out of my crystal radio than from any other present. To lie in my own cold bedroom on a wet night in the 60s and listen to match reports, plays, book readings and political discussion on the Home Service, all by myself, accompanied only by the limits of my imagination was heaven. And George was centre stage.

One wee quote which I've only ever read in this book. George once said " If I hadn't been born so good looking, you'd never have heard of Pele." Think about it. Interesting insight indeed.

INSIDE JIHAD

Tawfik Hamid (Mountain Lake Press, 2015, ISBN-13: 978-0990808916. RRP £16.50 paperback)

At the end of the last millennium, the native American Indians were asked for their verdict on the previous 2000 male dominated years. They said…" It's been a time of moral corruption, widespread abuse of the environment, testosterone driven wars, and huge misogyny." Their verdict was... "Koyaanisqatsi" - "Life is out of Balance."

As I write these summaries I am aware that the world is in turmoil and indeed appears indeed to be out of balance. Maybe it always was, or perhaps it's the growth of information technology and social media, that makes us all see what's always been there.

Religions have brought huge solace, hope, guidance, succour and purpose to those who have followed them. However, many men, and I'm sorry, but I do mean men, have misinterpreted and pivoted the core messages on many occasions to increase their own power and their following numbers.

All are guilty, without exception.

Islam is particularly under the spotlight in recent decades and Dr Hamid has written a wonderful book which explains why we are where we are, and indeed advises what we should do about the current impasse.

In summary he informs us that the particular brand of Islam that is unattractive to many is "Salafism". It started in Saudi in the 17th century, and lay fairly dormant for three hundred years until the Americans found oil in that country. The Saudis imported huge numbers of oil workers from the Muslim world, poor men with impoverished families at home who they were then able to comfortably support with the generous salaries they received. That got these workers to consider that Allah indeed must truly have chosen to supply the Saudis with a bountiful supply of oil because they were followers of Salafism, and so they all followed suit, hoping for the comparative rewards.

The problem starts because of one particular plank of Salafism, and this is the belief by its followers that the devil which must be fought, is not within, as it is say in Christianity and other forms of Islam, but is WITHOUT. The devil is you and I. We are the devil, the infidel. It's truly as simple as that.

Dr Tawfik Hamid was recruited in his first year of Medical school to be radicalised, to be informed, brain washed, whatever, to learn the 3 key steps involved in the process of moving from being an innocent, to becoming a violent jihadist. He clearly suggests three stages. Firstly, learn hatred of the infidel. Secondly, suppress conscience. Thirdly, desensitise the jihadist to violence. He says, "….radical Islam must remove from its followers any aversion to killing."

Dr Tawfik Hamid soon saw the error of his ways, and is now spending his time trying to correct a great wrong.

But as I write, there is hope. The Saudi crown Prince, Mohammed bin Salman, has just announced that the fundamental core elements of Salafism are to be readdressed. Let's hope, and indeed pray, that he has women on the committee.

Meanwhile, 'Inside Jihad' is an important read for all who care, believe and have hope.

Game Changers

ORAL DRUG THERAPY – IMPROVING SURVIVAL IN MALIGNANT MELANOMA

Dr CH O'Neill, Dr J Carser

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The incidence of melanoma continues to increase. In early-stage disease, 5-year survival rates with surgical resection exceed 90%, however, stage III and IV disease has a higher risk of recurrence after resection, and many will ultimately die from metastatic melanoma. Since 2012 there has been a rapid increase in NICE approved therapy for patients with metastatic melanoma, with long-term survival now a reality for selected patient groups.

Novel oral agents targeting the MAP kinase pathway, specifically oncogenic mutations in BRAF (present in approximately 40% of melanomas), have enhanced outcomes.[1,2] Treatment with the BRAF inhibitor, dabrafenib, plus the mitogen-activated protein kinase kinase (MEK) inhibitor, trametinib, result in clinical benefit in over 90% of patients treated (median survival now approaching 3 years). This combination is routine practice in Northern Ireland, allowing treatment of severely unwell and symptomatic patients who previously may not have been suitable for chemotherapy, with often rapid resolution of symptoms within days to weeks.

Furthermore, this therapy has shown response rates in excess of 50% in patients with symptomatic brain metastases, improving symptoms and quality of life, providing options where once there were few and has largely superseded whole brain radiotherapy in this setting.[3]

More recently, the adjuvant COMBI-AD trial[4] reported that patients with completely resected BRAF mutation melanoma treated with dabrafenib/trametinib for one year had improvement in the rate of relapse-free survival at 3 years of 58% vs. 39% with placebo, as well as improvement in survival at 3 years of 86% vs 77% . BRAF/MEK inhibitors in the adjuvant setting are expected to enter routine clinical practice following regulatory approvals.

1. Long G, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J et al. Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma. *New England Journal of Medicine*. 2014;**371(20)**:1877-1888.
2. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D et al. Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib. *New England Journal of Medicine*. 2015;**372(1)**:30-39.
3. Davies M, Saiag P, Robert C, Grob J, Flaherty K, Arance A et al. Dabrafenib plus trametinib in patients with BRAF V600 -mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *The Lancet Oncology*. 2017;**18(7)**:863-873.
4. Long G, Hauschild A, Santinami M, Atkinson V, Mandalà M, Chiarion-Sileni V et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *New England Journal of Medicine*. 2017;**377(19)**:1813-1823.

RADIOFREQUENCY ABLATION AND ENDOSCOPIC MUCOSAL IN TREATMENT OF EARLY NEOPLASTIC BARRETT'S OESOPHAGUS

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Barrett's Oesophagus (BO) is a precancerous condition, associated with chronic gastro-oesophageal reflux, resulting in a change of normal squamous epithelium of the lower oesophagus to columnar epithelium. In non-dysplastic BO, the cancer conversion rate is 0.9%/year with increasing cancer risk of 9.1%/year with low-grade dysplasia (LGD) and 25.6% risk with high-grade dysplasia (HGD) over a 3 year period.[1]

Within Northern Ireland, endoscopic therapy for early neoplastic changes has offered patients a less invasive treatment option with curative intent in comparison to the conventional surgical intervention. These include radiofrequency ablation (RFA) of dysplastic BO and endoscopic mucosal resection (EMR) for nodular BO as per NICE recommendations.[2]

All cases are carefully selected and discussed through the regional upper GI cancer multidisciplinary meeting prior to onward referral to an advanced endoscopist competent in performing these procedures.

To date, a total of 282 EMR's have been successfully performed on visible oesophageal lesions and a total of 238 RFA on dysplastic BO with curative intent.

These procedures are generally well tolerated with minimal recovery time and same day discharge. They are performed under conscious sedation and have much lower morbidity and mortality in comparison to an oesophagectomy.

The future reduction in oesophageal cancer risk due to the fact BO can be eradicated highlights the importance of this therapeutic endoscopic intervention for the future.

1. Fitzgerald, R.C., et al., British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut, 2013.
2. NICE, Endoscopic radiofrequency ablation for Barrett's oesophagus with lowgrade dysplasia or no dysplasia. http://www.nice.org.uk/guidance/IPG496/chapter/1-Recommendations, 2014.

DUAL ENERGY SINGLE SOURCE CT CORONARY PERFUSION ANGIOGRAPHY – A HELPFUL FUNCTIONAL ADJUNCT TO ANATOMICAL INFORMATION

Dr A Canning, Dr S Hughes, Dr JA Purvis

Depts of Radiology and Cardiology, Omagh Hospital and Primary Care Complex, Western HSC Trust.

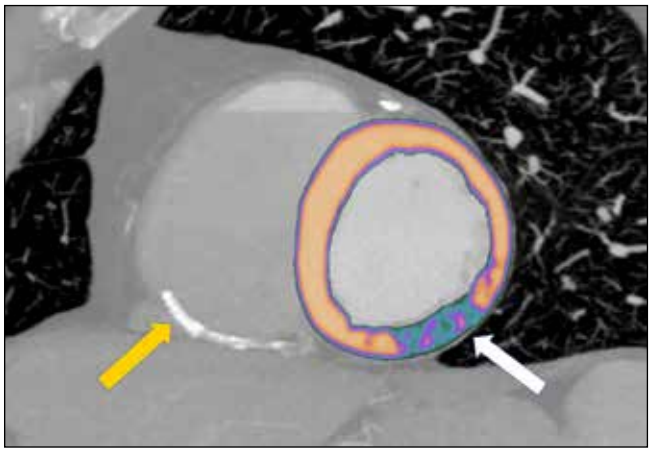

Fig 1. Short axis view of left ventricular myocardium showing decreased perfusion (blue/purple colour, white arrow) in the zone of previous myocardial infarction.

CT coronary angiography (CTCA) is recommended by NICE for noninvasively assessing coronary anatomy in patients suffering stable chest pain.[1]

CTCA is however, an anatomical test and yields no information about blood flow in ischaemic myocardium.

Our new General Electric Revolution HD CT scanner allows "mapping" of iodine-based contrast into myocardial tissue. Images are acquired at 2 energy levels during a single scan by passing a filter in and out of the x-ray beam. This produces a map showing the concentration of iodine in myocardium consistent with blood flow. The scan is then repeated using a stressor agent (such as adenosine) to induce ischaemia.

Comparison of rest and stress images outlines ischaemia or old scars from myocardial infarction. The map is then superimposed on the coronary artery images to produce composite functional and anatomical information. Total radiation dose is similar to coronary angiography or myocardial perfusion scintigraphy.

In the accompanying rest image (Figure 1), a patient with previous right coronary artery stenosis treated with stent complained of further chest pain. CTCA showed a patent stent (yellow arrow) and the superimposed perfusion map showed a defect (white arrow) which did not enlarge with stress – consistent with old myocardial infarction scar only with no ischaemia.

1. NICE guidance on investigating people presenting with stable chest pain. https://www.nice.org.uk/guidance/cg95/chapter/Recommendations#people-presenting-with-stable-chest-pain Last accessed 1st December 2017.

So you want to be a **Summer Student?**

Hannah Gardiner

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INTRODUCTION

Around the world, studentships facilitate undergraduate medical students to experience research in a variety of disciplines. Many laboratories are willing to host medical students and there are funding bodies in the UK which provide financial support for student projects. At Queen's University Belfast, funded places for medical students are available on 8-week summer studentship programmes in the Centre for Cancer Research and Cell Biology (CCRCB), Centre for Experimental Medicine (CEM), Centre for Medical Education (CME), and the Centre for Public Health (CPH). Details of these funded projects are released annually in December, although students can also approach a specific Principal Investigator and apply for funding individually. Applications are open to medical students from any part of the UK as well as to international students, and some placements are also suitable for students from scientific degree courses.

MY EXPERIENCE

I completed my studentship in the Summer of 2016, in Dr Derek Brazil's laboratory in the Centre for Experimental Medicine (CEM). Summer students learn research methodology, undertake a specific research project under supervision and are often able to avail of other opportunities - for example, attending scientific or career orientated seminars, and establishing contacts for possible future projects.

In Dr Brazil's laboratory, I learnt how to perform basic laboratory techniques and conduct experiments independently. The focus of my project was to investigate repurposing FDA-approved drugs for use in cancer treatment, using a bioinformatics tool called QUADrATiC. The cells I was working with were from a thyroid cancer cell line containing high levels of a protein called Gremlin 1, which is implicated in several diseases. The cells were treated with 3 different drugs predicted by QUADrATiC to reduce levels of Gremlin 1, after which the level of Gremlin mRNA in the cells was measured.

At the end of the studentship, all the students hosted by CEM presented their work to at the CEM Summer Student Symposium.

In CEM, in addition to undertaking a research project, summer students also have the opportunity to meet other students and researchers and learn more widely about research through attendance at the REMERGE (QUB Regenerative Medicine Research Groups) symposium, research seminars and careers and ethics workshops.

CHALLENGES

It may be hard to contemplate giving up a precious summer to do something which is not essential for your current course, especially when it requires the development of a new skillset in an unfamiliar environment. Inevitably, during the first few days, students will feel a little in the way and there is an expectation that a student will become competent enough to work independently in some basic laboratory techniques within a very short time.

For some students, studentships can feel quite pressurised, working to deadlines and staying late until the experiment is complete; for others, especially in some of the written projects in the CME and CPH, the working hours may be more regular or flexible. The working pattern depends on what project you are doing and how much effort you are prepared to put into it.

BENEFITS

A studentship gives you the opportunity to be involved in an intellectually stimulating activity over the summer, to have ownership over a project and to experience something new. It is also a great way to make friends, especially from other countries, diverse courses and different years - and the programme also includes fun social events. From a networking perspective, a studentship can also help with making important contacts if you decide to undertake a research project and to hear from researchers about their own career pathways. Additionally, a stipend is attached to these studentships so those students who support themselves financially need not feel that they are excluded from this opportunity.

Involvement in a small piece of research can be particularly useful for medical students considering doing an intercalated degree, particularly if, like the author, you have no previous experience of laboratory work. Thinking even further ahead, it may turn out to be valuable encouragement to apply for postgraduate research as a Clinical Academic Trainee and advancing medical knowledge. All students are invited to present their research at the end of their studentship. There is also the opportunity to submit abstracts for consideration of presentation at student research symposia and to submit work for publication in conjunction with the project supervisor.

OVERALL

My studentship was a really worthwhile experience. I worked hard, but reaped the benefits of my efforts and came away feeling confident doing Western Blots and PCRs, which I never could have imagined 8 weeks earlier. I made friends with people I would otherwise never have met and learned what I can achieve if I put my mind to it. For anyone considering a summer studentship, I would urge you to grasp this opportunity, and, if nothing else, get a behind-the scenes look at life in a lab!

Thank you to CEM for allowing me to have this opportunity and special thanks to Dr Derek Brazil, Dr Rachel Chambers and Dr Deborah Lavin for taking the time to teach and support me during my time in their lab.

My thanks to Prof. Keith Gardiner for his help in preparing this manuscript.

THE ULSTER MEDICAL JOURNAL

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The Journal's links with the Ulster Medical Society and Queens University Belfast are reflected in regular publication of Medical History and Medical Education articles. **The front cover** of the journal usually includes an image related to an article within, but the editor is keen to consider publishing images that reflect "**Ulster medical life**" in a broader context. Please contact the editor for further details.

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Manuscripts should be accompanied by a covering letter **signed** by all the authors agreeing to publication and stating that the work has not been published elsewhere; and stating that they have been actively involved in the preparation of the paper and outlining their contribution to the paper. Any conflict of interest should be declared.

A **PDF** copy of the printed and signed covering letter is ideal for electronic submission.

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Colour images and tables are encouraged and there is currently no charge for colour reproduction.

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Dr Purvis will be pleased to advise on the preparation of manuscripts on request.

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    4. the year.
    5. volume number and issue number (in brackets) **in bold**.
    6. first and last pages.

- *Example:* Devlin LA, Price JH, Morrison PJ. Hereditary non-polyposis colon cancer. *Ulster Med J* 2005;**74(1)**: 14-21.
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